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Article

In vitro dissolution kinetic for mycophenolic acid derivatives tablets

André Lima de Oliveira Costa[1,*], Paula Cristina Rezende Enéas[1], Tiago Assis Miranda[1], Sueli Aparecida Mingoti[2], Cristina Duarte Vianna Soares[1], Gerson Antônio Pianetti[1]

[1]Departament of Pharmaceutical Products, Faculty of Pharmacy, [2]Departament of Statistics, Institute of Exact Sciences, Federal University of Minas Gerais

Mycophenolate mofetil (MMF) and mycophenolate sodium (MPS) are an ester and a salt of mycophenolic acid. They have different kinetic *in vivo* characteristics due to differences in molecular structures, physicochemical properties and formulations administered. In this study, dissolution profiles of reference products were tested in different media to evaluate the effect of pH, kinetic dissolution and the best statistical model that can be used to predict the release of both drugs. The drug release was determined by using a validated ultraviolet spectrophotometry method, λ 250 nm. The method showed to be selective, linear, precise and accurate for MMF in 0.1 M HCl and MPS in sodium phosphate buffer pH 6.8. Dissolution kinetics models of zero order, first order, Higuchi, Hixson-Crowell and Weibull were applied to data in order to select the best fit by linear regression. The regression parameters were estimated and the models were evaluated with the results of residuals and coefficient of determination. The residuals obtained from dissolution kinetics models were random, uncorrelated, and normally distributed with constant variance. The R^2 values (74.7% for MMF and 95.8% for MPS) demonstrated good ability of the Weibull regression to explain the variability and to predict the drugs' release.

Uniterms: Mycophenolate sodium. Mycophenolate mofetil. Dissolution profiles. Weibull kinetics.

Micofenolato de mofetila (MMF) e micofenolato sódico (MPS) são, respectivamente, éster e sal sódico do ácido micofenólico. Os fármacos possuem características farmacocinéticas distintas em função das diferenças na estrutura molecular, nas propriedades físico-químicas e nas formulações administradas. Neste trabalho, os perfis de dissolução dos medicamentos referências foram testados em diferentes meios de dissolução com o objetivo de avaliar o efeito da variação de pH, a cinética de dissolução e o modelo estatístico mais adequado para prever a dissolução dos fármacos. A liberação dos fármacos foi determinada com método validado por espectroscopia no ultravioleta, λ 250 nm. O método mostrou-se seletivo, linear, preciso e exato para dissolução de MMF em 0,1 M HCl e MPS em tampão fosfato pH 6,8. Os modelos cinéticos de dissolução de ordem zero, primeira ordem, Higuchi, Hixson-Crowell e Weibull foram aplicados com o objetivo de selecionar aquele com o melhor ajuste por regressão linear. Os parâmetros de regressão foram estimados e os ajustes dos modelos foram verificados pelos resíduos e coeficientes de determinação. Os resíduos obtidos foram aleatórios, independentes, apresentaram variância constante e seguiram a distribuição normal. Os valores de R^2 (74,7% para MMF e 95,8% para MPS) indicaram bom ajuste da regressão de Weibull para explicar a variabilidade e estimar a liberação dos fármacos.

Unitermos: Micofenolato sódico. Micofenolato de mofetila. Perfil de dissolução. Cinética de Weibull.

INTRODUCTION

Mycophenolic acid (MPA), commonly used in the immunosuppressive therapy of post-transplant patients, is a specific, non-competitive and reversible inhibitor of inosine monophosphate dehydrogenase (Noronha *et al.*, 2005; Sánchez-Fructuoso, 2005; Staatz, Tett, 2007). It is administered as a pro-drug, the ester mycophenolate mofetil (MMF), or its salt, mycophenolate sodium (MPS) (Figure 1).

