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Mycophenolate Mofetil for Oral Suspension

DEFINITION

Mycophenolate Mofetil for Oral Suspension is a dry mixture of mycophenolate mofetil and one or more suitable buffers, colors, diluents, and flavors. It contains NLT 90.0% and NMT 110.0% of the labeled amount of mycophenolate mofetil ($C_{23}H_{31}NO_7$).

IDENTIFICATION

Change to read:

• **▲A.▲** **Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*: 197U.**▲ (CN 1-May-2020) [Note—Alternatively, the UV spectra of the major peaks of the *Sample solution* and the *Standard solution*, as obtained in the *Assay*, may also be used to meet the *Acceptance criteria*.]

Standard stock solution: 0.5 mg/mL of USP Mycophenolate Mofetil RS prepared as follows. Transfer a suitable amount of USP Mycophenolate Mofetil RS to a volumetric flask, add water equivalent to 15% of the flask volume, shake, and mix. Add acetonitrile equivalent to 70% of the flask volume, and sonicate to dissolve. Dilute with acetonitrile to volume.

Standard solution: 0.01 mg/mL of USP Mycophenolate Mofetil RS in acetonitrile, from *Standard stock solution*

Sample stock solution: Nominally equivalent to 0.5 mg/mL of mycophenolate mofetil prepared as follows. Constitute the Mycophenolate Mofetil for Oral Suspension as directed in the labeling. Transfer a suitable amount of reconstituted oral suspension to a volumetric flask, add water equivalent to 15% of the flask volume, shake, and mix. Add acetonitrile equivalent to 70% of the flask volume and sonicate to dissolve. Dilute with acetonitrile to volume. Pass a portion of this solution through a suitable filter of 0.45-µm pore size.

Sample solution: Nominally equivalent to 0.01 mg/mL of mycophenolate mofetil in acetonitrile, from *Sample stock solution*

Acceptance criteria: The UV absorption spectrum of the *Sample solution* exhibits maxima and minima at the same wavelengths as those of the *Standard solution*.▲ (USP 1-May-2019)

Change to read:

• **▲B.▲** (USP 1-May-2019) 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**

Protect solutions from light.

Buffer 1: Pipet 10 mL of triethylamine into a 1000-mL volumetric flask containing about 950 mL of water, and mix. Adjust with phosphoric acid to a pH of 7.2, and dilute with water to volume.

Buffer 2: Pipet 10 mL of triethylamine into a 1000-mL volumetric flask containing about 950 mL of water, and mix. Adjust with phosphoric acid to a pH of 3.0, and dilute with water to volume.

Solution A: *Buffer 1* and water (4:9)

Extraction solvent: Acetonitrile, *Buffer 2*, and water (13:4:9)

Diluent: Acetonitrile, *Buffer 2*, and water (7:4:9)

Mobile phase: Acetonitrile and *Solution A* (3:7)

Standard stock solution: 4 mg/mL of USP Mycophenolate Mofetil RS in *Extraction solvent*. Sonicate to aid the dissolution.

Standard solution: 0.4 mg/mL of USP Mycophenolate Mofetil RS in *Diluent*, from the *Standard stock solution*

Sample stock solution: Nominally equivalent to 4 mg/mL of mycophenolate mofetil prepared as follows. Constitute Mycophenolate Mofetil for Oral Suspension as directed on the label. Prepare a composite sample by mixing NLT 4 bottles of the constituted Mycophenolate Mofetil for Oral Suspension. Transfer a volume of the composite sample so obtained, equivalent to 800 mg of mycophenolate mofetil, to a 200-mL volumetric flask, and dilute with *Extraction solvent* to volume.

Sample solution: Nominally equivalent to 0.4 mg/mL of mycophenolate mofetil prepared as follows. Transfer 5.0 mL of the *Sample stock solution* to a 50-mL volumetric flask, and dilute with *Diluent* to volume. Pass through a filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 249 nm. ▲If this procedure is used for *Identification A*, use a diode array detector in the range of 200–400 nm.▲ (USP 1-May-2019)

Column: 4.6-mm × 25-cm; 5-µm packing L11

Temperatures

Autosampler: 5°

Column: 45°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of mycophenolate mofetil ($C_{23}H_{31}NO_7$) in the portion of Mycophenolate Mofetil for Oral Suspension 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 Mycophenolate Mofetil RS▲ (USP 1-May-2019) in the *Standard solution* (mg/mL)

C_U = nominal concentration of mycophenolate mofetil in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

