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ORIGINAL RESEARCH

Pharmacokinetics and Bioequivalence of Mycophenolate Sodium Enteric-Coated Tablets Under Fasting and Fed Conditions: A Single-Dose, Open-Label, Four-Period Replicated Crossover Study in Healthy Chinese Male Subjects

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Aim: Enteric-coated mycophenolate sodium (EC-MPS) is an immunosuppressant used to prevent organ rejection in kidney transplant patients. This study assesses the pharmacokinetics and bioequivalence of a generic EC-MPS formulation (180 mg) relative to the branded product (Myfortic®), and investigates the effect of food on its pharmacokinetic behavior.

Methods: A single-dose, open-label, four-period replicated crossover study with a 7-day washout was conducted in 60 healthy Chinese male subjects under fasting and fed conditions. Eligible subjects were enrolled in two independent trials (fasting and fed conditions) and randomized 1:1 into two treatment sequence groups, with 15 subjects per group. In each group, subjects received a single 180 mg oral dose of the generic or branded product after a 10-hours overnight fast. Plasma concentrations of mycophenolic acid were quantified using a validated LC-MS/MS method. Primary pharmacokinetic parameters (C_{max}, AUC_{0-48}, and AUC_{0-inf}) were evaluated via a non-compartmental model and analyzed by analysis of variance. Bioequivalence was determined using reference-scaled average bioequivalence (RSABE) for highly variable parameters (CV ≥30%) and average bioequivalence (ABE) otherwise, with 90% confidence intervals (CIs) within 80.00%-125.00%.

Results: All subjects completed the study. Bioequivalence was established between the generic and branded formulations under both fasting and fed conditions. In the fasting cohort, 90% CIs for the geometric mean ratios (GMRs) of C_{max}, AUC_{0-48}, and AUC_{0-inf} all fell within 80.00%-125.00%, meeting ABE criteria. In the fed cohort, GMRs for C_{max} and AUC_{0-inf} were 119.74% and 99.87%, respectively, within RSABE acceptance limits. Food intake delayed drug absorption, resulting in a notable lag time (median T_{max} 7.0 h vs 2.5–3.0 h, $p<0.01$) and increased inter- and intra-individual variability. Twenty mild adverse events (AEs) were reported; no serious AEs occurred.

Conclusion: The generic EC-MPS demonstrated bioequivalence to the branded product under all tested conditions, supporting its clinical interchangeability. Both formulations were well tolerated in healthy Chinese males.

Clinical Trial Registration: http://www.chictr.org.cn/, Registration No: ChiCTR2300075403.

Plain Language Summary:

Why was the study done?

This study compared a generic enteric-coated mycophenolate sodium (EC-MPS) tablet to the branded product to confirm bioequivalence and evaluate how food affected drug absorption in healthy Chinese males.

What did the researchers do and find?

A carefully designed study where 60 healthy Chinese male participants took the drug at different times, both with and without food. Blood tests confirmed bioequivalence between the generic and branded tablets. Food delayed the time to peak drug levels and increased variability in pharmacokinetic parameters. Mild side effects occurred but were not severe.

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What do these results mean?
The generic EC-MPS is a safe, effective alternative to the branded product. However, food delays drug absorption, highlighting the need for fasting administration to ensure consistent drug levels. Clinicians should monitor patients closely, especially those taking EC-MPS with meals. These findings are based on healthy male participants in China, and need further verification in female groups and transplant patients.

Keywords: pharmacokinetics, bioequivalence, enteric-coated mycophenolate sodium, four-period, food effect

Introduction

Renal transplantation remains the principal treatment approach for end-stage renal disease.[1] However, managing immunosuppression post-transplantation presents substantial challenges, including graft rejection risks and drug-related adverse effects.[2] Achieving optimal immunosuppression after organ transplantation requires a balance of therapeutic efficacy with acceptable safety profiles.[3] Yet, accomplishing this goal is complex, driving ongoing research into regimens that minimize toxicity to both grafts and patients.

Mycophenolic acid (MPA), discovered in 1969, acts as a selective and reversible immunosuppressant by inhibiting inosine monophosphate dehydrogenase (IMPDH).[4] However, its clinical utility has been limited by poor oral bioavailability and gastrointestinal side effects.[5] Mycophenolate mofetil (MMF, CellCept®), an ester prodrug of MPA, was developed by Roche Pharmaceuticals in the late 1980s - early 1990s and received regulatory approval in 1995.[6] Despite its efficacy, MMF is associated with hematological and gastrointestinal complications such as nausea, vomiting, ulcers, gastritis, diarrhea, and abdominal pain.[7] These safety issues are primarily associated with β-glucuronidase-producing bacteria in the gastrointestinal tract, which enhance enterohepatic circulation (EHC) by converting liver-formed MPA metabolites back to MPA.[8]

In 2004, Novartis developed enteric-coated mycophenolate sodium (EC-MPS, Myfortic®), contains MPA in its active form, designed to minimize upper gastrointestinal adverse events.[9] EC-MPS releases MPA in the intestine rather than the stomach,[10] with time to peak plasma concentrations (T_{max}) occurring between 1.5 h and 2.75h and a lag time (T_{lag}) of 0.25h to 1.25h. The mean absolute bioavailability of EC-MPS is 72%,[11] and the steady-state volume of distribution (Vd) is 54 ± 25 L.[12] As a Biopharmaceutics Classification System (BCS) Class II drug (low solubility, high permeability), EC-MPS's enteric coating is critical to bypass gastric degradation and ensure targeted intestinal release.[13]

EC-MPS is expected to be an effective alternative in long-term post-transplant therapy, minimizing dose- and formulation-related side effects. A twice-daily regimen of 720 mg EC-MPS can achieve systemic exposure equivalent to 1000 mg MMF, demonstrating comparable efficacy in graft rejection.[14] However, its enteric coating design requires a thorough evaluation of food effects, as gastric emptying dynamics may alter drug dissolution and absorption.[15] While manufacturer guidelines recommend fasting administration, studies reported conflicting food effects: a high-fat meal (55 g fat, 1000 kcal) did not affect MPA-AUC in EC-MPS recipients, but delayed T_{max} and reduced C_{max} by 33% in other cohorts.[16] EC-MPS is considered a highly variable drug with an intra-individual coefficient variation (CV) of 68% under fasting conditions.[17] This variability is hypothesized to increase under fed conditons,[18] emphasizing the need for standardized dosing protocols to ensure therapeutic consistency. To date, limited data exist on food's impact on EC-MPS pharmacokinetics (PKs), particularly in Chinese populations.

Regulatory authorities mandate that generic drugs should demonstrate equivalence to reference products and meet strict quality and efficacy standards. Interchangeability and therapeutic equivalence are key concerns. This study utilizes a four-period replicated crossover design to assess the bioequivalence between a generic EC-MPS tablet and its reference product, as well as to investigate the food effect on PK profiles in healthy Chinese male subjects.

Materials and Methods

Study Drugs

The test formulation (T) was a generic EC-MPS tablet (Strength: 180 mg, Batch Number: 2211013; Expiry Date: October 2024), manufactured by Zhejiang Meidishen Biomedical Co., Ltd. under license from Huayi Pharmaceutical

Technology (Anhui) Co., Ltd. The reference formulation (R) was the branded EC-MPS tablet (Strength: 180 mg, Batch Number: WWX46; Expiry Date: September 2024), produced by Novartis Pharma GmbH, Germany. Both formulations were supplied by Zhejiang Meidishen Biomedical Co., Ltd.