Following oral administration, MMF undergoes rapid and extensive absorption and complete pre-systemic

***Correspondence:** A.L.O. Costa. Departamento de Produtos Farmacêuticos, Faculdade de Farmácia, Universidade Federal de Minas Gerais, 31.270-901 - Belo Horizonte - MG, Brasil. E-mail: sodioepotassio@hotmail.com

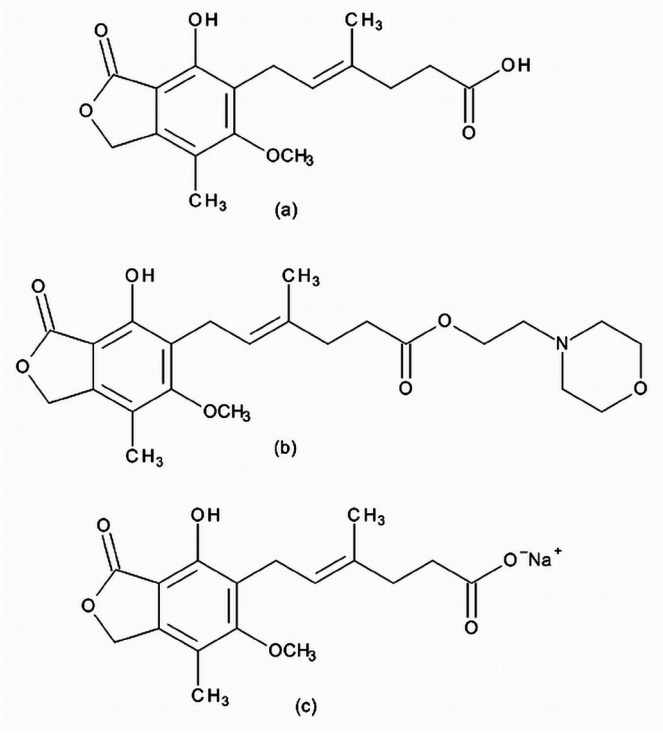

FIGURE 1 – Chemical structures of (a) mycophenolic acid, (b) mycophenolate mofetil and (c) mycophenolate sodium.

metabolism to MPA. The active metabolite reaches maximum plasma concentration after 1 h and a secondary increase in plasma is observed at approximately 6-12 h post dose (Staatz, Tett, 2007; Lee *et al*., 1990; Jeong, Kaplan, 2007).

Enteric-coated mycophenolate sodium (EC-MPS) was developed to reduce the incidence and severity of gastric side effects of mycophenolate mofetil immediate release tablets (MMF-IR) used in immunosuppressive therapy. The goal of this formulation development was delaying release and absorption of MPA to reduce the incidence of gastrointestinal effects (Arns, 2007; Budde *et al*., 2004; Sábada *et al*., 2005). After oral administration of EC-MPS the absolute bioavailability is greater than 71% and peak plasma concentration is reached within 1.5 to 2 h (Sánchez-Fructuoso, 2005; Zolezzi, 2005).

Several analytical methods for MPA have been established to support pharmacokinetics studies of EC-MPS compared with MMF-IR in human and animal models (Tsina *et al*., 1996; Barkosi, 2005; Wiwattanawongsa, 2001). The drugs demonstrated similar efficacy and safety profile, indicating that patients receiving MMF-IR as maintenance therapy can be safely interchanged to EC-MPS. However, there is no consensus on reducing the adverse effects (Sánchez-Fructuoso, 2005; Arns, 2007; Budde *et al*., 2004; Sábada *et al*., 2005; Zolezzi, 2005).

Despite similar safety and efficacy, the tablets may present different drug releases after oral administration. The objectives of this work were evaluated dissolution profiles of MMF-IR and EC-MPS in different media to determine the pH effect on drug release and applied statistical models to describe the dissolution kinetics.

MATERIAL AND METHODS

Reagents and chemicals

MPA from Sigma-Aldrich® (St. Louis, MO, USA, batch 097K4005) and MMF reference standard from European Pharmacopoeia, batch 2.0, were obtained. The reference tablets CellCept® 500 mg (MMF-IR, Roche) and Myfortic® 360 mg (EC-MPS, Novartis) were used. The analytical reagents concentrated hydrochloric acid, methanol, sodium monobasic phosphate and sodium tribasic phosphate were purchased (J.T. Baker®, Phillipsburg, NJ, USA). High purity water was used (Milli-Q, Millipore®, Bedford, MA, USA).

Instrumentation and analytical conditions

The dissolution profiles were performed in a dissolution system (Erweka® DT80) in accordance to specifications of The United States Pharmacopeia (USP 34, 2011). The drug release percentage was determined in a UV-Vis spectrophotometer (HP8453, Agilent, Palo Alto, CA, USA) at λ 250 nm, in adequate diluents.

