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RESEARCH ARTICLE

ANALYTICAL CHEMISTRY

COMPARATIVE ASSESSMENT OF PLASMA CONCENTRATIONS OF MYCOPHENOLATE MOFETIL CAPSULES WITH RESPECT TO ITS PURE FORM IN MAMMALIAN RODENT *(Oryoctolagus cuniculus)* USING UV-SPECTROPHOTOMETRY

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ABSTRACT

The present study involves the determination of the plasma concentration of Mycophenolate mofetil (MMF) by performing biological sample analysis of the plasma sample of rabbit using UV-Visible spectrophotometer and comparative study of the MMF in capsules with reference to the standard MMF.

The plasma concentration of pure MMF and MMF in marketed capsules after administering a single oral dose were determined individually and the percentage relative plasma concentration of MMF in capsule with reference to that of the pure MMF at all the predetermined time intervals were found out in respect of comparative study. The plasma concentration of the standard MMF and MMF in capsule at different time intervals were found out. The mean maximum plasma mycophenolate mofetil concentration (Cmax) after a mycophenolate mofetil 100 mg dose in healthy rabbits was 43.67 µg/ml for reference MMF and 42.67 µg/ml for sample MMF in capsule formulation occurred at 1 hour postdose, decayed with a mean apparent half-life ($t_{1/2}$) of around 16 hours. Relative plasma concentration of sample with reference standard at peak concentration at one hour was found to be 102.34%.

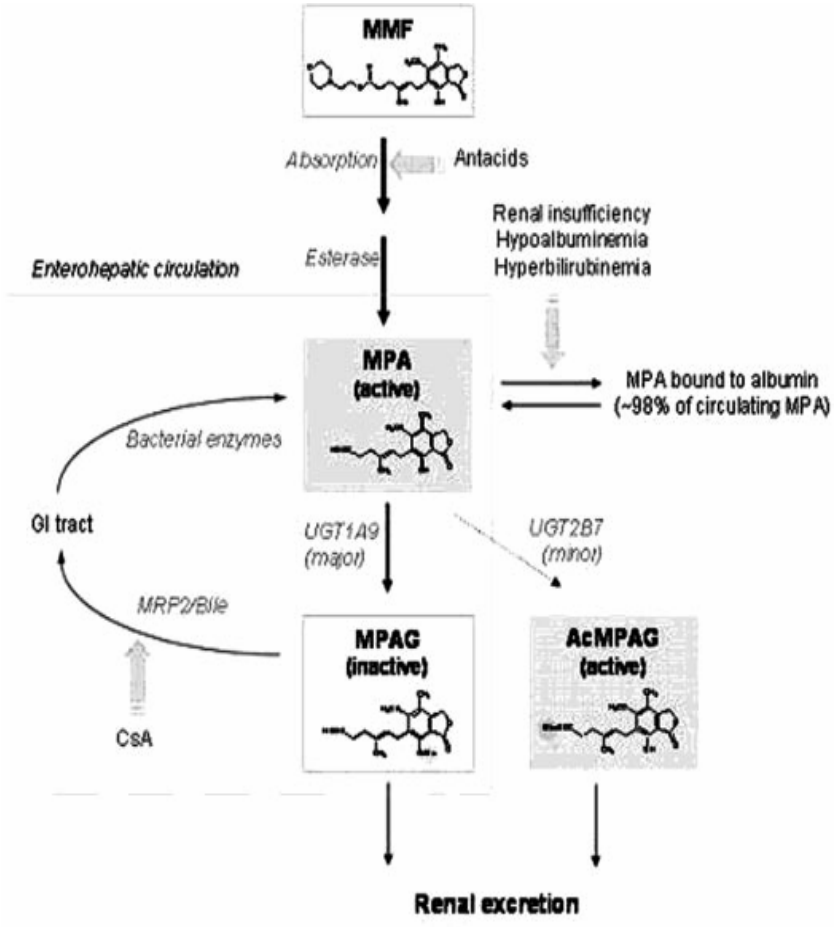
KEY WORDS

Mycophenolate mofetil, Mycophenolic acid, MMF, MPA, IMPDH, Immuno suppressant, Spectrophotometry.

INTRODUCTION

Mycophenolate mofetil (MMF), a prodrug of mycophenolic acid (MPA) is and immunosuppressive agent and is chemically known as 2- morpholinoethyl (E)-6- (1, 3-dihydro-4-hydroxy- 6- methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate[1]. It is a selective, reversible and non-competitive inhibition of ionosine monophosphate dehydrogenase (IMPDH) By the biological sample analysis the pharmacokinetic monitoring of MPA that mediates its effect by the inhibition of IMPDH, a key enzyme in the de novo biosynthesis of purines.

