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RESEARCH PAPER

Influence of Ferrous Sulfate on the Solubility, Partition Coefficient, and Stability of Mycophenolic Acid and the Ester Mycophenolate Mofetil

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ABSTRACT

Studies were performed to (1) evaluate whether the presence of iron affected the physicochemical properties of mycophenolate mofetil (MMF) and mycophenolic acid (MPA), and (2) determine whether alteration of these properties was indicative of formation of an MMF–iron complex. The solubility, stability (chemical reactivity), and partitioning properties of MMF and MPA were evaluated over a pH range of 2–7 in the presence and absence of ferrous sulfate. In addition, the solubility and partitioning properties of MMF were assessed after the MMF drug product, CellCept® capsules, was combined with an iron tablet (Fero-Gradumet®, ferrous sulfate, tablets). The results of studies showed that:

- *The solubility of MMF in the presence of ferrous sulfate was generally unaffected over a pH range of 2–7; a small increase in solubility was observed in pH 5.2 buffer solution. The solubility of MPA decreased in pH 5.2 and 7.0 buffer solutions.*
- *Both MMF and MPA were more stable in the presence of ferrous sulfate at pH 2.0; ferrous sulfate had no effect on the stability of MMF and MPA at pH 7.0.*
- *Overall, the partitioning of MMF and MPA was unaffected by the addition of ferrous sulfate.*

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- *The solubility and partitioning of MMF from CellCept® capsules combined with Fero-Gradumet® (ferrous sulfate) tablets showed a twofold increase in aqueous solubility of MMF as well as increased concentration of MMF in both the* n*-octanol and aqueous phases, leading to a decrease in the octanol/water partition coefficient due to a reduction in pH of the aqueous phase.*

Based on these results, it was concluded that the physicochemical properties of MMF and MPA were generally not affected by the presence of ferrous sulfate. Further, the presence of ferrous sulfate did not suggest the formation of an MMF–iron complex.

Key Words: *Mycophenolate mofetil; Mycophenolic acid; Ferrous sulfate; Interaction*

INTRODUCTION

Mycophenolate mofetil (MMF) is the 2-morpholinoethyl ester[1] of mycophenolic acid (MPA). It is an immunosuppressant that effectively suppresses acute allograft rejection following renal,[2–4] cardiac,[5] or hepatic[6] transplantation. It is marketed under the trade name CellCept®, and in most countries is indicated in combination with cyclosporin and corticosteroids for the prevention of organ rejection in renal, cardiac, or hepatic transplant recipients. After oral administration, MMF is rapidly absorbed and de-esterified to MPA; MPA is then glucuronidated to a stable, pharmacologically inactive, phenolic glucuronide (MPAG). The pharmacokinetics of MMF have been characterized in both healthy volunteers and renal transplant recipients.[7]

The aqueous solubility profile of MMF shows greater solubility at pH<5 and poor solubility at pH>6. In contrast, MPA shows poor solubility at pH<5 and greater solubility at pH>6. While MMF has a pK_a of approximately 5.6 and an intrinsic solubility of approximately 39 μg/mL,[1] MPA has a pK_a of approximately 4.5 and an intrinsic solubility of approximately 13 μg/mL.[1] In aqueous media, the major degradation pathway is hydrolysis leading to formation of MPA, the major degradation product.[1,8]

In a recent publication, Morii et al.[9] evaluated the pharmacokinetics of MMF in healthy, fasted volunteers after coadministration with ferrous sulfate. The results of this study showed that both MPA AUC and C_{max} were significantly decreased after coadministration of MMF with ferrous sulfate compared to the same parameters obtained after administration of MMF alone. Morii suggested that a possible mechanism for the reduction of MPA AUC and C_{max} might be due to the formation of a drug–iron complex leading to impaired absorption. Drug interactions with metal ions have been identified (with drugs such as tetracycline, phenytoin, etc.), and these interactions generally lead to alteration of the drug's dissolution properties and consequently impact the drug's systemic absorption.[10,11]

In vitro studies were conducted to determine whether, and to what extent, ferrous sulfate may influence the chemical properties of MMF and MPA. A series of four studies were conducted, each designed to determine whether the presence of ferrous sulfate had an impact on: (1) the solubility of MMF and MPA over a physiologically relevant pH range (pH 2–7); (2) the chemical reactivity, or stability, of MMF and MPA; (3) the octanol/water partitioning properties of MMF and MPA; and (4) the solubility and partitioning properties of MMF from the formulated capsule product, CellCept®, combined with Fero-Gradumet®, ferrous sulfate, tablets.