Dissolution profiles

Immediate release profile of MMF was carried out using six units in each medium: 0.1 M HCl, 0.01 M HCl and 0.1 M sodium phosphate buffer (PBS) pH 3.0 maintained at 37±0.5 °C. Paddle apparatus were used at 50 rpm and dissolution points were defined at 5, 10, 15, 30, 45 and 60 min. The samples were filtered through a 0.45 µm membrane and exactly diluted to approximately 25 µg/mL. The amount of MMF dissolved was determined against MMF standard solution in dissolution medium at same concentration.

Dissolution profiles for EC-MPS tablets were obtained according to USP general method <711> for dissolution of enteric-coated tablets. The dissolution started with 750 mL 0.1 M HCl at 37±0.5 °C and paddle apparatus at 50 rpm. After 120 min, an aliquot was collected and 250 mL of 0.20 M sodium phosphate buffer tribasic, 37±0.5 °C, were added. The pH of each vessel was rapidly adjusted to 6.8±0.05. The amount of MPS dissolved

was determined after 10, 20, 30, 45, 60, 90 e 120 min in buffer medium. A stock solution of MPA standard was prepared in methanol at 450 μg/mL and diluted in dissolution media to final concentration of 18 μg/mL. The same procedure was performed to obtain dissolution profiles at adjusted pH values of 6.0±0.05 and 5.5±0.05.

Statistical comparison was performed by Duncan test at 95% of confidence for the selection of an ideal medium and, dissolution test specifications were proposed for each drug. The difference of average drug release at each time point was considered significantly if it was larger than the critical value. Similarity factor (f_2) was also determined to compare the curves of dissolution. In Equation 1 for f_2 factor, n is the number of dissolution points, Rt and T_t are the reference and test dissolution values at time t. Values of f_2 between 50 and 100 ensure the sameness of two dissolution profiles (USA, 1997).

$$f_2 = 50\ log\left\{\left[1 + \frac{1}{n}\Sigma_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} x\ 100\right\} \qquad \text{Eq. 1}$$

Dissolution kinetics

Mathematical models are often used to describe dissolution profiles and to compare drug release by dependent method. The evaluation of dissolution kinetics allows knowing the rate of the process, the maximum concentration dissolved and when significant, changes occur (Patel *et al*., 2008; Raslan, Maswadeh, 2006; Demirturk, Oner, 2005; Serra, Storpirtis, 2007).

The release kinetics of MMF-IR tablets in 0.1 M HCl and EC-MPS in PBS pH 6.8 were analyzed by linear regression using different mathematical models (see Table I). The general function of a simple linear regression is described by Equation 2, where β_0 is the intercept, β_1 is the slope and ε the random error (residual) with zero mean and variance σ^2.

$$f_{(xi)} = \beta_0 + \beta_1 x_i + \varepsilon_i \qquad \text{Eq. 2}$$

Regression parameters (β_0 and β_1) were estimated by least squares method and the best fit model was selected for each drug based on the results of the coefficient of determination (R^2) and residual analyses. The observations at 5, 10, 15 and 30 min were used for MMF-IR. The kinetics studied for EC-MPS were assessed in the time interval 10-45 min in the buffered stage.

Pharmaceutical dosage forms that follow zero order kinetics, release the same amount of drug per unit of time. In the first order kinetics, the plot of dissolution time versus natural logarithm of the percentage dissolved drug was evaluated. Drug release occurs proportionally to the drug amount remaining inside the dosage form, so that the amount of drug released per unit time decreases (Manadas *et al*., 2002).

Higuchi developed several theoretical models to study the release of soluble and poorly soluble drugs incorporated in solid and semi-solid matrices. The simplified Higuchi model is based on Fick's law of diffusion and the square root of time is described versus drug release (Manadas *et al*., 2002). The equation of the Hixson-Crowell model considers the principle that the area of a particle is proportional to the cube root of its volume. This model assumes that the release rate is limited by the dissolution of the particles of the drug and not by diffusion in the matrix tablet.