Ethic

The study protocol and amendments were approved by the Independent Ethics Committee of Deyang People's Hospital (Approval Numbers: 2023–01-021-H01, 2023–01-021-K01). Conducted in compliance with Good Clinical Practice (GCP) and International Council for Harmonisation (ICH) guidelines, and all relevant regulations for clinical and bioequivalence studies, the study also adhered to the ethical principles of the Declaration of Helsinki. All subjects were fully informed about the study's objectives, procedures, and potential risks, and provided written informed consent before enrollment. The study was registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cn/; Registration No: ChiCTR2300075403).

Study Population

MPA - containing medications are associated with an increased risk of first - trimester pregnancy loss and congenital malformations if taken during pregnancy.[19] To prevent unintended pregnancies and minimize fetal exposure in patients using MPA - containing drugs, the study's gender - related recommendations are based on the Draft Guidance on Mycophenolic Acid from US Food and Drug Administration[20] and the Bioequivalence Study Guidelines from China's National Medical Products Administration.[21]

The study included healthy Chinese males, aged 18–55 years, non-smokers, with a body mass index (BMI) between 18.6 and 26.0 kg/m². Comprehensive medical evaluations were conducted, including medical history review, physical examination, 12-lead electrocardiography, chest computed tomography scans, and laboratory tests covering hematology, urinalysis, blood chemistry, coagulation function, hepatitis and HIV screening. Subjects adhered to sun protection protocols throughout the trial.

Exclusion criteria included significant laboratory abnormalities, major disease within two weeks prior to the study drug administration, participation in clinical trial within the last three months, or the use of prescription/non-prescription drugs or hepatic enzyme-inducing or -inhibiting drugs within two weeks before the first administration of the study drug. Additional exclusions involved known or suspected allergies to the study drugs or related compounds, positive screening tests for morphine, methamphetamine, tetrahydrocannabinol acid, 2,5-dimethoxyamfetamine, or ketamine, significant blood loss (>400 mL) within two months prior to study initiation, and consumption of grapefruit or grapefruit juice during the trial.

Study Design and Sample Size

A single-dose, open-label, four-period replicated crossover design was implemented under fasting and fed conditions, to increase statistical power for highly variable drugs. We assumed a one-sided $\alpha = 0.05$, $\beta = 0.2$, an intra-individual coefficient of variation for the reference formulation of 30% - 70%, and a geometric mean ratio for the test and reference formulations of 0.92–1.08. The calculated sample size was 24 subjects. To account for potential dropouts due to adverse events, protocol deviations, or personal reasons, 30 subjects per cohort were enrolled.

We enrolled 60 eligible subjects into two independent cohorts (fasting and fed conditions). Each cohort was randomized 1:1 into two dosing sequence groups, with 15 subjects per group. Subjects were randomly assigned to either the T-R-T-R sequence group (receiving test formulation in cycles 1 and 3; reference formulation in cycles 2 and 4) or the R-T-R-T group (receiving reference formulation in cycles 1 and 3; test formulation in cycles 2 and 4). A 7 - day washout period between each cycle ensured drug elimination. The fasting cohort received a single 180 mg tablet after a ≥10-hours (h) fast. The fed cohort consumed a standardized high-fat meal (800–1000 kcal: 500–600 kcal fat, 150 kcal protein, 250 kcal carbohydrates) 30 minutes before dosing. On days 1, 8, 15, and 22, all subjects received the test or reference formulations between 08:00 and 08:30 with 240 mL of warm water. Liquid intake was prohibited 1 hour pre-dose and 2 hours post-dose.

Pharmacokinetic Blood Sampling

Previous studies reported a second MPA concentration peak 6–8h after administration, consistent with the reabsorption of hydrolyzed MPA.[16] Given that EC-MPS's enteric coating inherently delays drug release, and a high-fat meal may further prolong this process, we set the sampling times for the fasting and fed cohorts in this study as follows:

Venous blood samples (2 mL) were collected pre- and post-dose at specified intervals. For the fasting cohort, sampling collections occurred at 0, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 12, 14, 24, 36, and 48 hours. The fed cohort conducted at 0, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 24, 36, and 48 hours. Blood samples were drawn into pre-cooled heparinized tubes, transported on ice, centrifuged at 1600 ×g for 10 minutes at 4°C to separate the plasma, and stored at ≤ − 60°C until analysis.

Analytical Procedure

Plasma concentrations of MPA were quantified by a sensitive, validated, and specific liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.[19] The analytical system comprised an ExionLC liquid chromatograph (AB Sciex, USA) coupled with a TRIPLE AB 5500+ mass spectrometer (AB Sciex, USA), equipped with a Turbo Spray ionization source, operating in the positive ion multiple reaction monitoring mode.

MPA-13C-d3 was used as the internal standard (IS). Chromatographic separation was performed on an Agilent Eclipse XDB-C18 column (2.1 × 100 mm, 3.5 μm) using a gradient elution program. Mobile phases included solvent A (5 mM ammonium formate and 0.1% formic acid in water) and solvent B (methanol), with the following gradient: 55% B (0.00–1.19 min), 98% B (1.20–2.20 min), and 55% B (2.21–3.00 min). The flow rate was set at 0.60 mL/min, and the injection volume was 2 μL. Plasma sample preparation involved protein precipitation with methanol, followed by vortex mixing and centrifugation at 2450 g for 10 min at 4 °C. The resultant supernatant was analyzed via high-performance liquid chromatography (HPLC), and data were processed using Analyst 1.7.2 software.

Pharmacokinetic Analysis

PK parameters were calculated using a non-compartmental model with Phoenix WinNonlin software (version 8.4). The key parameters included peak plasma concentration (C_{max}) and time to peak concentration (T_{max}). The elimination rate constant (λ_z) was determined by linear regression of the terminal log-linear phase of the concentration-time curve, allowing for the calculation of the elimination half-life ($t_{1/2}$) as $t_{1/2} = 0.693/\lambda_z$. The area under the concentration-time curve from time zero to the last measurable concentration ($AUC_{0\text{-}t}$) was calculated using the trapezoidal rule, while the area under the curve from time zero to infinity ($AUC_{0\text{-}inf}$) was computed as $AUC_{0\text{-}t} + Ct/\lambda_z$, where Ct represents the last measurable concentration. The partial drug-time curve was measured by the linear trapezoidal linear interpolation method. The percentage of extrapolated AUC ($AUC_{\_\%Extrap}$) was determined using the formula: ($AUC_{0\text{-}inf}$ - $AUC_{0\text{-}t}$) /$AUC_{0\text{-}inf}$ × 100%. The intra-individual variability (coefficient of variation, CV) for these PK parameters was also assessed.

Primary PK parameters (C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$) were log-transformed and subjected to a multivariate analysis of variance (ANOVA). T_{max} was analyzed using a nonparametric signed-rank test. Statistical analyses were conducted with SAS software (version 9.4; SAS Institute, Cary, NC). The geometric mean ratios (GMRs) and 90% confidence intervals (CIs) for the primary PK parameters were calculated, as well as the 95% CIs for the within-subject standard deviation (S_{WR}) of the reference. Point estimates of the GMRs between the test and reference formulations were also obtained. The influence of food on the PKs was assessed using a descriptive analysis via an independent samples *t*-test. A p-value of ≤ 0.05 was considered statistically significant.

