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Physicochemical evalution of mycophenolate mofetil's dispersion: stability and administration in tubes

Avaliação físico-química da dispersão de micofenolato de mofetila: estabilidade e administração em sondas

Evaluación fisicoquímica de la dispersión de micofenolato mofetil: estabilidad y administración en sondas

Flavio Rodrigues Lopes Filho[1]
Maria Aparecida Alexandre Josino[2]
Said Gonçalves da Cruz Fonseca[3]
Marta Maria de França Fonteles[4]

[1] PhD candidate in Pharmaceutical Sciences with an emphasis on Clinical Pharmacy and Health Surveillance at the Federal University of Ceará (UFC). Holds a Master's degree in Pharmaceutical Sciences with an emphasis on Clinical Pharmacy and Health Surveillance from UFC. Specialist in Clinical Pharmacy and Pharmaceutical Prescribing from the Faculdade de Quixeramobim. Coordinator of the Pharmacy undergraduate program at the educational group *Aqui Você Pode*. **E-mail:** frodrigues996@gmail.com, **ORCID:** https://orcid.org/0000-0002-1301-5020

[2] PhD in Medical Microbiology from the Federal University of Ceará (UFC). Bachelor's degree in Pharmacy from UFC. Conducts research in the field of antimicrobial drug synergism, with an emphasis on studying the antimicrobial potential of drugs originally indicated for other therapeutic uses, development of formulations with antimicrobial activity and pediatric formulations, physicochemical quality control, analytical validation, and evaluation of pharmacokinetic parameters of formulations administered to transplant patients. **E-mail:** maajosino@gmail.com, **ORCID:** https://orcid.org/0000-0002-4700-9796

[3] PhD in Pharmaceutical Development and Technological Innovation from the Federal University of Rio Grande do Norte (UFRN). Master's degree in Pharmaceutical Sciences from the Federal University of Pernambuco (UFPE). Bachelor's degrees in Pharmacy and Industrial Pharmacy from the Federal University of Ceará (UFC). Associate Professor at UFC. Has experience in the field of Pharmacy, with an emphasis on pharmaceutical development (galenic development), mainly working on quality control, pharmaceutics, and herbal medicines. **E-mail:** said@ufc.br, **ORCID:** https://orcid.org/0000-0001-8183-4960

[4] Postdoctoral training in Clinical Pharmacy at the University of Auckland, New Zealand. PhD and Master's degrees in Pharmacology from the Federal University of Ceará (UFC). Bachelor's degree in Pharmacy from UFC. Full Professor at UFC, ad hoc consultant to the Federal Council of Pharmacy, and full member of the Ceará Academy of Sciences (ACECI). CNPq Research Fellow (PQ 1D). Also serves as the general didactic-pedagogical coordinator of the Multiprofessional Residency Program in Hospital Health Care at UFC, within the university hospital complex (Walter Cantídio University Hospital / Assis Chateaubriand Maternity School). Vice-coordinator of the Graduate Program in Pharmaceutical Development and Technological Innovation (PPGDITM/UFC, joint doctoral program); co-tutor of PET–Pharmacy/UFC, and member of the Pharmacy and Therapeutics Committee (PTC) and the Clinical Pharmacy Management Committee of the Ceará State Health Department (SESA). **E-mail:** martafonteles@yahoo.com.br, **ORCID:** https://orcid.org/0000-0002-2570-9265

Abstract: The aim of this study was to evaluate the stability of a liquid formulation of MMF 10 mg/mL at temperature of 20ºC-25ºC and 2ºC-8ºC. The vehicle was developed in the Pharmacotechnical Laboratory at the Federal University of Ceará, and the formulations were monitored for changes in pH, density, viscosity and sedimentation. The formulation showed good stability across all parameters at both temperatures, with a decrease in the active ingredient nearly to 90% after 15 days at 20ºC-25ºC, and after 47 days at 2ºC-8ºC. When administered via simulated nasoenteral tube, 95.75% of the drug was recovered as identified by High Performance Liquid Chromatography (HPLC). The formulation appears stable and represents a suitable option for patients who require enteral administration, simplifying the operations for nursing staff.