The general empirical equation described by Weibull (Equation 3) was applied to the drug release processes and provides satisfactory results for almost all types of dissolution curves.

$$\log[-\ln(1-m)] = \beta\log(t - T_i) - \log\alpha \qquad \text{Eq. 3}$$

In Weibull model, the statistical parameter α defines the time scale of the process estimated from X value (t=1), T_i represents the time interval before dissolution starts ($T_{i=0}$) and β is the shape parameter that characterizes the curve as exponential (β=1), sigmoid (β>1) or parabolic (β<1).

TABLE I - Regression models applied to dissolution profiles of MMF-IR and EC-MPS tablets

Model	Equation	β_0	β_1
Zero order	$Q_t = Q_0 + k_0 t$	Q_0	k_0
First order	$\ln Q_t = \ln Q_0 + k_1 t$	$\ln Q_0$	k_1
Higuchi	$Q_t = Q_0 + k_H t^{1/2}$	Q_0	k_H
Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} = k_w t$	$Q_0^{1/3}$	k_W
Weibull	$\log[-\ln(1-m)] = \beta\log(t - T_i) - \log\alpha$	$-\log\alpha$	β

Q_t: amount of drug released in time t; Q_0: initial amount of drug in dissolution media; k_0, k_1, k_H, k_W: release rate constants; m: accumulated fraction of the drug; α: scale parameter; β: shape parameter; T_i: location parameter.

The Weibull linear relationship was obtained by log-log plot of time versus *-ln (1-m)*, where *m* is the cumulative fraction of drug dissolved over a time *t* (Manadas *et al*., 2002; Yukse *et al*., 2000).

Method validation

Spectrophotometric method was validated regarding merit figures specificity, linearity, accuracy, precision, detection (LOD) and quantitation limits (LOQ) for MMF-IR in 0.1 M HCl and, for EC-MPS in PBS pH 6.8, according to ICH guidelines (ICH, 2005). EC-MPS determination was expressed in the equivalent amount of MPA.

Placebo enriched by standard solutions was used to evaluate selectivity over the range 200-400 nm. MMF-IR placebo formulation contained microcrystalline cellulose, croscarmellose sodium, magnesium stearate, Povidone K-90, Hypromellose, titanium dioxide, indigo carmine and yellow iron oxide. EC-MPS placebo was composed by corn starch, Povidone K-90, Crospovidone, lactose, colloidal silicon dioxide, magnesium stearate, Hypromellose, titanium dioxide, indigotine, yellow iron oxide and red iron oxide.

Linearity was evaluated by thirty determinations across the range 5.0-50.0 µg/mL for MMF and by twenty four determinations across the range 6.0-34.0 µg/mL for MPA. The results were analyzed by visual inspection and a regression model estimated by the least squares method. Detection and quantitation limits were estimated based on the standard deviation of the intercept (s_a) and the slope (b) of the respective analytical curve were used following Equations 4 and 5.

$$LOD = 3.3\, s_a / b \qquad \text{Eq. 4}$$

$$LOQ = 10\, s_a / b \qquad \text{Eq. 5}$$

Precision was investigated in the tablets by repeatability (intra-day) and intermediate precision (inter-day) using six determinations in three different days. Final test concentrations were 25 µg/mL for MMF and 18 µg/mL for MPA. Intra-day precision was reported as relative standard deviation (RSD) and inter-day precision was evaluated by comparison of the means in different days, by Anova (α=0.05).

In order to evaluate accuracy, three placebo samples were added of different standard concentrations of MMF (17.5, 25.0, 32.5 µg/mL) and of MPA (12.6, 18.0, 23.4 µg/mL). Recovery was expressed by the ratio of experimental to nominal drug percentage concentrations.

RESULTS

Dissolution profiles

The MMF-IR dissolution profiles shown in Figure 2a were statistically different at all sampling times ($p<0.05$). It was observed that the amount of MMF released in PBS pH 3.0 was significantly different to that released in 0.1 M HCl ($p<0.05$) at all points. The dissolution profile in 0.01 M HCl was not significantly different to that in PBS pH 3.0 at initial points ($p>0.05$). However, the dissolution curves in media 0.01 M HCl and 0.1 M HCl yield superposed points, starting at 30 min, in the plateau region (see Table II).