The relationship between MPA concentration in plasma, IMPDH activity in whole blood, and nucleotide concentration in lymphocytes was investigated in renal-transplant recipients, who were randomized to receive either Mycophenolate mofetil (MMF) The peak concentration of MPA achieved at 1 hr after dosing resulted in approximately 40% inhibition of IMPDH activity. As the MPA concentration decreased throughout the dosing interval, there was a gradual restoration of IMPDH activity[2].



The reviewed literature infers that only a few pharmacokinetic studies were reported for MMF and/or MPA[3-8] So in the view of improvising, it is advisable to perform a study on the in vivo bioavailability by carrying the therapeutic drug monitoring using the biological sample as per OECD guidelines [9]

The objective of the present study is to perform biological sample analysis of Mycophenolate mofetil in the plasma sample of rabbit using UV-Visible spectrophotometer and comparative study of the MMF in capsules with reference to the standard MMF.

EXPERIMENTAL

MATERIALS AND METHODS

Mycophenolate mofetil is a gift sample taken from Concord Biotech Ltd.. The reference standard mycept capsule 250mg was procudes from local market and other chemical solvents used Acetonitrile, Hydrochloric acid, Acetone and Sodium citrate.

The drug substance and marketed product were transferred to the 'Drug' containers labeled with details as follows: Investigational Product Name, Strength and dosage form, Period number, Product type, Dose, Manufacturer's Name, Subject number, Storage condition, Dosing condition, Principal Investigator's name and study site.

Investigational products not intended for immediate use were retained in their original containers. Any product that has not been used (e.g., Dropout, withdrawal) was identified and stored as per the in house standard operating procedure. After the completion of the study the remaining investigational products were retained at the study site for a period of 10 years.

Pre study evaluation

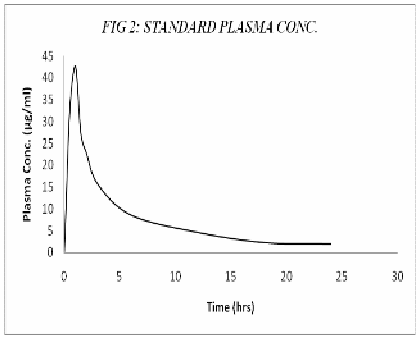
Healthy male rabbits were selected in three groups and the prestudy evaluation regarding the weights and corresponding volumes were performed.

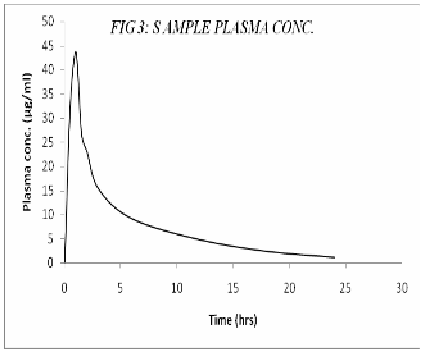
Three groups of healthy male rabbits, for standard, sample and control, each group containing six were selected and were maintained in the fasting condition overnight only with the aid of water. After the administration of the standard MMF and the marketed capsule doses observed for 14 days and a special attention is maintained for the first four hours.

By the ethical standards 0.5 ml of the whole blood was collected via the marginal vein in to containing sodium citrate anticoagulant. Blood samples collected at pre-dose (within 1 hour prior to dosing 0.5, 1, 1.5, 2, 2.5, 3, 6, 12, 24 hours post dose within 2 minutes of scheduled sampling time during each study period and the estimation of MMF in plasma was planned.

To 0.5 ml of sample,1.5 ml of water and 0.5 ml of 0.15 mol/L HC1 and were then centrifuged extracted and diluted to 1ml with Acetonitrile. The supernatant liquids from each subject plasma samples were separated and the absorbances were measured at 305 nm [10].

RESULTS AND DISCUSSION





Time interval (hrs)	Avg Cp of sample (µg/ml)	Avg Cp of standard (µg/ml)	% Relative Cp
0 hrs	0	0	0%
0.5 hrs	32.97	32.83	100.43%
1 hrs	43.67	42.67	102.34%
1.5 hrs	26.67	27.00	98.77%
2 hrs	22.87	22.67	100.88%
3 hrs	15.33	15.67	97.83%
6 hrs	9.12	8.56	105.19%
12 hrs	4.80	4.58	104.80%
18 hrs	2.38	2.25	105.77%
24 hrs	1.14	1.97	57.86%

MMF is an immunosuppressive agent. The plasma concentration of pure MMF and MMF in marketed capsules after administering a single oral dose were determined individually and the percentage relative plasma concentration of MMF in capsule with reference to that of the pure MMF at all the predetermined time intervals were found out in respect of comparative study.

The plasma concentration of the standard MMF and MMF in capsule at different time intervals and the results of the comparative study are presented in table no.1 and graphically represented in fig. nos. 1 and 2.

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