Bioequivalence Analyses

Bioequivalence was assessed by evaluating the S_{WR} of the reference formulation.[22] If $S_{WR} < 0.294$ (indicating that the coefficient of variation within subject (CV_{WR}) < 30%), the average bioequivalence (ABE) method was applied. This

involved performing two one-sided t-tests and calculating 90% CIs. Bioequivalence was established if the 90% CIs of the GMRs fell entirely within the range of 80.00% - 125.00%.

If $S_{WR} \geq 0.294$ (indicating that $CV_{WR} \geq 30\%$), the reference-scaled average bioequivalence (RSABE) method was employed. The upper bound of the 95% CI was calculated using Howe's first-order approximation method. For this, $\overline{Y}_T$and $\overline{Y}_R$represent the mean values of AUC or C_{max} derived from the log-transformed data of the test and reference formulations, respectively. Bioequivalence was considered established if the upper bound of the 95% CI of $(\bar{Y}_T - \bar{Y}_R)^2 - \theta s^2_{WR}$ was ≤ 0, and the GMRs of the primary PK parameters were within the range of 80.00% - 125.00%.

Safety

Safety profiles were evaluated based on vital signs, clinical symptoms, physical examinations, laboratory tests, and electrocardiograms. Any abnormalities deemed clinically significant by the investigators following treatment were recorded as adverse events (AEs).

Results

Demographics and Baseline Characteristics

Figure 1 illustrated the study design and subjects disposition across the two cohorts. A total of 164 healthy Chinese male subjects were screened, and 60 subjects were successfully enrolled, all of them completed the study in accordance with the protocol. Table 1 summarized the demographic characteristics. The baseline characteristics of both cohorts were comparable.

Pharmacokinetic Properties

Following the administration of a single oral dose of 180 mg for both the test and reference formulations, the descriptive statistical analysis of PK parameters was presented in Table 2. The mean plasma concentration-time profiles of EC-MPS in the fasting and fed cohorts were illustrated in Figures 2Aand B, respectively. No significant differences were observed in the primary PK parameters between the test and the reference formulations under either fasting or fed conditions, and the PK curves were essentially consistent.

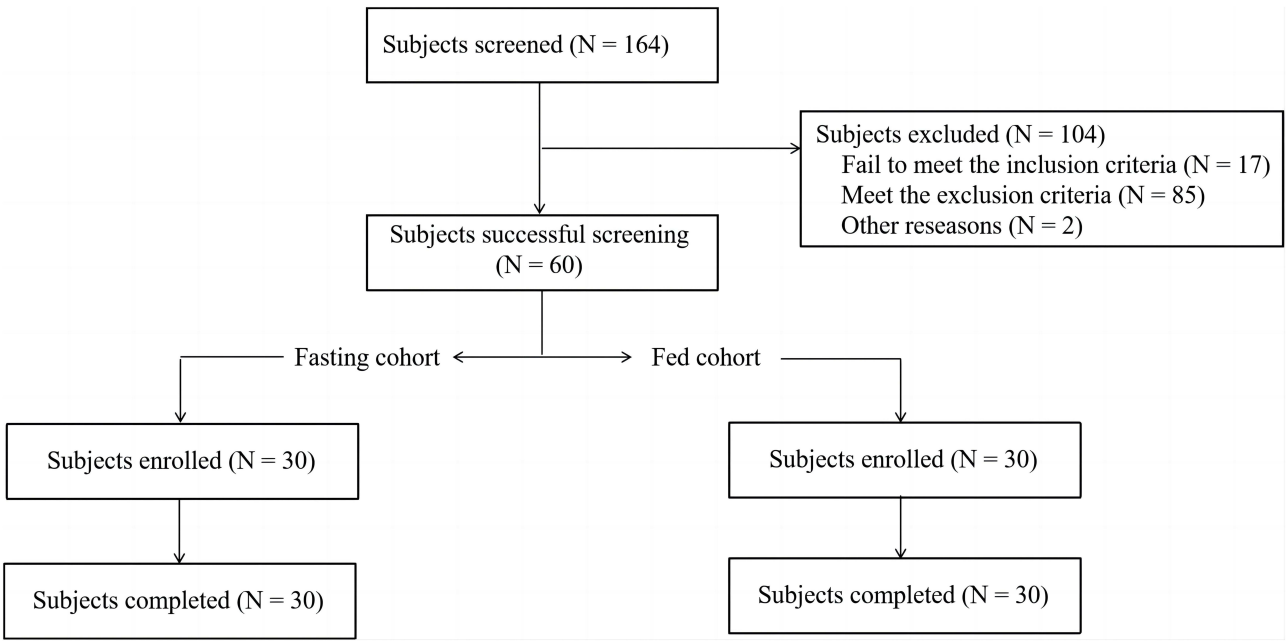

Figure 1 Study participation chart.

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Table 1 Demographic Characteristics

Sequence	Fasting Cohort (N = 30)	Fed Cohort (N = 30)
Age (years)		
Mean ± SD	25.00 ± 4.51	24.57 ± 4.85
Median (Min, Max)	23.50 (20.00, 37.00)	23.50 (18.00, 38.00)
Height (cm)		
Mean ± SD	169.13 ± 5.70	168.61 ± 6.29
Median (Min, Max)	167.95 (155.00, 179.80)	169.45 (157.20, 177.60)
Weight (kg)		
Mean ± SD	63.43 ± 5.75	62.61 ± 7.17
Median (Min, Max)	64.25 (52.50, 75.60)	60.85 (52.10, 77.70)
BMI (kg/m^2)		
Mean ± SD	22.15 ± 2.12	21.97 ± 2.13
Median (Min, Max)	22.10 (18.90, 25.70)	21.40 (18.80, 25.80)

Abbreviation: BMI, body mass index.

Table 2 Main Pharmacokinetic Parameters for Generic and Branded Formulations in the Fasting and Fed Cohorts

PK Parameter	Generic EC-MPS (N = 120)		Branded EC-MPS (N = 120)	
	Fasting Cohort (N = 60) (Mean ± SD (CV %))	Fed Cohort (N = 60) (Mean ± SD (CV %))	Fasting Cohort (N = 60) (Mean ± SD (CV %))	Fed Cohort (N = 60) (Mean ± SD (CV %))
T_{max} (h)	3.00 (1.00, 5.00)	7.00 (2.49, 18.00)	2.50 (1.50, 5.00)	7.00 (4.49, 18.00)
C_{max} (μg/mL)	8.84 ± 3.42 (38.69)	10.01 ± 3.36 (33.60)	8.50 ± 2.49 (29.32)	8.96 ± 3.52 (39.26)
AUC_{0-48} (μg·h/mL)	19.11 ± 4.05 (21.22)	18.88 ± 7.63 (40.40)	18.82 ± 3.80 (20.21)	17.73 ± 4.91 (27.69)
AUC_{0-inf} (μg·h/mL)	20.72 ± 4.76 (22.96)	21.13 ± 6.17 (29.20)	20.24 ± 4.37 (21.60)	23.57 ± 22.69 (96.28)
λ_z (h^{-1})	0.06 ± 0.02 (33.88)	0.06 ± 0.02 (41.26)	0.06 ± 0.02 (27.94)	0.05 ± 0.02 (44.02)
$t_{1/2}$ (h)	12.84 ± 3.70 (28.85)	15.47 ± 8.76 (56.64)	12.20 ± 3.42 (28.01)	22.82 ± 47.10 (206.34)
$AUC\_{\%Extrap}$ (%)	7.32 ± 4.53 (61.84)	12.31 ± 11.04 (89.68)	6.69 ± 4.30 (64.17)	15.39 ± 16.20 (105.20)

Abbreviations: CV, coefficient of variation; CV% = (SD/mean) × 100; T_{max} is expressed as median (min, max).