The similarity factor was applied to compare the dissolution profile over 0-30 min (critical interval of dissolution). In a similar drug dissolution was observed the curves in 0.1 M HCl vs. 0.01 M HCl ($f_2 = 53.15$), as well as for those in 0.01 M HCl vs. PBS pH 3.0 media ($f_2 = 70.37$). However, the curves were considered statistically different

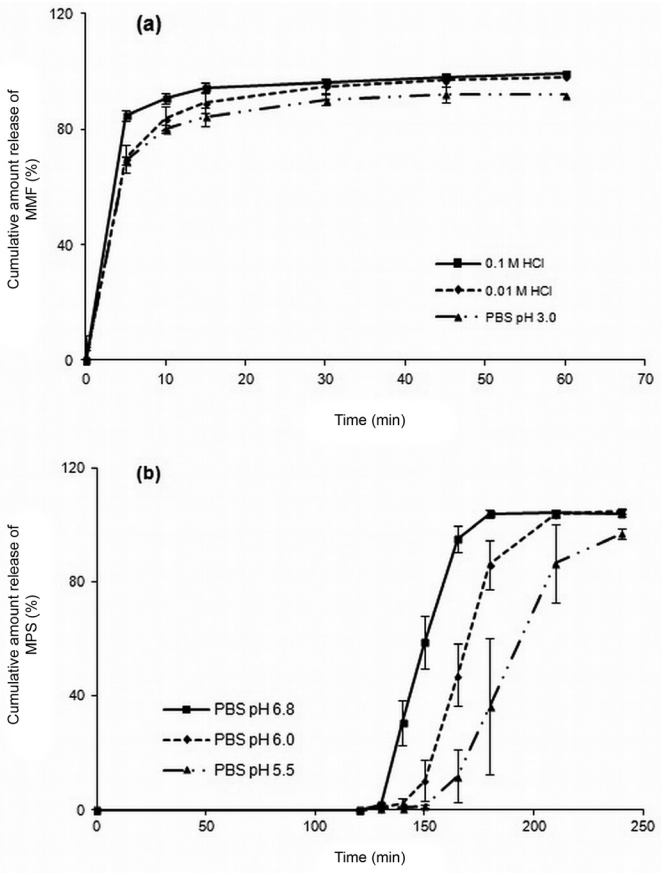

FIGURE 2 - Cumulative amount release for (a) MMF-IR in 0.1 M HCl, 0.01 M HCl and PBS pH 3.0 and for (b) EC-MPS in PBS pH 5.5, 6.0 and 6.8 at 37±0.5 °C, paddles, 50 rpm, using UV method, λ 250 nm.

between the tested media 0.1 M HCl vs. PBS pH 3.0 (f_2 = 47.75). Despite the difference of drug dissolution found in 0.1 M HCl, 0.01 M HCl and PBS pH 3.0 media, the cumulative amount (94.44%, 89.07% and 84.33%, respectively) was greater than 80% in all media in the time point 15 min.

Figure 2b depicts the EC-MPS tablets dissolution profile. The first stage release was performed during 120 min in 0.1 M HCl with the aim to evaluate the resistance of the enteric coating. In the second stage, the aim was to characterize the delayed release profile during 120 min in the media PBS pH 5.5, 6.0 and 6.8. The tablets remained visually intact in the acid stage and the amount of drug released was negligible (0.0%). Moreover, there was a greater drug release with the increase of pH. The dissolution steady state was first achieved within 60 min in PBS pH 6.8. EC-MPS dissolution profile was significantly different in the media at all sampling times (p<0.05). Duncan test showed that the amounts of MPS dissolved in PBS pH 6.8 were significantly different when compared to those in PBS pH 5.5. The drug dissolution profile in PBS pH 6.0 was similar to that in PBS pH 5.5 at the two initial points and closer to that in PBS pH 6.8 at the final three dissolution points (Table III).

By using the similarity factor approach over the first 45 min for the second stage of the dissolution profile of EC-MPS tablets, f_2 values were smaller than 50 and pointed for no similarity observed between the curves (f_2 = 21.71 for pH 6.8 vs. 6.0; f_2 = 13.93 for pH 6.8 vs. 5.5; f_2 = 36.87 for pH 6.0 vs. 5.5). Hence, the pH was critical for the drug dissolution profile at this stage.