MATERIALS AND METHODS

Materials

For studies evaluating the solubility, chemical reactivity, and partitioning properties of the pure drug substance, MMF and/or MPA in the presence of ferrous sulfate, the following chemicals were used: MMF, lot CC99040015, obtained from Roche, Ireland; MPA, lot CC99110040, obtained from Roche Diagnostics GmbH; iron (II) sulfate heptahydrate, from Aldrich Chemical Company; *n*-octanol,

Table 1

HPLC Methodology

Parameter	Description
Equipment	Waters 2690 and/or Hewlett Packard 1090
Column	Zorbax SB-Phenyl, 3.5 μm, 4.6 × 150 mm
Mobile phase	Isocratic, 70/30 tetrahydrofuran (0.1% in water)/acetonitrile
Mobile phase flow rate	1.0 mL/min
Injection volume	25–75 μL
Detection wavelength	250 nm
Temperature	Ambient
Retention time	MMF: 10–12 min MPA: 17–20 min
Acquisition time	30 min

lot F4758A, obtained from Avocado Research Chemicals, Ltd., Hersham, U.K.

Evaluation of the solubility and partitioning properties of MMF from CellCept® capsules in the presence of a formulated tablet of ferrous sulfate included the following materials: CellCept®, 250 mg capsules, lot U2596, manufactured by Roche; Fero-Gradumet®, 525 mg ferrous sulfate tablets (105 mg elemental iron), lot 1950814, manufactured by Abbott, Japan; and *n*-octanol, lot CO00343BS, from Aldrich Chemical Company, Milwaukee, WI.

Buffers

The following nine buffers were prepared: (1) pH 2.0 buffer comprised of 0.2% (w/v) sodium chloride and 0.7% (v/v) HCl in water; (2) pH 2.0 buffer, as above, with 0.4 mg/mL iron (II) sulfate heptahydrate; (3) pH 2.0 buffer, as above, with 4.0 mg/mL iron (II) sulfate heptahydrate; (4) pH 5.2 buffer consisting of 0.05 M sodium acetate and 0.1 M sodium chloride in water; (5) pH 5.2 buffer, as above, with 0.4 mg/mL iron (II) sulfate heptahydrate; (6) pH 5.2 buffer, as above, with 4.0 mg/mL iron (II) sulfate heptahydrate; (7) pH 7.0 buffer comprised of 0.68% (w/v) potassium phosphate monobasic and 19.0% (v/v) 0.2 N sodium hydroxide in water; (8) pH 7.0 buffer, as above, with 0.4 mg/mL iron (II) sulfate heptahydrate; and (9) pH 7.0 buffer, as above, with 4.0 mg/mL iron (II) sulfate heptahydrate. The final pH of each buffer was adjusted to the target pH (2.0, 5.2, and 7.0) after addition of iron.

At pH 5.2, the buffer solutions containing ferrous sulfate (0.4 mg/mL and 4 mg/mL) were initially clear and free of precipitate; however, after approximately 3 hr, the solutions showed precipitation. Likewise, at pH 7.4, ferrous sulfate did not completely dissolve at either concentration studied. Therefore, these experiments were performed in saturated solutions of ferrous sulfate.

High-Performance Liquid Chromatography Methodology

Samples were analyzed by high-performance liquid chromatography (HPLC) using the equipment and parameters described in Table 1.

pH Determination

pH Solution measurements were made at room temperature using an Orion Triode™ pH meter (model 611, Orion Research Inc.) electrode calibrated with aqueous standard buffer solutions.

