

BRIEFING

Mycophenolate Mofetil Tablets. This monograph proposal was posted on the USP Pending Monographs Web page as a draft USP Pending Monograph on December 29, 2008, for public comments for more than 90 days. The MD-OOD Expert Committee has reviewed all the comments that were received and has approved the monograph as an Authorized USP Pending Monograph.

Comment 1: It was suggested that the *Infrared Absorption test* (197M) or (197A) should be performed for *Identification*.

Response 1: The comment was not incorporated because the comment is more relevant to the USP monograph rather than the USP pending monograph, as described in the *Pending Monographs Guideline* posted on the USP website. The commentator is encouraged to submit comments for USP Mycophenolate Mofetil Tablets monograph being published in PF 35(4).

Comment 2: It was requested that in the test for *Organic Impurities* the limit for mycophenolic acid should be increased from 0.5% to 1.0% and the limit for total impurities should be increased from 0.8% to 1.2%, to be consistent with the approved NDA.

Response 2: The comment was not incorporated because the comment is more relevant to the USP monograph rather than the USP pending monograph, as described in the *Pending Monographs Guideline* posted on the USP website. The commentator is encouraged to submit comments for USP Mycophenolate Mofetil Tablets monograph being published in PF 35(4).

Comment 3: It was suggested that the same mobile phase, sample solution, standard solution and diluent are used for both *Assay* and the test for *Organic Impurities*. It was also recommended a guard column for both the *Assay* and the test for *Organic Impurities*.

Response 3: The comment was not incorporated because the comment is more relevant to the USP monograph rather than the USP pending monograph, as described in the *Pending Monographs Guideline* posted on the USP website. The commentator is encouraged to submit comments for USP Mycophenolate Mofetil Tablets monograph being published in PF 35(4).

Comment 4: It was requested to change the limit for *Dissolution* from NLT 70% (Q) in 15 min to NTL 85% (Q) in 15 min. It was also requested to add a control of NTL 75% (Q) in 5 min to assure optimized uniformity of the performance characteristics.

Response 4: The comment was not incorporated because the comment is more relevant to the USP monograph rather than the USP pending monograph, as described in the *Pending Monographs Guideline* posted on the USP website. The commentator is encouraged to submit comments for USP Mycophenolate Mofetil Tablets monograph being published in PF 35(4).

The proposed chromatographic procedure in the *Assay* is based on analyses performed with a Zorbax Rx-C8 brand of L7 column; the typical retention time for mycophenolate mofetil is about 5 min. The proposed chromatographic procedure in the test for *Organic Impurities* is based on analyses performed with a Zorbax SB-C8 brand of L7 column; the typical retention time for mycophenolate mofetil is about 21 min.

(MD-OOD: F. Mao. BPC: M. Marques.) RTS—C68496

Mycophenolate Mofetil Tablets

v. 1 Authorized July 1, 2009

DEFINITION

Mycophenolate Mofetil Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of mycophenolate mofetil (C₂₃H₃₁NO₇).

IDENTIFICATION

• **A. ULTRAVIOLET ABSORPTION** (197U)

Sample solution: 10 µg/mL in acetonitrile

• **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: Mix 2 mL of triethylamine and 650 mL of water. Adjust with phosphoric acid to a pH of 5.3.

Mobile phase: Acetonitrile and *Solution A* (3:2)

Diluent: Acetonitrile and water (4:1)

Standard solution: 0.4 mg/mL of USP Mycophenolate Mofetil RS in *Diluent*

Sample stock solution: Transfer an equivalent to 200 mg of mycophenolate mofetil, from finely powdered Tablets (NLT 20), into a 100-mL volumetric flask. Add 60 mL of *Diluent*. Sonicate for 30 min with intermittent shaking. Dilute with *Diluent* to volume, and mix.

Sample solution: 0.4 mg/mL of mycophenolate mofetil from the *Sample stock solution* in *Diluent*. Pass a portion through a filter having a 0.45-µm or finer porosity.

Chromatographic system

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

Mode: LC

Detector: UV 250 nm

Column: 4.6-mm × 25-cm column; 5-µm packing L7

Column temperature: 45 ± 5°

Flow rate: 1 mL/min

Injection size: 10 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 C₂₃H₃₁NO₇ in the portion of Tablets 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 mycophenolate mofetil 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

• **DISSOLUTION** (711)

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 15 min

Sample solution: Pass a portion of the solution under test through a suitable 0.45-µm filter. Dilute 2.0 mL of the filtrate with *Medium* to 50 mL.

Standard solution: 0.022 mg/mL of USP Mycophenolate Mofetil RS in *Medium*

Detector: UV 250 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of C₂₃H₃₁NO₇ dissolved:

$$(A_U/A_S) \times (C_S \times V/L) \times 100$$

A_U = absorbance from the *Sample solution*

A_S = absorbance from the *Standard solution*

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

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

Tolerances: NLT 70% (Q) of the labeled amount of C₂₃H₃₁NO₇ is dissolved.

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- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

IMPURITIES

Organic Impurities

• PROCEDURE

Solution A: Proceed as directed in the Assay.

Mobile phase: Acetonitrile and *Solution A* (7:13)

Standard solution: 0.02 mg/mL of USP Mycophenolate Mofetil RS in acetonitrile

Sample solution: Transfer an equivalent to 200 mg of mycophenolate mofetil, from finely powdered Tablets (NLT 20), into a 100-mL volumetric flask. Add 60 mL of acetonitrile. Sonicate in ice-cold water for 30 min with intermittent shaking. Dilute with acetonitrile to volume, and mix. Pass a portion through a filter having a 0.45- μ m or finer porosity. [NOTE—Store the *Sample solution* at 5°.]

Chromatographic system

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

Mode: LC

Detector: UV 250 nm

Column: 4.6-mm \times 25-cm column; 5- μ m packing L7

Column temperature: 45 \pm 5°

Flow rate: 1.5 mL/min

Run time: 3.3 times the retention time of the mycophenolate mofetil peak, *Sample solution*

Injection size: 10 μ L

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

- r_U = response of each individual impurity from the *Sample solution*
- r_S = response of mycophenolate mofetil from the *Standard solution*
- C_S = concentration of mycophenolate mofetil in the *Standard solution* (mg/mL)
- C_U = concentration of mycophenolate mofetil in the *Sample solution* (mg/mL)
- F = relative response factor for each individual impurity (see *Impurity Table 1*)

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 0.8%

[NOTE—Disregard any peaks less than 0.05%.]

Impurity Table 1

Name	Relative Retention Time (RRT)	Relative Response Factor	Acceptance Criteria, NMT (%)
Mycophenolic acid ^a	0.3	1.4	0.5
Mycophenolate mofetil	1.0	—	—
Any unspecified impurity	—	1.0	0.1

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

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.
- **USP REFERENCE STANDARDS (11)**
USP Mycophenolate Mofetil RS