Dissolution kinetics

Dissolution kinetics was studied considered the dissolution profiles of MMF-IR and EC-MPS in 0.1 M HCl and PBS pH 6.8, respectively. The mathematical models for zero order, first order, Higuchi, Hixon-Crowel and Weibull were applied to determine the best model to represent the dissolution process. Results of R^2 (coefficient of determination), intercept (β_0) and slope (β_1), normality test for standardized residual and significance of parameters were evaluated for MMF-IR and EC-MPS, according to Tables IV and V.

Method validation

Interference of placebo was not observed over the range 200-400 nm, attesting for the method selectivity. The calibration curves showed linearity over the ranges 5.0-50.0 μg/mL for MMF and 6.0-34.0 μg/mL for MPA determinations. The regressions were significant (p<0.05) and data showed good curve fits. All R^2 values were greater than 99.9%, which is the proportion explained by the

TABLE II - Duncan test (α=0.05) for MMF-IR dissolution profiles in the media 0.1 M HCl, 0.01 M HCl and PBS pH 3.0 using UV method, λ 250 nm

Dissolution media	Time (min)					
	5	10	15	30	45	60
0.1 M HCl vs. PBS pH 3.0	15.45	10.52	10.11	6.01	5.95	7.24
0.1 M HCl vs. 0.01 M HCl	14.63	7.12	5.37	1.26*	1.10*	1.23*
0.01 M HCl vs. PBS pH 3.0	0.82*	3.40*	4.74	4.75	4.85	6.01
Critical value	7.56	3.91	3.53	3.75	2.37	2.73

*No significant difference.

TABLE III - Duncan test (α=0.05) for EC-MPS dissolution profiles in media PBS pH 5.5, 6.0 and 6.8, using UV method, λ 250 nm

Dissolution media	Time (min)						
	10	20	30	45	60	90	120
PBS pH 6.8 vs. PBS pH 5.5	1.19	29.83	57.32	83.08	67.55	17.58	7.03
PBS pH 6.8 vs. PBS pH 6.0	1.01	28.32	48.35	47.68	17.79*	0.44*	0.95*
PBS pH 6.0 vs. PBS pH 5.5	0.18*	1.51*	8.97	35.40	49.76	17.14	7.98
Critical value	0.37	6.30	8.67	11.16	18.84	10.20	1.83

*No significant difference.

TABLE IV - Results of the regression fit models for MMF-IR dissolution profile in selected medium 0.1 M HCl, using UV method, λ 250 nm

Model	R^2 (%)	β_0		β_1		Tests for normality of residuals *(p-value)*
		Estimated value	*p*-value	Estimated value	*p*-value	
Zero order	56.2	85.322	< 0.001	0.406	< 0.001	0.452
First order	54.5	4.446	< 0.001	0.005	< 0.001	0.331
Higuchi	64.2	78.780	< 0.001	3.427	< 0.001	0.460
Hixson-Crowell	55.1	0.239	< 0.001	− 0.007	< 0.001	0.369
Weibull	74.7	0.059	0.201	0.321	< 0.001	0.418

TABLE V - Results of the regression fit models for EC-MPS dissolution profile in selected medium PBS pH 6.8, using UV method, λ 250 nm

Model	R^2 (%)	β_0		β_1		Tests for normality of residuals *(p-value)*
		Estimated value	*p*-value	Estimated value	*p*-value	
Zero order	97.0	−23.163	< 0.001	2.654	< 0.001	0.016
First order	76.2	0.405	0.278	0.104	< 0.001	< 0.005
Higuchi	96.7	−83.813	< 0.001	26.302	< 0.001	0.120
Hixson-Crowell	87.0	3.835	0.001	− 0.091	< 0.001	0.018
Weibull	95.8	−5.118	< 0.001	3.457	< 0.001	0.059

total variance of the response by the regression models (Table VI). The LOD and LOQ limits were calculated from the response standard deviation of the intercept and the slope of the analytic regression line. Estimated LOD value for MMF was 0.32 µg/mL and 0.13 µg/mL for MPA. The estimated LOQ values were 0.97 µg/mL for MMF and 0.45 µg/mL for MPA.