Solubility Determination

Excess drug was weighed into clear glass vials (4 mL capacity) with teflon-lined screw caps. Approximately 2 mL of buffer was added to each vial and the contents were mixed by vortexing. The pH of the mixture was measured immediately after vortexing. The samples were then placed in a 37°C oven for 3 hr with vigorous shaking for 1 min at 30-min intervals. After the 3-hr incubation, the samples were cooled to room temperature and the pH was measured. The samples were then filtered via centrifugation at 150,000 rpm for 5 min through a non-sterile microspin centrifuge tube containing a 0.22-μm filter. The filtrates were then analyzed by HPLC.

Chemical Reactivity

Reaction solutions containing approximately 19 µg/mL of either MMF or MPA were prepared with pH 2.08 or pH 7.04 buffer with and without ferrous sulfate. These reaction solutions were filled into HPLC vials, and placed in the HPLC autosampler, set at 37°C (controlled by a water bath). The first injection of each sample vial was made immediately after the vial was put into the HPLC and served as the control point (zero time) for the calculation of percent remaining for all the other time points.

Partition Coefficients of MMF and MPA

Portions of *n*-octanol and the various buffer solutions containing 0, 0.4, and 4.0 mg/mL ferrous sulfate were mixed together to presaturate each of the phases; these phases were then separated for later use.

Solutions of MMF or MPA were each prepared at concentrations of approximately 0.05 and 0.5 mg/mL in presaturated *n*-octanol. All solutions were prepared in duplicate. In a disposable glass centrifuge tube (10 mL capacity), a 4-mL aliquot of each of the drug solutions in *n*-octanol was added to a 4-mL aliquot of presaturated buffer solution. Each octanol–water mixture was vortexed and placed in a 37°C oven. Each mixture was agitated hourly for 3 hr and then processed for HPLC analysis. Analytical controls of 0.05 and 0.5 mg/mL of MMF or MPA were also prepared in unsaturated *n*-octanol using the same drug stock solution as used for the partition samples. The controls were also processed for HPLC analysis.

Prior to HPLC analysis all partition samples were centrifuged at 3500 rpm for 10 min to separate the *n*-octanol and aqueous phases. The *n*-octanol phase samples for MMF and MPA were diluted 1:10 or 1:5 before HPLC analysis. The aqueous phase samples for MMF in pH 2.08 buffer and MPA in pH 7.04 buffer were similarly diluted 1:10 before HPLC analysis. The aqueous samples for MMF in pH 7.04 buffer and MPA in pH 2.08 buffer were analyzed without further dilution. The aqueous phase samples for MMF and MPA in pH 5.19 solution were also analyzed without further dilution. The analytical controls for both MMF and MPA were diluted 1:10 or 1:5 before HPLC analysis.

Solubility and Partitioning Properties of MMF from CellCept® Capsules in the Presence of Fero-Gradumet® Tablets

Solubility

Four capsules of CellCept®, equivalent to 1.0 g MMF, were placed into each of two 50-mL volumetric flasks. Five Fero-Gradumet® tablets, equivalent to 525 mg ferrous ion, were added to one of the flasks. Approximately 30 mL of the pH 5.2 buffer (not presaturated) was added to each flask and sonicated (without temperature control) for approximately 30 min. The pH was not adjusted after capsules, tablets, and buffer solution were combined. After sonication each preparation (appearing as a suspension due to the large amount of undissolved solids) was allowed to cool to room temperature, and buffer solution was added to each flask to bring it to a final volume of 50 mL. Each 50-mL preparation was divided between two centrifuge tubes and labeled appropriately. The samples were placed in a 37°C oven and incubated for 3 hr, with agitation at 30-min intervals. After incubation the samples were vortexed and portions transferred to 10-mL centrifuge tubes. They were centrifuged at 3600 rpm for 15 min, and 1.5 mL of the supernatants taken into microfuge tubes and centrifuged again at 15,000 rpm for 30 min. The final supernatants were filtered through 0.45-µm filters, diluted 1:10 with 30% acetonitrile in water, and analyzed by HPLC.

Partitioning Properties

Portions of *n*-octanol and the pH 5.2 buffer were mixed together to presaturate each phase.