A multivariate ANOVA was performed to evaluate the effects of administration sequence, period, and formulation on these parameters (Table 3). The results indicated no significant differences between the formulations across administration sequences, although significant differences in C_{max} and AUC_{0-inf} were observed across the administration cycles in the fasting cohort. A non-parametric test of T_{max} for both formulations revealed no significant differences.

Bioequivalence Analysis

Bioequivalence assessment between the test and reference formulations under fasting and fed conditions was summarized in Table 4 and Table 5, respectively. Bioequivalence was established in both cohorts, meeting the relevant regulatory criteria.

In the fasting cohort, the CV% for the reference formulation's PK parameters of C_{max}, AUC_{0-t} and AUC_{0-inf} were 17.55%, 6.44% and 8.05%, respectively. The 90% CIs for the natural log-transformed ratios of C_{max}, AUC_{0-48}, and AUC_{0-inf} were 93.69%-110.14%, 98.36%-104.53%, and 99.21%-105.06%, respectively. These values fell within the predefined bioequivalence range of 80.00%-125.00%, thereby fulfilling the criteria for the ABE method under fasting conditions.

In the fed cohort, the CV% for C_{max} and AUC_{0-inf} of the reference formulation were 47.11% and 34.93%, respectively, indicating substantial inter- and intra-individual variability (>30%) for EC-MPS. The corresponding S_{WR} for C_{max} and AUC_{0-inf} were 0.448 and 0.339, respectively. The GMRs for C_{max} and AUC_{0-inf} were 119.74% and 99.87%,

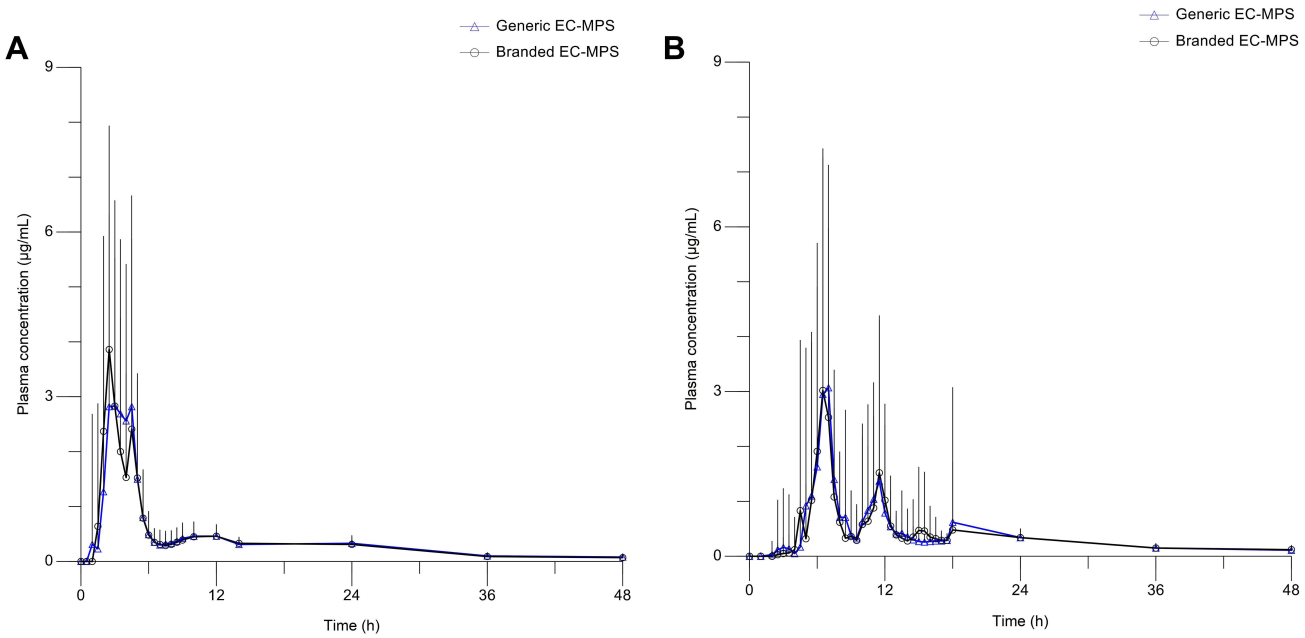

Figure 2 Mean plasma concentration–time profiles of the generic EC-MPS (Δ, blue) and branded EC-MPS (○, black) after a single oral dose of 180 mg of EC-MPS in the fasting (**A**) and fed (**B**) cohorts, respectively (mean ± SD, N = 120).

respectively, both within the acceptable limits for the RSABE method. Additionally, the CV% for AUC_{0-48} of the reference formulation was 29.41%, with an S_{WR} of 0.288, which was below the threshold of 0.294. Consequently, the ABE method was applied for AUC_{0-48}, with the 90% CI for the natural log-transformed ratio being 100.05%-114.86%, also within the regulatory bioequivalence limits.

Table 3 Multivariate Analysis of Generic and Branded Formulations in the Fasting and Fed Cohorts

Factors	Fasting cohort (N = 120)			Fed cohort (N = 120)		
	LnC_{max}	$LnAUC_{0-48}$	$LnAUC_{0-inf}$	LnC_{max}	$LnAUC_{0-48}$	$LnAUC_{0-inf}$
Sequence	0.921	0.869	0.999	0.491	0.995	0.630
Formulation factors	0.746	0.444	0.228	0.059	0.097	0.965
Cycle	0.021*	0.001**	0.121	0.195	0.411	0.953

Notes: *P<0.05, **P<0.01 for the generic EC-MPS versus branded EC-MPS.
Abbreviations: C_{max}, the maximal plasma concentration; AUC_{0-48}, the area under the plasma concentration-time curve; AUC_{0-inf}, the area under the plasma concentration-time curve extrapolated to infinity. Values are given as log-transformed.

Table 4 Bioequivalence Statistics of Generic and Branded Formulations in the Fasting Cohort

PK Parameter	RSABE			ABE		
	Estimated GMR Points (%)	One-Side 95% CI Upper Limit[<=0]	S_{WR}	GMR (%)	90% CIs (%)	CV (%)
C_{max} (μg/mL)	101.58	−0.013	0.174	101.58	93.69 - 110.14	17.55
AUC_{0-48} (μg·h/mL)	101.40	−0.001	0.064	101.40	98.36 - 104.53	6.44
AUC_{0-inf} (μg·h/mL)	102.10	−0.002	0.080	102.10	99.21 - 105.06	8.05

Abbreviations: GMR, Geometric mean ratio; CV, coefficient of variation; 90% CIs, 90% confidence intervals.