The Table VII shows the precision and accuracy results. Precision was calculated by MMF and MPA determinations in tablets in three days. All RSD values were lower than 2.0% and there was no significant difference between averages in the three-day analyses (p>0.05). Accuracy, investigated by standard recovery over three different concentrations, resulted in experimental values near the nominal concentrations. Recovery means were 99.28% for MMF and 99.84% for EC-MPS.

DISCUSSION

The dissolution media used was defined based on the best solubility and characteristics of the drug formulations. MMF is formulated as immediate release tablets, nevertheless, the drug is poorly soluble in water. Hence, an increase in hydrogen ion concentration of the

TABLE VI - Results of linearity, LOD and LOQ for MMF and MPA in selected media 0.1 M HCl and PBS pH 6.8, respectively, using UV method, λ 250 nm

Coefficients	MMF in 0.1 M HCl	MPA in PBS pH 6.8
R^2 (%)	99.98	99.99
Slope ± standard deviation	0.0203 ± 0.0001	0.0292 ± 0.0001
Intercept ± standard deviation	0.0030 ± 0.0020	0.0003 ± 0.0013
LOD (µg/mL)	0.32	0.13
LOQ (µg/mL)	0.97	0.45

TABLE VII - Precision (n=18) and recovery (n=12) data for MMF-IR and EC-MPS tablets, in selected media 0.1 M HCl and PBS pH 6.8, respectively, using UV method, λ 250 nm

Precision for MMF-IR			Precision for EC-MPS		
Day	Mean (%)	RSD (%)	Day	Mean (%)	RSD (%)
1	99.11	0.33	1	99.78	0.66
2	99.88	0.90	2	99.94	1.30
3	99.25	0.89	3	100.36	0.61
Recovery for MMF-IR			Recovery for EC-MPS		
Standard added (μg/mL)	Mean (%)	RSD (%)	Standard added (μg/mL)	Mean (%)	RSD (%)
17.5	99.83	0.37	12.6	100.79	0.39
25.0	99.03	0.13	18.0	99.30	0.99
32.5	98.97	0.34	23.4	99.42	0.17

medium favors its solubility (Lee *et al*., 1990). Because of this feature, the acidic dissolution media 0.1 M HCl, 0.01 M HCl and 0.1 M PBS pH 3.0 were selected to determine the dissolution profile of MMF tablets.

The mean release at 15 min in 0.1 M HCl was almost complete (94.44%) for MMF-IR. According to the regulatory agency Food and Drug Administration (USA, 1997), a drug product undergoing 85% dissolution in 15 min under mild dissolution test conditions behaves like a solution. Thus, generally, it should not have any bioavailability problems since the mean gastric emptying time ($t_{50\%}$) is 15 to 20 min under fasting conditions. The use of 0.1 M HCl as the dissolution medium was appropriate for MMF-IR and the acceptance criteria, Q=85%, for a very fast dissolving release (94.44%, in 15 min) can be applied as a quality control.

For EC-MPS, no drug release was detected at the acid stage. The MPS mean dissolution at 45 min of the buffered stage was 95.01% in pH 6.8, 47.33% in pH 6.0 and 11.93% in pH 5.5. The USP general method acceptance criteria for enteric-coated tablets consider the limit of 10% of the amount of drug dissolved in each unit after 120 min in 0.1 M HCl. A minimum of 80% of the dissolved amount for each unit after 45 min of dissolution is recommended at the buffered stage. These criteria are suitable for analysis of EC-MPS dissolution evaluation in PBS pH 6.8.

A regression model is well adjusted when the average of the response variable Y is a linear function of the predictor variable X, the variance of the residuals is constant, the residuals follow the normal distribution with zero mean and are independent. The value of R^2 represents the proportion of the total variability of the variable Y that is explained by the variable X. This index is widely used to classify a set of regression because it scales the ability of the predictor variable in determining the response variable. However, R^2 should not be used as an isolated parameter without the validation of the assumptions established for the residuals in order to fit the regression model.

