Stability of Mycophenolate Mofetil in a 1:1 Mixture of Ora-Sweet and Ora-Plus

Use of the immunosuppressant mycophenolate mofetil in solid-organ transplantation is increasing. A suspension (CellCept, Hoffmann-La Roche, Nutley, New Jersey) is marketed in the United States, but an oral liquid formulation is not yet commercially available in Canada. Therefore, extemporaneous compounding of oral suspensions is required for children and adults who are unable to swallow capsules or tablets. Stability data are available for suspensions of this drug prepared with cherry-flavoured syrup,[1] with Ora-Plus (a suspending agent) and cherry syrup,[2] and with Ora-Plus, artificial cherry flavouring, and aspartame.[3] However, no information is available on the stability of mycophenolate mofetil in a 1:1 mixture of Ora-Sweet (a sweetening agent) and Ora-Plus.

The objective of this study was to examine the physical characteristics and chemical stability (defined as maintenance of more than 90% of initial concentration) of extemporaneously prepared oral suspensions of mycophenolate mofetil in a 1:1 mixture of Ora-Sweet and Ora-Plus (Paddock Laboratories Inc., Minneapolis, Minnesota) stored at either 25°C or 4°C throughout a 91-day study period.

Mycophenolate mofetil suspensions (50 and 100 mg/mL) were prepared from commercially available 250-mg CellCept capsules (Hoffmann-La Roche, Mississauga, Ontario; lot W10960) and equal parts Ora-Sweet and Ora-Plus. Six replicates of each concentration were prepared in separate 50-mL amber

plastic prescription bottles; 3 of these were stored at 25°C (room temperature) and 3 were stored at 4°C (refrigerated). Physical appearance was evaluated qualitatively on initiation of the study and at weekly intervals up to 91 days. All suspensions were shaken vigorously and examined (against both white and black backgrounds) for colour changes and precipitates, layering, and sedimentation; odour changes, ease of resuspension, and gas formation were also assessed. Immediately after these physical observations (on initiation of the study and at weekly intervals), each bottle was manually shaken for 10 s, pH was determined, and samples were removed and stored at –85°C until batch analysis by a stability-indicating high performance liquid chromatography (HPLC) method.

Stock solutions of the drug (5.0, 2.5, 1.0, 0.5, and 0.25 mg/mL) were prepared by dilution of analytical-grade mycophenolate mofetil (Roche Bioscience, Palo Alto, California) in HPLC-grade methanol. The internal standard was indomethacin (Sigma Aldrich, Oakville, Ontario) 1.0 mg/mL in HPLC-grade methanol. Standard solutions were prepared by further diluting a 0.1-mL aliquot of each stock solution and a 0.1-mL aliquot of indomethacin 1.0 mg/mL to 1 mL with HPLC-grade methanol to obtain final concentrations of 0.50, 0.25, 0.10, 0.05, and 0.025 mg/mL of mycophenolate mofetil.

The HPLC instrumentation (Waters Ltd., Mississauga, Ontario) consisted of a delivery pump, an automatic injector equipped with a 200-µL injector, a Nova-Pak 3.9 x 20 mm guard column, a Nova-Pak C_{18} 3.9 x 150 mm column, and an ultraviolet detector set at 254 nm. The mobile phase was developed in the authors' laboratory and consisted of a 25:25:25:25 (v/v) gradient mixture of water, methanol, acetonitrile, and 0.05 mol/L potassium phosphate buffer (pH 3.0). All solvents were HPLC grade and were filtered before use. The flow rate was set at 1.5 mL/min.

A 5-point calibration curve was prepared, with a blank (methanol only) at the beginning of each run. The range of this calibration curve (0.25 to 5.0 mg/mL before dilution) encompassed the diluted test concentrations of the 50 and 100 mg/mL samples. Acceptable limits for the coefficients of variation were defined *a priori* as less than 10%.

Degradation of the drug was achieved as follows: mycophenolate mofetil 1 mg/mL (in methanol) was diluted 1:5 in water to a concentration of 0.2 mg/mL, and 0.25 mL of 6N hydrochloric acid was added. This solution was incubated in a water bath at 95°C for 1 h. Then, 0.25 mL of 10N sodium hydroxide was added and the solution was returned to the water bath at 95°C for 1 h. After incubation, the solution was boiled for 15 min.

For each study sample, mycophenolate mofetil 50 and 100 mg/mL was diluted to theoretical concentrations of 0.5 and 0.1 mg/mL, respectively. The diluted samples were centrifuged at 10 000 rpm for 5 min and then processed in a manner similar to that for the stock solutions. Each solution was passed through a 0.45-µm microfilter before a 10-µL sample was withdrawn and injected onto the column.