▲Protect solutions from light.▲ (USP 1-May-2019)

Medium: 0.1 N hydrochloric acid; 900 mL, deaerated

Apparatus 2: 40 rpm

Time: 20 min

Standard solution: 0.278 mg/mL of USP Mycophenolate Mofetil RS in *Medium*

Sample solution: Reconstitute Mycophenolate Mofetil for Oral Suspension according to the labeling instructions. Shake well. Use a separate 3-mL syringe for each vessel. Withdraw 2 mL of suspension. Remove air bubbles from the syringe. Adjust the volume to 1.2 mL and accurately weigh the filled syringe. Operate the apparatus, holding the syringe above the surface of the medium, at a location that is halfway between the paddle shaft and the vessel wall. Carefully introduce the sample to the vessel over a 5–10 s period. Weigh the empty syringe and determine the weight of the sample (g). At the time specified, withdraw an aliquot and immediately pass through a suitable filter of 10-µm pore size, discarding the first few milliliters.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV

Analytical wavelength: 304 nm

Cell: 0.2 cm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of mycophenolate mofetil dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times (V_1/V_2) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of ▲USP Mycophenolate Mofetil RS▲ (USP 1-May-2019) in the *Standard solution* (mg/mL)

L = suspension label claim of mycophenolate mofetil (mg/mL)

V_1 = volume of *Medium*, 900 (mL)

V_2 = volume of sample (mL), weight (g) of the sample divided by the density of the suspension (g/mL)

Tolerances: NLT 80% (*Q*) of the labeled amount of mycophenolate mofetil is dissolved.

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

• **Deliverable Volume ⟨698⟩:** Meets the requirements

IMPURITIES

Change to read:

• **Organic Impurities**

Protect solutions from light.

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

System suitability solution: 0.01 mg/mL of USP Mycophenolate Mofetil Related Compound A RS and 0.01 mg/mL of USP Mycophenolate Mofetil Related Compound B RS in *Diluent*. [Note—The relative retention times for mycophenolate mofetil related compound A and mycophenolate mofetil related compound B are 0.40 and 0.46, respectively, measured with respect to mycophenolate mofetil.]

Sensitivity solution: 0.2 µg/mL in *Diluent* from the *Standard solution*

System suitability

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

Suitability requirements

Resolution: NLT 2.0 between mycophenolate mofetil related compound A and mycophenolate mofetil related compound B, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

[Note—The run time for the *Sample solution* is NLT 1.5 times the retention time of the mycophenolate mofetil peak.]

Calculate the percentage of each impurity in the portion of Mycophenolate Mofetil for Oral Suspension taken:

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

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

r_S = peak response of mycophenolate mofetil from the *Standard solution*

C_S = concentration of ▲USP Mycophenolate Mofetil RS▲ (USP 1-May-2019) in the *Standard solution* (mg/mL)

C_U = nominal concentration of mycophenolate mofetil in the *Sample solution* (mg/mL)

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

Acceptance criteria: See *Table 1*. ▲The reporting threshold is 0.05%.▲ (USP 1-May-2019)

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Mycophenolic acid[a]	0.12	1.4	3.3
▲Sorbitolyl▲ (USP 1-May-2019) ester of mycophenolic acid[b]	0.24	0.77	0.2
Mycophenolate mofetil	1.00	—	—
Any individual unspecified impurity	—	1.0	0.1
Total impurities	—	—	3.8

[a] (*E*)-6-(1,3-Dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoic acid.

[b] Sorbitol (*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate.

SPECIFIC TESTS

• **pH ⟨791⟩**

Sample: The suspension constituted as directed in the labeling

Acceptance criteria: 6.0–7.0

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature.
- **USP Reference Standards** ⟨11⟩

USP Mycophenolate Mofetil RS

USP Mycophenolate Mofetil Related Compound A RS

2-Morpholinoethyl (*E*)-6-(1,3-dihydro-4,6-dihydroxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate.
$C_{22}H_{29}NO_7$ 419.47

USP Mycophenolate Mofetil Related Compound B RS

(*RS*)-7-Hydroxy-5-methoxy-4-methyl-6-[2-(5-methyl-2-oxo-tetrahydrofuran-5-yl)ethyl]-3*H*-isobenzofuran-1-one.
$C_{17}H_{20}O_6$ 320.34

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

Topic/Question	Contact	Expert Committee
MYCOPHENOLATE MOFETIL FOR ORAL SUSPENSION	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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