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Table 5 Bioequivalence Statistics of Generic and Branded Formulations in the Fed Cohort

PK Parameter	RSABE			ABE		
	Estimated GMR points (%)	One-side 95% CI upper limit[<=0]	S_{WR}	GMR (%)	90% CIs (%)	CV (%)
C_{max} (μg/mL)	119.74	−0.033	0.448	119.74	102.44–139.96	47.11
AUC_{0-48} (μg·h/mL)	107.20	−0.037	0.288	107.20	100.05–114.86	29.41
AUC_{0-inf} (μg·h/mL)	99.87	−0.062	0.339	99.75	90.78–109.61	34.93

Abbreviations: GMR, Geometric mean ratio; CV, coefficient of variation; 90% CIs, 90% confidence intervals.

Effect of Food on Pharmacokinetics

The impact of food on the PKs of EC-MPS was further investigated. The mean plasma concentration–time profiles of MPA with food effect were illustrated in Figures 3A and B, respectively. Compared to the fasting condition, the curve under fed conditions were significantly different, with a notable lag time (median T_{max} 7.0 h vs 2.5–3.0 h, $p<0.01$) was observed prior to the rise in plasma MPA levels (Table 6).

In the fed cohort, there was a marked increase in the CV% for the PK parameters, indicating greater variability under fed conditions (Table 5). Furthermore, a carryover effect of MPA release was observed. The $AUC_{\_\%Extrap}$ of MPA was increased by 68% and 130% for test and reference formulations, respectively (Table 6).

Safety Assessment

A total of 20 mild AEs were reported during the study, with no serious AEs observed (Table 7). In the fasting cohort, 8 subjects reported 9 AEs, of which 7 were deemed drug-related. These included giddiness (n = 1), abdominal pain (n = 1), diarrhea (n = 1), and abnormal laboratory findings such as hematuria (n = 1), elevated serum uric acid (n = 1), and increased triglycerides (n = 2). In the fed cohort, 10 subjects reported 11 AEs, 10 of which were classified as drug-related. These included toothache (n = 1), abdominal pain (n = 1), nausea (n = 1), and abnormal laboratory test results, including anemia (n = 1), increased low-density lipoprotein (n = 1), increased bile acid (n = 1), and elevated triglycerides (n = 4). No subjects discontinued the study due to safety concerns.

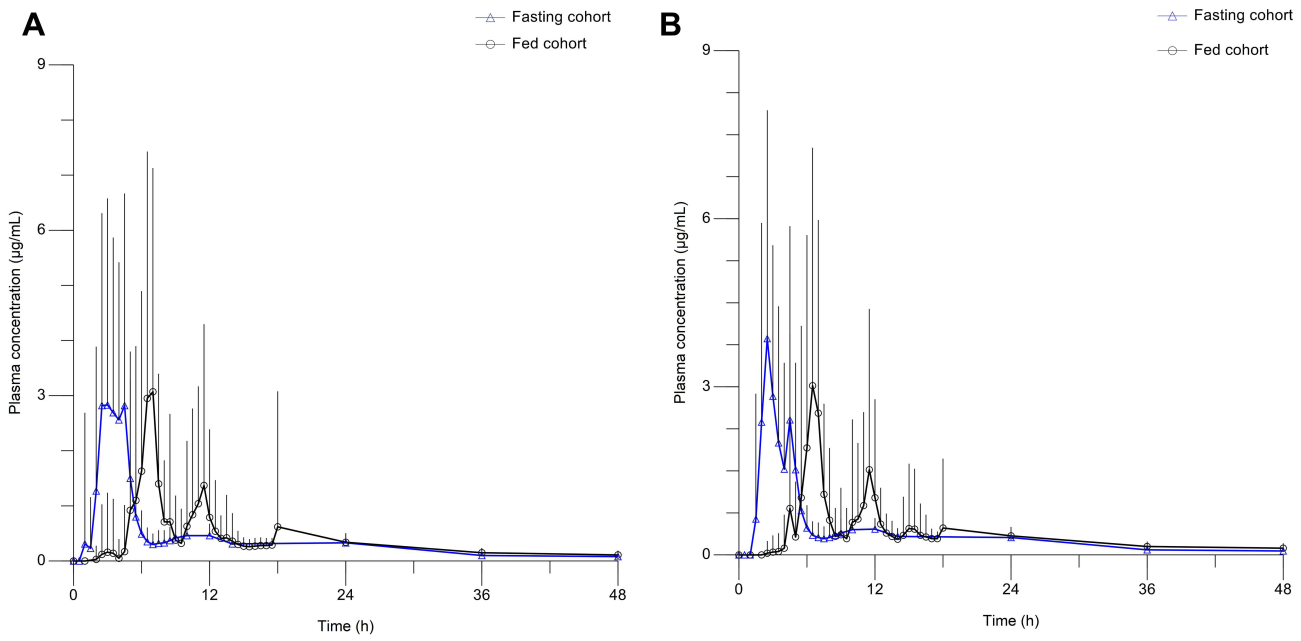

Figure 3 Mean plasma concentration–time profiles of the generic EC-MPS (**A**) and branded EC-MPS (**B**) after a single oral dose of 180 mg of EC-MPS under fasting (Δ, blue) and fed (○, black) conditions (mean ± SD, N = 120).

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Table 6 Food Effect on the Pharmacokinetic Parameters of Generic and Branded Formulations

PK Parameter	Fasting cohort		Fed cohort	
	Generic EC-MPS (N = 60, Mean ± SD)	Branded EC-MPS (N = 60, Mean ± SD)	Generic EC-MPS (N = 60, Mean ± SD)	Branded EC-MPS (N = 60, Mean ± SD)
T_{max} (h)	3.00 (1.00, 5.00)	2.50 (1.50, 5.00)	7.00 (2.49, 18.00)*	7.00 (4.49, 18.00)*
C_{max} (μg/mL)	8.84 ± 3.42	8.50 ± 2.49	10.01 ± 3.36	8.96 ± 3.52
$t_{1/2}$ (h)	12.84 ± 3.70	12.20 ± 3.42	15.47 ± 8.76*	22.82 ± 47.10*
AUC_{0-48} (μg·h/mL)	19.11 ± 4.05	18.82 ± 3.80	18.88 ± 7.63	17.73 ± 4.91
AUC_{0-inf} (μg·h/mL)	20.72 ± 4.76	20.24 ± 4.37	21.13 ± 6.17	23.57 ± 22.69
$AUC_{\_\%Extrap}$ (%)	7.32 ± 4.53	6.69 ± 4.30	12.31 ± 11.04**	15.39 ± 16.20

Notes:*P<0.05, **P<0.01 for the fed cohort versus fasting cohort.
Abbreviation: T_{max} is expressed as median.