The zero order model was not ideal for evaluating the kinetics release of the drugs. The model did not show good ability to explain the data variation for MMF-IR (R^2 = 56.2%). The R^2 value was larger for EC-MPS (97.0%) but the residuals were not random and did not follow the normal distribution (p<0.05). The first order model had no advantage over the initial results compared to the zero order model.

Weibull transformation resulted in a significant (p<0.001) and valid regression for MMF-IR dissolution profile (Figure 3a). This model explained 74.7% of total variance of observations. The final regression model could be described by the Equation 6, where m is the cumulative fraction of drug dissolved over a time t.

For EC-MPS study, Higuchi transformation resulted in residuals with best fit to normal distribution. Noteworthy, β_0 parameter was not significantly different from zero (p>0.05) only in first order model. This result is ideal because the drug release at time zero is null. Despite the merits of first order and Higuchi models, the best fit was yet obtained with Weibull transformation. The residuals showed to be random with constant variance (Levene test p=0.700) only with Weibull model. Data transformation resulted in a significant regression (p<0.001) and the model was able to explain 95.8% of the total data variation (Figure 3b). The regression could be described by Equation 7.

$$\log(-\ln(1-m)) = 0.05912 + 0.3210 \log t \quad \text{Eq. 6}$$

$$\log(-\ln(1-m)) = -5.118 + 3.457 \log t \quad \text{Eq. 7}$$

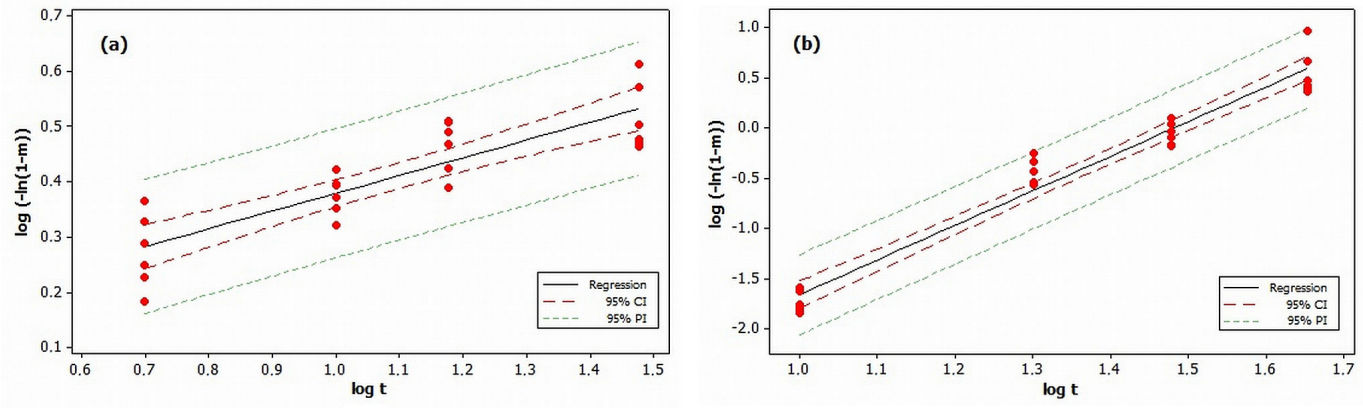

FIGURE 3 - Weibull regression for (a) MMF-IR and (b) EC-MPS profiles in selected media 0.1 M HCl and PBS pH 6.8, respectively, using UV method, λ 250 nm.

CONCLUSIONS

The results obtained for determination of mycophenolic acid derivatives after tablets dissolution by using UV spectrophotometry at λ 250 nm showed to be selective, linear, precise and accurate. The use of 0.1 M HCl as a dissolution medium for MMF-IR was appropriate, considering dissolution acceptance criteria Q=85% of the labeled amount in 15 min. A minimum criterion of 80% of the dissolved amount after 45 min is proposed for EC-MPS in PBS pH 6.8.

Weibull model showed a significant ($p<0.001$) and best fit to linear regression for dissolution profile of MMF-IR and EC-MPS tablets. The obtained residuals were random, uncorrelated, and normally distributed with constant variance. The R^2 values (74.7% for MMF-IR and 95.8% for EC-MPS) demonstrated good ability of the Weibull regression to explain the variability and to predict the drug release from the reference dosage forms.

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