Four CellCept® capsules were placed in each of two 50-mL volumetric flasks and five Fero-Gradumet® tablets added to one of the flasks. Approximately 30 mL of the presaturated pH 5.2 buffer was added to each flask and sonicated (without temperature control) for about 30 min. The resulting suspensions were cooled to room temperature, diluted to a final volume of 50 mL, and vortexed to mix. Each sample was split into two 25-mL portions and placed into 50-mL-capacity centrifuge tubes. Each 25-mL portion was processed differently. To one sample, 25 mL of presaturated *n*-octanol was added; the second sample was centrifuged at 3600 rpm for 15 min to remove suspended solids. Fifteen milliliters of the supernatants were placed in fresh 50-mL centrifuge tubes and 15 mL presaturated *n*-octanol added. All

Table 2

Solubility of MMF (μg/mL) in the Absence and Presence of Ferrous Sulfate

Target pH	MMF, No Ferrous Sulfate (μg/mL)	MMF, 0.4 mg/mL Ferrous Sulfate (μg/mL)	MMF, 4.0 mg/mL Ferrous Sulfate (μg/mL)
2[a]	4072, 4078[b]	4046, 4046	4189, 4194
5.2	183, 365, 180	221, 366, 190	546, 491, 321
7.0	40, 40	41, 40	39, 38

[a]After addition of MMF the actual pH was approximately 4.
[b]Values separated by commas represent duplicate samples.

Table 3

Solubility of MPA (μg/mL) in the Absence and Presence of Ferrous Sulfate

Target pH	No Ferrous Sulfate (μg/mL)	0.4 mg/mL Ferrous Sulfate (μg/mL)	4.0 mg/mL Ferrous Sulfate (μg/mL)
2	14, 16[a]	16, 16	17, 16
5.2	112, 76, 104	102, 68, 104	26, 13, 11
7.0	3970, 3934	4119, 4086	2898, 2906

[a]Values separated by commas represent duplicate samples.

samples were vortexed and placed in a 37°C oven to incubate for 3 hr. The samples were agitated at 30-min intervals. After incubation, the samples were vigorously vortexed. Ten milliliters aliquots of each sample were centrifuged at 3600 rpm for 15 min to separate the aqueous and organic layers and to remove suspended solids. One and a half milliliters of each aqueous and organic layer were further centrifuged at 15,000 rpm for 30 min and filtered through 0.45-μm filters.

The aqueous layers were diluted 1:10 and analyzed by HPLC. The *n*-octanol layers were diluted 1:10, then 1:50 in duplicate (equivalent to 1:500 dilution) and analyzed by HPLC.

RESULTS AND DISCUSSION

Solubility of MMF and MPA

The pH of the buffer solutions was checked and adjusted to the target pH (2.0, 5.2, 7.0) after addition of ferrous sulfate. The pH was then measured and recorded after addition of either MMF or MPA; the pH was measured again after incubation. Except for solutions containing MMF at pH 2.0, all other solutions (MMF at pH 5.2 and 7.0; MPA at pH 2, 5.2, and 7.0) remained at or near (±0.2 pH units) the target pH value. The addition of excess MMF to pH 2.0 buffer caused upward drift of approximately 2 pH units, giving a final pH of approximately 4. This upward pH drift is attributed to the addition of excess free base (MMF) to the acidic media.

The solubility of MMF decreased with increasing pH. The solubility of MMF was not influenced by the presence of ferrous sulfate in pH 2 or 7 buffer solutions; however, there was a slight increase in solubility in pH 5.2 buffer solution (Table 2).

The solubility of MPA increased with increasing pH. The higher concentration of ferrous sulfate appeared to decrease the solubility of MPA in both pH 5.2 and 7.0 buffer solutions (Table 3).