Table 7 Total Number of AEs and Percentage of Healthy Subjects Experiencing in the Fasting and Fed Cohorts

Parameter	Fasting Cohort		Fed Cohort	
	Generic EC-MPS (N = 30)	Branded EC-MPS (N = 30)	Generic EC-MPS (N = 30)	Branded EC-MPS (N = 30)
Total subjects with at least 1 AE	3 (10.0)	5 (16.7)	6 (20.0)	10 (33.3)
AEs may relate to drug				
Hematuria	0	1 (0.03)	0	0
Anemia	0	0	0	1 (0.03)
Increased serum uric acid	1 (0.03)	0	0	0
Increased triglycerides	2 (0.06)	0	2 (0.06)	2 (0.06)
Increased low-density lipoprotein	0	0	1 (0.03)	0
Increased bile acid	0	0	1 (0.03)	0
Giddiness	0	1 (0.03)	0	0
Abdominal pain	1 (0.03)	0	1 (0.03)	0
Diarrhea	0	1 (0.03)	0	0
Nausea	0	0	0	1 (0.03)
Toothache	0	0	0	1 (0.03)
AEs may not relate to drug				
Hand trauma	0	1 (0.03)	0	0
Epistaxis	0	1 (0.03)	0	0
Pharyngeal discomfort	0	0	1 (0.03)	0

Notes: Values are given as N (%); N represents the number of subjects included in the safety analysis sets.

Discussion

The PKs and bioequivalence of a generic 180 mg EC-MPS tablet and the branded tablet were evaluated in 60 healthy Chinese male subjects under both fasting and fed conditions.

MPA was glucuronidated by uridine diphosphate-glucuronosyltransferase (UGT) to form the inactive primary metabolite 7-O-MPA-glucuronide (MPAG), with minor metabolites acyl glucuronide (Ac-MPAG) and phenolic glucoside.[23] Steady-state exposure ratios for MPA, MPAG, and Ac-MPAG are 1:23:0.28.[24] EHC played a critical role in maintaining MPA blood concentrations by regenerating the drug from its metabolites.[25] This study found that under fed conditions, the delayed T_{max} (median 7.0 h vs 2.5–3.0 h fasting; Table 6) aligned with EC-MPS's enteric coating. The fed cohort also showed delayed MPA release with a prolonged $t_{1/2}$ (22.82 h vs 12.20 h fasting; Table 6). Food intake stimulated bile secretion, which affected MPA metabolism via EHC.[26] Variability in EHC may lead to inconsistent immunosuppression.[8] Kidney transplant patients with pronounced EHC may experience up to a 2.5-fold increased diarrhea risk.[27] The fed cohort had a higher drug-related AE rate (20.0–33.3% vs 10.0–16.7%; Table 7), which may be associated with delayed release and potentially worsened by EHC under fed conditions.[28]

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MPA-AUC was a predictive marker for acute rejection risk, especially in the early post-transplant period.[29,30] Systemic MPA exposure increased over time, rising by 60% - 90% over six months.[31] This study found no significant EHC impact on overall exposure. However, food intake increased residual exposure, as shown by higher $AUC_{\_\%Extrap}$ (12.31% vs 7.32% fasting; Table 6) and a secondary MPA peak beyond 10 h (Figure 3). Similarly, trace levels of MPA from the previous evening's dose were detected at time zero (pre-dose) in some patients receiving both MMF and EC-MPS.[32,33] Renal transplant patients receiving EC-MPS exhibited higher MPA trough concentrations than those receiving MMF.[34] Circadian fluctuations in EHC may account for a substantial proportion of the observed intra-individual variability.[26] We found that food intake increased the CV% of $AUC_{\_\%Extrap}$, aligning with high inter-individual variability in EHC efficiency.[35] The elevated upper 90% CI for C_{max} under fed conditions highlighted significant inter-individual variability (47.11%) in peak exposure.

The clinical PKs of EC-MPS exhibited wide inter- and intra-patients variability.[36] Factors like the recipient population and gender may affect the variability in MPA exposure and adverse effects.[37] Differences in drug behavior have been observed between Asians and Caucasians.[38] The recommended EC-MPS dose in Chinese patients is generally lower than in Caucasians (1000 mg/day), typically 720 mg/day.[39] UGT1A9 polymorphisms, particularly −275T>A and −2152C>T, have been strongly associated with MPA exposure variability in Asians.[40] Past studies have shown that when EC-MPS was used with calcineurin inhibitors in kidney transplant patients, there were clear gender differences.[41] Males had more extensive deconjugation of MPAG to MPA by UGT, leading to faster clearance.[42] Females had reduced MPA clearance and more severe gastrointestinal AEs. But because EC-MPS may affect female fertility and reproductive genetics,[19] few bioequivalence studies on EC-MPS in healthy females have been published. In this study, we observed the impact of EHC on the PK behavior of EC-MPS in healthy Chinese male subjects. Since metabolic differences between genders can lead to variations in EHC,[43] more studies in female populations are warranted.

Previous studies have not fully explored the complete PK profile of EC-MPS. This may be related to unaccounted food effects on enteric coating and limitations in sampling strategies.[26] In this study, the sampling points nearly encompassed the absorption and distribution phases of MPA in vivo, and captured the enteric-coating hydrolysis process. In the fasting cohort, the reference formulation $AUC_{0\text{-}12}$ was 11.44±2.34 μg·h/mL (accounting for 56.52% of total AUC), and $AUC_{12\text{-}24}$ was 3.98±1.15 μg·h/mL (accounting for 19.67% of total AUC). In the fed cohort, the corresponding values were 8.41±3.26 μg·h/mL and 4.45±2.21 μg·h/mL, representing 35.68% and 18.88%, respectively. $AUC_{0\text{-}12}$ was widely regarded as a standard parameter for monitoring MPA. It reflected the drug's exposure over the entire dosing interval and the contribution of EHC.[36] However, a significant reduction in $AUC_{0\text{-}12}$ was observed after a fatty meal. As the variability of EHC in MPA ranged from 10–60%,[44] it would be worthwhile to opt for meal-based sampling, thus helping us to understand the dynamics of EC-MPS.[26]

We measured total plasma MPA concentration rather than MPAG, as the PK profile of the prodrug was more sensitive to inter-formulation differences than metabolites.[45] Following oral administration, MPA and MPAG are highly albumin bound, at 97% and 82%, respectively,[46] with only the free fraction being pharmacologically active.[44] Although free MPA was crucial for efficacy, Reine et al reported a positive correlation between free MPA and total MPA, indicating that both could predict IMPDH activity.[47] Pathological conditions like uremia, hepatic impairment, or hypoalbuminemia, reduced protein binding, increased free MPA concentrations and altered the drug's PK behavior.

This study used a single 180 mg dose of EC-MPS, the lowest available strength, unlike previous studies. At this dose, the terminal elimination phase could not be a precisely determined due to limited $AUC_{0\text{-}inf}$ extrapolation. This was because MPA elimination via bile and urine was slower than gastrointestinal absorption. The population mean estimated absorption rate constant (ka) was roughly 1.5-fold higher than the elimination constant (k10 = 0.409/h).[48] In contrast, in the highest dose groups (2160 mg) has less than 10% extrapolated AUC, validating $AUC_{0\text{-}t}$ as a reliable indicator for overall exposure. Consequently, $AUC_{0\text{-}t}$, rather than $AUC_{0\text{-}inf}$, was used as the primary PK parameter for MPA.[49]

Conclusions

This study assessed the bioequivalence of generic and the branded EC-MPS under different conditions. Food significantly altered the PK parameters of EC-MPS in healthy Chinese males, causing longer T_{max} and $t_{1/2}$. While C_{max} and $AUC_{0\text{-}48}$ were not affected, their CV% increased. These findings stress the importance of understanding EHC for EC-

MPS efficacy and safety assessment. Clinicians should closely monitor patients, particularly those taking EC-MPS with meals and those with marked EHC. Due to the variability under fed conditions, fasting administration may be preferable for transplant recipients.