The regression analysis of the HPLC assay validation showed linearity over the working range of concentrations, with coefficients of determination (r^2) greater than 0.994 (n = 5). The intra-day (n = 5) and inter-day

Table 1. Mean Concentration of Mycophenolate Mofetil (and Percent of Initial Concentration Remaining) during Storage at 25°C and 4°C

	50 mg/mL Suspensions				100 mg/mL Suspensions			
Study Day	25°C		4°C		25°C		4°C	
0	53.5	(100.0)	51.5	(100.0)	112.9	(100.0)	112.0	(100.0)
7	53.7	(100.4)	48.7	(94.6)	111.0	(98.3)	103.3	(92.2)
14	51.8	(96.8)	47.3	(91.8)	110.1	(97.5)	105.2	(93.9)
21	49.3	(92.1)	49.5	(96.1)	122.8	(108.8)	120.5	(107.6)
28	53.1	(99.3)	51.8	(100.6)	102.6	(90.9)	107.9	(96.3)
35	53.3	(99.6)	47.9	(93.0)	110.4	(97.8)	110.9	(99.0)
42	52.5	(98.1)	49.9	(96.9)	112.5	(99.6)	112.2	(100.2)
49	60.6	(113.3)	54.6	(106.0)	122.7	(108.7)	141.8	(126.6)
56	50.9	(95.1)	49.1	(95.3)	116.1	(102.8)	101.9	(91.0)
63	58.5	(109.3)	61.6	(119.6)	116.7	(103.4)	128.1	(114.4)
70	63.8	(119.2)	61.2	(118.8)	142.3	(126.0)	143.0	(127.7)
77	59.5	(111.2)	57.5	(111.6)	123.8	(109.6)	118.5	(105.8)
84	59.6	(111.4)	59.8	(116.1)	108.9	(96.5)	151.3	(135.1)
91	54.5	(101.9)	61.6	(119.6)	116.8	(103.5)	129.7	(115.8)
Mean	55.5	(103.7)	53.9	(104.7)	116.7	(103.4)	121.1	(108.1)

(n = 5) coefficients of variation for 3 different concentrations were within acceptable limits: 1.08% and 6.00%, respectively, for a concentration of 0.05 mg/mL; 0.85% and 5.14%, respectively, for a concentration of 0.125 mg/mL ; and 1.31% and 2.95%, respectively, for a concentration of 0.25 mg/mL.

When mycophenolate mofetil was subjected to degradation, a major degradation product eluted at 0.93 min. This product did not interfere with the quantification of the parent compound (retention time 2.29 min) or the internal standard, indomethacin (retention time 7.30 min).

No notable changes in physical appearance or odour of the suspensions were observed throughout the 91-day study period. Each cloudy white suspension had a faint sweet smell, maintained the same viscosity, and was easily resuspended throughout the study period. Furthermore, no notable fluctuations in pH were observed. The mean pH (± standard deviation) was 5.02 ± 0.08 for the 50 mg/mL suspension stored at 25°C, 5.33 ± 0.29 for the 50 mg/mL suspension stored at 4°C, 4.71 ± 0.11 for the 100 mg/mL suspension stored at 25°C, and 4.71 ± 0.10 for the 100 mg/mL suspension stored at 4°C.

More than 90% of the initial mycophenolate mofetil concentration, as determined by HPLC, remained on each study day at both storage temperatures for both the 50 and 100 mg/mL suspensions (Table 1). The average percent remaining on all study days ranged from 103.4% to 108.1%.

Until an oral liquid form of mycophenolate mofetil becomes commercially available in Canada, pharmacists can select from several extemporaneously compounded formulations. Mycophenolate mofetil 100 mg/mL suspensions prepared with cherry-flavoured syrup are reported to be stable for 121 days between 23°C and 25°C and between 2°C and 8°C;[1] 50 mg/mL suspensions prepared with Ora-Plus and cherry-flavoured syrup have demonstrated stability for at least 11 days at 45°C, at least 28 days at 37°C and 25°C, and at least 210 days at 5°C;[2] 100 mg/mL suspensions prepared with Ora-Plus, artificial cherry flavouring, and aspartame were stable for 120 days at 23°C to 25°C (but retained an acceptable cherry odour for only 28 days);[3] and now 50 and 100 mg/mL suspensions prepared with a 1:1 mixture of Ora-Sweet and Ora-Plus have demonstrated stability up to 91 days at 25°C and 4°C.

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