Chemical Reactivity

The stability results indicated that MMF was more stable at pH 2.0 compared to pH 7.0 (Table 4), and MPA was more stable at pH 7.0 compared to pH 2.0 (Table 5). The presence of ferrous sulfate did not accelerate degradation of either MMF or MPA. In fact, at pH 2.0 both MMF and MPA appeared more stable in the presence of ferrous sulfate compared with the absence of ferrous sulfate. Ferrous

Table 4

Relative Percent Remaining of MMF over 24 hr at 37°C

	% MMF Remaining					
	pH 2.08			pH 7.04		
Time (hr)	No Ferrous Sulfate	0.4 mg/mL Ferrous Sulfate[a]	4 mg/mL Ferrous Sulfate[a]	No Ferrous Sulfate	0.4 mg/mL Ferrous Sulfate[b]	4 mg/mL Ferrous Sulfate[b]
0	100	100	100	100	100	100
3	98.2	99.6		86.5	86.1	85.6
6	97.9	99.4	99.3	72.0	73.0	71.5
12	94.3	99.1	98.1	53.0	53.3	54.6
18	88.1	98.4	97.0	39.3	39.3	40.2
24	80.0	96.6	96.6	30.1	29.6	30.6

[a]After addition of ferrous sulfate, the pH values were 2.09 for 0.4 mg/mL and 2.18 for 4 mg/mL.
[b]After addition of ferrous sulfate, the pH values were 7.04 for 0.4 mg/mL and 6.94 for 4 mg/mL.

Table 5

Relative Percent Remaining of MPA over 24 hr at 37°C

	% MPA Remaining					
	pH 2.08			pH 7.04		
Time (hr)	No Ferrous Sulfate	0.4 mg/mL Ferrous Sulfate[a]	4 mg/mL Ferrous Sulfate[a]	No Ferrous Sulfate	0.4 mg/mL Ferrous Sulfate[b]	4 mg/mL Ferrous Sulfate[b]
0	100	100	100	100	100	100
3	99.9	100.5	101.3	99.8	101.0	97.7
6	96.9	100.5	99.8	99.0	100.6	97.2
12	87.4	99.2	99.0	98.4	98.5	95.3
18	76.6	99.7	98.0	96.5	98.8	94.6
24	66.0	99.0	98.6	97.4	98.9	95.4

[a]After addition of ferrous sulfate, the pH values were 2.09 for 0.4 mg/mL and 2.18 for 4 mg/mL.
[b]After addition of ferrous sulfate, the pH values were 7.04 for 0.4 mg/mL and 6.94 for 4 mg/mL.

sulfate had no impact on stability of either MMF or MPA at pH 7.0.

The major thermal degradation product of MMF is MPA, and the degradation pathway at pH 2 is more complex than at pH 7. At pH values greater than 6.0, MPA is the only observed degradation product whereas under more acidic conditions, < pH 3.5, more degradation products are formed: the lactone analogue of MPA, a hydroxylactone, and unidentified products.[8] The observation that ferrous sulfate stabilized MMF and MPA at pH 2 is not understood and needs additional investigation.

Partition Coefficients of MMF and MPA

The partition coefficients for MMF and MPA were determined after equilibration at 37°C in pH 2.0, 5.2, and 7.0 buffers. The logarithms of the partition coefficients ($\log P$) for MMF and MPA are provided in Table 6.

In pH 2.0 and 7.0 buffers, the partitioning properties of MMF were similar in the absence or presence of ferrous sulfate. In pH 5.2 buffer, MMF had a somewhat lower $\log P$ value in the presence of the higher concentration of ferrous sulfate (4 mg/mL),

Table 6

Log Partition Coefficient for MMF and MPA in the Absence and Presence of Ferrous Sulfate over the pH Range 2–7

	Log Partition Coefficient (Log *P*) Mean±SD		
	pH 2.0	pH 5.2	pH 7.0
MMF	−0.50±0.03	1.99±0.01	2.50±0.01
MMF with 0.4 mg/mL ferrous sulfate	−0.46±0.05	1.98±0.01	2.52±0.01
MMF with 4.0 mg/mL ferrous sulfate	−0.50±0.04	1.69±0.01	2.58±0.04
MPA	2.82±0.04	2.03±0.03	0.28±0.11
MPA with 0.4 mg/mL ferrous sulfate	2.57±0.28	2.09±0.02	0.24±0.03
MPA with 4.0 mg/mL ferrous sulfate	2.81±0.03	2.30±0.29	0.43±0.01

Table 7

Solubility of MMF from CellCept® Capsule in pH 5.2 Buffer

Sample	MMF Concentration (μg/mL)
1 g MMF[a], no iron	189, 188
1 g MMF[a], 525 mg elemental iron[b]	445, 442

[a]Contained in four CellCept® capsules.
[b]Contained in five Fero-Gradumet® tablets.

suggesting slightly greater water partitioning under these conditions. No difference was found for the partition coefficients when the experiments were performed at MMF concentrations of 0.05 and 0.5 mg/mL.