This study has some limitations. Conducted in healthy subjects with a single oral dose and a four-period replicated crossover design, it does not establish EC-MPS bioequivalence in solid organ transplant patients on concurrent immunosuppressive therapy. As EC-MPS is for b.i.d. dosing and patients may take doses near mealtimes, food-induced delayed drug release can add variability. Also, only healthy Chinese males were studied, ongoing data collection is needed to monitor EC-MPS and predict the relationship between MPA levels and factors in female patients as well as those with comorbidities.

Data-Sharing Statement

1. Intent to Share Data: We are committed to sharing individual de-identified participant data to support the transparency and reproducibility of our research.
2. Specific Data to Be Shared: The dataset will include individual participant data related to pharmacokinetic parameters, adverse events, and demographic information, with all personal identifiers removed to ensure anonymity.
3. Additional Study Documents: We will also make available the study procedures, sample analysis methods and any other relevant documents that are necessary for understanding and replicating the study.
4. Access to Data: Researchers interested in accessing the data may contact the first author or corresponding authors with a request detailing the purpose of the data use and their qualifications. Access will be granted in accordance with applicable data protection regulations and ethical guidelines.
5. Timeline and Duration: The data will be available starting from the date of publication of the paper and will remain accessible for a period of five years.

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Disclosure

The authors have declared that no conflict of interest exists.

References

1. Fredo T, Jonny KF, Agung S, et al. Global prevalence and potential factors influencing willingness for renal transplantation in end-stage renal disease patients: a systematic review and meta analysis. *Narra J*. 2024;4(3):e964. doi:10.52225/narra.v4i3.964
2. Nicole AP, Lyndsey JB, David JT. Immunosuppression trends in solid organ transplantation: the future of individualization, monitoring, and management. *Pharmacotherapy*. 2021;41(1):119–131. doi:10.1002/phar.2481
3. Hakan P, Mehmet G. Transplantation and immunosuppression: a review of novel transplant-related immunosuppressant drugs. *Immunopharmacol Immunotoxicol*. 2021;43(6):651–665. doi:10.1080/08923973.2021.1966033
4. Cheng L, Yao P, Weng BB, et al. Meta-analysis of the associations of IMPDH and UGT1A9 polymorphisms with rejection in kidney transplant recipients taking mycophenolic acid. *Eur J Clin Pharmacol*. 2022;78(8):1227–1238. doi:10.1007/s00228-022-03311-4
5. Halloran PF. Immunosuppressive drugs for kidney transplantation. *N Engl J Med*. 2004;351(26):2715–2729. doi:10.1056/NEJMra033540
6. Mele TS, Halloran PF. The use of mycophenolate mofetil in transplant recipients. *Immunopharmacology*. 2000;47(2–3):215–245. doi:10.1016/S0162-3109(00)00190-9

7. Datrino LN, Boccuzzi ML, Silva RM, et al. Safety and efficacy of mycophenolate mofetil associated with tacrolimus for kidney-pancreas and kidney transplantation: a systematic review and meta-analysis of randomized studies. *Transplant Proc*. 2024;56(5):1066–1076. doi:10.1016/j.transproceed.2024.05.014
8. Abdelrahman S, Brooke C, Christopher S, et al. Reduced enterohepatic recirculation of mycophenolate and lower blood concentrations are associated with the stool bacterial microbiome after hematopoietic cell transplantation. *Transplant Cell Ther*. 28;7:372.e1–372.e9.
9. Budde K, Dürr M, Liefeldt L, et al. Enteric-coated mycophenolate sodium. *Expert Opin Drug Saf*. 2010;9(6):981–994. doi:10.1517/14740338.2010.513379
10. Filler G, Peart JB, Christians U. Pharmacokinetics of mycophenolate mofetil and sirolimus in children. *Ther Drug Monit*. 2008;30(2):138–142. doi:10.1097/FTD.0b013e31816ba73a
11. Bullingham R, Monroe S, Nicholls A, et al. Pharmacokinetics and bioavailability of mycophenolate mofetil in healthy subjects after single-dose oral and intravenous administration. *J Clin Pharmacol*. 1996;36(4):315–324. doi:10.1002/j.1552-4604.1996.tb04207.x
12. Gabardi S, Tran JL, Clarkson MR. Enteric-coated mycophenolate sodium. *Ann Pharmacother*. 2003;37(11):1685–1693. doi:10.1345/aph.1D063
13. Charalabidis A, Sfouni M, Bergström C, et al. The Biopharmaceutics Classification System (BCS) and the Biopharmaceutics Drug Disposition Classification System (BDDCS): beyond guidelines. *Int J Pharm*. 2019;566:264–281. doi:10.1016/j.ijpharm.2019.05.041
14. Arns W, Breuer S, Choudhury S, et al. Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. *Clin Transplant*. 2005;19(2):199–206. doi:10.1111/j.1399-0012.2004.00318.x
15. Zenda N, Tagami T, Ozeki T. Development of a novel gastric process simulation model: the successful assessment of bioequivalence and bioinequivalence of a biopharmaceutics classification system class ii weak acid drug. *Biol Pharm Bull*. 2022;45(3):364–373. doi:10.1248/bpb.b21-01029
16. Novartis pharmaceuticals corporation. myfortic®: prescribing information. Available from: http://www.pharma.us.novartis.com/product/pi/pdf/myfortic.pdf. [Accessed March 2022.
17. Rupprecht K, Schmidt C, Raspé A, et al. Bioavailability of mycophenolate mofetil and enteric-coated mycophenolate sodium is differentially affected by pantoprazole in healthy volunteers. *J Clin Pharmacol*. 2009;49(10):1196–1201. doi:10.1177/0091270009344988
18. Chariyavilaskul P, Phaisal W, Kittanamongkolchai W, et al. Pharmacokinetics and pharmacodynamics profiles of enteric-coated mycophenolate sodium in female patients with difficult-to-treat lupus nephritis. *Clin Transl Sci*. 2022;15(7):1776–1786. doi:10.1111/cts.13295
19. Food US, Administration D. Questions and answers: FDA Approves a Single Shared Risk Evaluation and Mitigation Strategy (REMS) for Mycophenolate-containing Medicines. 2012.
20. U.S. Food and Drug Administration. Draft Guidance on Mycophenolic Acid. Available from: https://pharmadesk.com/crolibrary/USFDA-OGD-Recommendations/Mycophenolic_acid_DR_tab_50791_RV02-14.pdf. Accessed February 2014.
21. National Medical Products Administration. Technical guidelines for bioequivalence studies of chemical drug generics using pharmacokinetic parameters as endpoint evaluation index; 2016. Available from: https://www.nmpa.gov.cn/xxgk/ggtg/ypggtg/ypqtggtg/20160318210001725.html. Accessed March 2016.
22. Food US, Administration D. Center for Drug Evaluation and Research (CDER). Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations; 2014. Available from: https://www.fda.gov/media/88254/download. Accessed February 2014.
23. Guo M, Wang ZJ, Yang HW, et al. Influence of genetic polymorphisms on mycophenolic acid pharmacokinetics and patient outcomes in renal transplantation. *Curr Drug Metab*. 2018;19(14):1199–1205. doi:10.2174/1389200219666171227201608
24. T SH, Bastien MC, Choi L, et al. Mycophenolic acid metabolite profile in renal transplant patients receiving enteric-coated mycophenolate sodium or mycophenolate mofetil. *Transplant Proc*. 2005;37:852–855. doi:10.1016/j.transproceed.2004.12.186
25. Shaw LM, Pawinski T, Korecka M, et al. Monitoring of mycophenolic acid in clinical transplantation. *Ther Drug Monit*. 2002;24(1):68–73. doi:10.1097/00007691-200202000-00012
26. Alpízar M, JdJ R, Martínez EG, et al. Pharmacokinetic simulation and area under the curve estimation of drugs subject to enterohepatic circulation. *Pharmaceutics*. 2024;16(8):1044. doi:10.3390/pharmaceutics16081044
27. Sugioka N, Sasaki T, Kokuhu T, et al. Clinical pharmacokinetics of mycophenolate mofetil in Japanese renal transplant recipients: a retrospective cohort study in a single center. *Biol Pharm Bull*. 2006;29(10):2099–2105. doi:10.1248/bpb.29.2099
28. Durník R, Šindlerová L, Babica P, et al. Bile acids transporters of enterohepatic circulation for targeted drug delivery. *Molecules*. 2022;27(9):2961. doi:10.3390/molecules27092961
29. Neuberger M, Sommerer C, Böhnisch S, et al. Effect of mycophenolic acid on inosine monophosphate dehydrogenase (IMPDH) activity in liver transplant patients. *Clin Res Hepatol Gastroenterol*. 2020;44(4):543–550. doi:10.1016/j.clinre.2019.12.001
30. Jung HY, Seo YJ, Hwang D, et al. Safety of the reduced fixed dose of mycophenolate mofetil confirmed via therapeutic drug monitoring in de novo kidney transplant recipients. *Kidney Res Clin Pract*. 2025;44(1):200–209. doi:10.23876/j.krcp.23.274
31. Milesi J, Sampol E, Benyamine A, et al. Usefulness of monitoring mycophenolic acid exposure in systemic sclerosis-related interstitial lung disease: a retrospective cohort study. *BMC Pulm Med*. 2024;24(1):537. doi:10.1186/s12890-024-03361-7
32. Meur YL, Büchler M, Thierry A, et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. *Am J Transplant*. 2007;7(11):2496–2503. doi:10.1111/j.1600-6143.2007.01983.x
33. Budde K, Silva HT, Pestana JM, et al. Enteric-coated mycophenolate sodium provides higher mycophenolic acid predose levels compared with mycophenolate mofetil: implications for therapeutic drug monitoring. *Ther Drug Monit*. 2007;29(3):381–384. doi:10.1097/FTD.0b013e318068619d
34. Budde K, Bauer S, Hambach P, et al. Pharmacokinetic and pharmacodynamic comparison of enteric-coated mycophenolate sodium and mycophenolate mofetil in maintenance renal transplant patients. *Am J Transplant*. 2007;7(4):888–898. doi:10.1111/j.1600-6143.2006.01693.x
35. Ibarra M, Trocóniz IF, Fagiolino P. Enteric reabsorption processes and their impact on drug pharmacokinetics. *Sci Rep*. 2021;11(1):5794. doi:10.1038/s41598-021-85174-w
36. Mohamed ME, Saqr A, Staley C, et al. Pharmacomicrobiomics: immunosuppressive Drugs and Microbiome Interactions in Transplantation. *Transplantation*. 2024;108(9):1895–1910. doi:10.1097/TP.0000000000004926
37. Spasić A, Catićđorđević A, Veličković-Radovanović R, et al. Adverse effects of mycophenolic acid in renal transplant recipients: gender differences. *J Clin Pharmacol*. 2019;41:776–784. doi:10.1007/s11096-019-00837-z

