**Mycophenolate Mofetil Oral Suspension**

Details for the public consultation of this monograph are as follows:

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<th>EAG/Panel/Working Party</th>
<th>Medicinal Chemicals 1</th>
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| **Notes** | New monograph  
If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required. |

**Action and use**

Inhibitor of nucleic acid synthesis; immunomodulator.

**DEFINITION**

Mycophenolate Mofetil Oral Suspension is a suspension of Mycophenolate Mofetil in a suitable vehicle. It is prepared by dispersing the dry ingredients in the specified volume of water just before issue for use.

*The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Suspensions stated under Oral Liquids*

*For the following tests prepare the Oral Suspension as directed on the label. The suspension, examined immediately after preparation unless otherwise indicated, complies with the requirements stated under Oral Liquids and with the following requirements.*

**Content of mycophenolate mofetil, C_{17}H_{20}O_{6}**

90.0 to 105.0% of the stated amount.

**IDENTIFICATION**

A. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions.

Solution A 1 volume of a solution of 0.05M ammonium phosphate in water, pH adjusted the pH to 3.0 with orthophosphoric acid or 1M potassium hydroxide and 1 volume of acetonitrile.

(1) Shake a quantity of the oral suspension containing 0.5 g of Mycophenolate Mofetil with 25 mL of solution A. Dilute to produce 50 mL with solution A, and further dilute 1 volume to 10 volumes with solution A, filter and use the filtrate.
(2) 0.1% w/v of mycophenolate mofetil BPCRS in acetonitrile.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel F$_{254}$ (Merck silica gel 60 F$_{254}$ plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and examine immediately under ultraviolet light (254 nm).

MOBILE PHASE

1 volume of ammonium hydroxide, 7 volumes of methanol, 17 volumes of toluene and 75 volumes of acetonitrile.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity and alkalinity

pH of the suspension, 6.0 to 7.0, Appendix V L.

Dissolution

Comply with the requirements in the dissolution test for tablets and capsules, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 40 revolutions per minute.
(b) Use 900 mL of 0.1M hydrochloric acid, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 20 minutes withdraw a sample of the medium, and filter (a 0.45-µm nylon filter is suitable). Dilute the filtered sample with dissolution medium, if necessary to produce a solution containing 0.0056% w/v of Mycophenolate Mofetil. Immediately measure the absorbance of the solution, Appendix II B, at 304 nm using dissolution medium in the reference cell.

(2) Measure the absorbance of a 0.0056% w/v solution of mycophenolate mofetil BPCRS in the dissolution medium.

DETERMINATION OF CONTENT

Calculate the total content of mycophenolate mofetil, C$_{17}$H$_{20}$O$_{6}$, in the medium using the declared content of C$_{17}$H$_{20}$O$_{6}$ in mycophenolate mofetil BPCRS.

LIMITS

The amount of mycophenolate mofetil released is not less than 80% (Q) of the stated amount.
Related substances

Carry out the method for liquid chromatography, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light.

Solution B 20 volumes of solution containing 1% v/v triethylamine in water, pH adjusted to 3.0 with orthophosphoric acid or 1m potassium hydroxide, 35 volumes of acetonitrile and 45 volumes of water.

Solution C 15 volumes of solution containing 1% v/v triethylamine in water, pH adjusted to 3.0 with orthophosphoric acid or 1m potassium hydroxide, 35 volumes of water and 50 volumes of acetonitrile.

(1) Shake a quantity of the oral suspension containing 80 mg of Mycophenolate Mofetil with 100 mL of solution C. Dilute to 200 mL with solution C. Dilute 5 volumes of this solution to 50 volumes with solution B and filter through a 0.45-µm PVDF filter to produce a solution containing 0.05% w/v of Mycophenolate Mofetil.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution B.

(3) Dilute 1 volume of solution (2) to 10 volumes with solution B.

(4) 0.05% w/v of mycophenolate mofetil impurity standard BPCRS (mycophenolate mofetil with impurities A, B, C, F and G) in solution B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm packed with phenylsilyl silica gel for chromatography (5 µm) (Inertsil Phenyl is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 45°.
(e) Use a detection wavelength of 249 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of mycophenolate mofetil.

MOBILE PHASE

217 volumes of solution containing 1% v/v of triethylamine in water, adjusted to pH 7.2 with orthophosphoric acid or 1m potassium hydroxide, 300 volumes acetonitrile and 483 volumes of water.

When the chromatograms are recorded under the prescribed conditions the retention times relative to mycophenolate mofetil (retention time about 27 minutes) are: impurity F, about 0.1; impurity 1, about 0.2; impurity G, about 0.3; impurity A, about 0.4; impurity H, about 0.45; impurity B, about 0.9 and impurity C, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the resolution between the peaks due to mycophenolate mofetil and impurity C is at least 2.0

LIMITS

In the chromatogram obtained with solution (1), identify any peaks due to impurities A, B, F and G using the chromatogram obtained with solution (4). Multiply the area of any peak corresponding to impurity A by a correction factor of 0.6; multiply the area of any peak corresponding impurity B by a correction factor of 2.1 and multiply the area of any peaks corresponding impurity F and impurity G by a correction factor of 0.7.

In the chromatogram obtained with solution (1):
the area of any peak corresponding to impurity F is not greater than 3.3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.3%);

the area of any peaks corresponding to impurity B or impurity 1 is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2% of each);

the area of any other secondary peak is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the sum of the areas of all secondary peaks, excluding impurity F, is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Carry out the method for liquid chromatography, Appendix III D, using the following solutions freshly prepared.

Solution B 20 volumes of solution containing 1% v/v triethylamine in water, pH adjusted to 3.0 with orthophosphoric acid or 1M potassium hydroxide, 35 volumes of acetonitrile and 45 volumes of water.

Solution C 15 volumes of solution containing 1% v/v triethylamine in water, pH adjusted to 3.0 with orthophosphoric acid or 1M potassium hydroxide, 35 volumes of water and 50 volumes of acetonitrile.

(1) Shake a weighed quantity of oral suspension containing 80 mg of Mycophenolate Mofetil with 100 mL of solution C. Dilute to 200 mL with solution C. Dilute 1 volumes of this solution to 10 volumes with solution B and filter through a 0.45-µm PVDF filter to produce a solution containing 0.05%w/v of Mycophenolate Mofetil.

(2) 0.05% w/v of mycophenolate mofetil BPCRS.

(3) 0.05% w/v of mycophenolate mofetil impurity standard BPCRS (mycophenolate mofetil with impurities A, B, C, F and G) in solution B.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to mycophenolate mofetil and impurity C is at least 2.0

DETERMINATION OF CONTENT

Determine the weight per mL of the oral suspension, Appendix V G, and calculate the content of \( C_{17}H_{20}O_6 \) weight in volume, using the declared content of \( C_{17}H_{20}O_6 \) in mycophenolate mofetil BPCRS.

Repeat the procedure using a portion of the oral suspension that has been stored at the temperature and for the period stated on the label during which it may be expected to be satisfactory for use.

IMPURITIES
The impurities limited by the requirements of this monograph include those listed under *Mycophenolate Mofetil* and impurity 1:

1. sorbitol ester of mycophenolic acid