The partitioning properties of MPA were generally similar in the absence or presence of ferrous sulfate. In pH 5.2 and 7.0 buffer solutions a slightly higher log *P* value was obtained in the presence of the higher concentration of ferrous sulfate (4 mg/mL), suggesting slightly greater *n*-octanol partitioning under these conditions. In general, no difference was found for the partition coefficients when the experiments were performed at MPA concentrations of 0.05 and 0.5 mg/mL.

Solubility and Partitioning Properties of MMF from CellCept® Capsules in the Presence of Fero-Gradumet® Tablets

The solubility and partitioning properties of MMF from CellCept® capsules in a pH 5.2 buffer were determined after equilibration at 37°C in the presence and absence of ferrous sulfate tablets.

The mean solubility of MMF (from the capsule dosage form) in buffered pH 5.2 medium was approximately twice as much when ferrous sulfate was present vs. when it was absent (Table 7). In this experiment, a large excess of iron was used, consequently the pH of the solution containing iron was reduced (Table 9). The observed increase in solubility is not completely understood, but an increase would be expected based on the reduction of the pH of the solution in the presence of ferrous sulfate.

Consistent with the results of the solubility experiment, the partitioning study showed that the amount of MMF in both the *n*-octanol and aqueous phases was higher in the presence of ferrous sulfate. The log *P* results for samples that had ferrous sulfate present were lower than those that did not have ferrous sulfate present (Table 8). This reduction in partitioning may be a result of increased ionization of MMF due to the reduction of pH in the presence of ferrous sulfate (Table 9).

A comparison of log *P* values for MMF only (no ferrous sulfate) shows no differences between samples that contained suspended solids before

Table 8

Partition of MMF from CellCept® Capsule in pH 5.2 Buffer

Sample	MMF Conc. (μg/mL) in the Octanol Phase	MMF Conc. (μg/mL) in the Water Phase	Partition Coefficient (*P*)	Log Partition Coefficient
MMF, no iron	16,867, 16,884[a]	161, 160	105, 105	2.02, 2.02
MMF, no iron[b]	162, 156	1.7, 1.6	93, 98	1.97, 1.99
MMF, 525 mg elemental iron	20,465, 20,348	606, 604	34, 34	1.53, 1.53
MMF, 525 mg elemental iron[b]	769, 764	68, 68	11, 11	1.05, 1.05

[a]Values separated by commas represent duplicate samples.
[b]Samples in pH 5.2 buffer precentrifuged to remove suspended solids before adding *n*-octanol.

Table 9

pH Measurement of MMF (from Capsules) with and without Ferrous Sulfate in pH 5.2 Buffer

Sample	Measured pH
Solubility, MMF+0 mg iron	5.27
Solubility, MMF+525 mg elemental iron	4.40
Partition, MMF+0 mg iron	5.58
Partition, MMF+525 mg elemental iron	3.75

addition of *n*-octanol to those that were centrifuged to remove suspended solids. However, in the presence of ferrous sulfate there are differences in log *P* values between samples with and without suspended solids prior to addition of *n*-octanol.

CONCLUSIONS

In general, the presence of ferrous sulfate in solution did not show a large effect on the solubility or partitioning properties of MMF or MPA in these studies. Additionally, ferrous sulfate did not accelerate degradation of either MMF or MPA. While interactions between ferrous sulfate and MMF or MPA cannot be ruled out, the results of these studies do not support the formation of an MMF–iron complex that might lead to significantly reduced in vivo absorption of MMF. Because the addition of ferrous sulfate creates a more acidic environment, the change in pH would impact solubility and partitioning properties. However, because of the complexity of the gastrointestinal environment, the extent of pH modification by ferrous sulfate and the resulting impact on the bioavailability of MMF are not known.

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