38. Pengmei Li NS, Hesselink DA, Ron HNVS, van Schaik RHN, Zhang X, van Gelder T. Do Asian renal transplant patients need another mycophenolate mofetil dose compared with Caucasian or African American patients? *Transpl Int*. 2014;27(10):994–1004. doi:10.1111/tri.12382
39. Wuttiputhanun T, Naiyarakseree N, Udomkarnjananun S, et al. Therapeutic drug monitoring of mycophenolic acid and clinical outcomes of lupus nephritis: a systematic review and meta-analysis. *Lupus Sci Med*. 2024;11(1):e001093. doi:10.1136/lupus-2023-001093
40. Jiang ZW, Hu N. Effect of UGT polymorphisms on pharmacokinetics and adverse reactions of mycophenolic acid in kidney transplant patients. *Pharmacogenomics*. 2021;22(15):1019–1040. doi:10.2217/pgs-2021-0087
41. Calvin JM, Patcharaporn S, Joseph DC, et al. Influence of calcineurin inhibitor and sex on mycophenolic acid pharmacokinetics and adverse effects post-renal transplant. *J Clin Pharmacol*. 2019;59(10):1351–1365. doi:10.1002/jcph.1428
42. Kathleen MT, Calvin JM, Gregory EW, et al. Influence of sex and race on mycophenolic acid pharmacokinetics in stable African American and caucasian renal transplant recipients. *Clin Pharmacokinet*. 2015;54(4):423–434. doi:10.1007/s40262-014-0213-7
43. Connor JM, Christopher PH, Jason AP. Metabolic modeling of sex-specific tissue predicts mechanisms of differences in toxicological responses. *bioRxiv*. 2023;7:2023.02.07.527430.
44. Bullingham RE, Nicholls AJ, Kamm BR. Clinical pharmacokinetics of mycophenolate mofetil. *Clin Pharmacokinet*. 1998;34(6):429–455. doi:10.2165/00003088-199834060-00002
45. Tett SE, Saint-Marcoux F, Staatz CE, et al. Mycophenolate, clinical pharmacokinetics, formulations, and methods for assessing drug exposure. *Transplantation Rev*. 2011;25:47–57. doi:10.1016/j.trre.2010.06.001
46. Behrend M, Braun F. Enteric-coated mycophenolate sodium tolerability profile compared with mycophenolate mofetil. *Drugs*. 2005;65 (8):1037–1050. doi:10.2165/00003495-200565080-00001
47. Reine PA, Vethe NT, Kongsgaard U. Mycophenolate pharmacokinetics and inosine monophosphate dehydrogenase activity in liver transplant recipients with an emphasis on therapeutic drug monitoring. *Scand J Clin Lab Invest*. 2013;73(2):117–124. doi:10.3109/00365513.2012.745947
48. Sam WJ, Akhlaghi F, Rosenbaum SE. population pharmacokinetics of mycophenolic acid and its 2 glucuronidated metabolites in kidney transplant recipients. *J Clin Pharmacol*. 2009;49(2):185–195. doi:10.1177/0091270008329558
49. Arns W, Gies W, Choi L, et al. Absorption characteristics of EC-MPS – an enteric-coated formulation of mycophenolic sodium. *Int J Clin Pharmacol Ther*. 2006;44:375–385. doi:10.5414/CPP44375