Keywords: mycophenolate mofetil; immunosuppressive agents; enteral feeding; pharmaceutical technology; suspensions.

Resumo: O objetivo deste estudo foi avaliar a estabilidade de uma formulação líquida de micofenolato de mofetila (MMF) 10 mg/mL em temperaturas de 20°C-25ºC e 2°C-8ºC. O veículo foi desenvolvido no Laboratório de Farmacotécnica da Universidade Federal do Ceará e as formulações foram monitoradas em relação às mudanças de pH, densidade, viscosidade e sedimentação. A formulação mostrou boa estabilidade através dos parâmetros nas duas faixas de temperaturas, com uma diminuição do princípio ativo próximo a 90% após 15 dias a 20°C-25ºC e 47 dias a 2°C-8ºC. Quando simulado a administração por sonda nasoenteral, 95,75% do fármaco foi recuperado, após avaliação em Cromatografia Líquida de Alta Eficiência (Clae). A formulação apresenta estabilidade e representa uma opção viável para pacientes que necessitam de administração enteral, simplificando a atividade da equipe de enfermagem.

Palavras-chave: micofenolato de mofetil; imunossupressores; nutrição enteral; tecnologia farmacêutica; suspensões.

Resumen: El objetivo de este estudio fue evaluar la estabilidad de una formulación líquida de micofenolato mofetilo (MMF) 10 mg/mL a temperaturas de 20ºC-25ºC y 2ºC-8ºC. El vehículo fue desarrollado en el Laboratorio de Farmacotécnica de la Universidad Federal de Ceará y las formulaciones fueron monitorearon cambios de pH, densidad, viscosidad y sedimentación. La formulación mostró buena estabilidad entre parámetros en ambos rangos de temperatura, con una disminución del ingrediente activo cercana al 90% después de 15 días a 20°C-25ºC y después de 47 días a 2°C-8ºC. Cuando se simuló la administración por sonda nasoenteral, se recuperó el 95,75% del fármaco, previa evaluación mediante Cromatografía Líquida de Alta Resolución (HPLC). La formulación es estable y representa una opción viable para pacientes que requieren administración enteral, simplificando la labor del equipo de enfermería.

Palabras clave: mofetil micofenolato; inmunosupresores; nutrición enteral; tecnología farmacéutica; suspensiones.

1 INTRODUCTION

Mycophenolate mofetil (MMF) is a derivative of mycophenolic acid (MPA), specifically (2-morpholin-4-ylethyl(E)-6 (4-hydroxy-6-methoxy -73-oxo- 1H-2- benzofuran5-yl)-4-methylex-4-enoate) used therapeutically as an immunosuppressant. Pharmaceutically, it is available as a prodrug known as morpholinoethyl ester. MMF is used as adjunctive therapy in prevention of allograft transplant rejection and in the treatment of serious autoimmune diseases.

Some countries face challenges because liquid pharmaceutical forms (LPF) of this drug are needed for pediatrics use and tube administration. The administration via enteral tubes is a challenging because not every solid tablet can be crushed and dispersed and some do not have a registered liquid form in the country. Film-coated, enteric-coated or modified-released tablets are not recommended for administration due to the presence of excipients and the type of coating, which can result in ineffectiveness, toxicity or increased side effects.

Mycophenolate mofetil is not available as a liquid form in Brazil, so for tube administration the drug needs to be dispersed or crushed, but it is a cytotoxic molecule, making the process difficult. In Brazil, according to Director's Collegiate Resolution (RDC) n. 67 (Brasil, 2007), the legislation that approaches good practices for handling magistral preparations states that the pharmaceutical specialty is a product from the industry and it can be altered when there's no a raw material available or when the absence of a dose or concentration recommended to the patient

A 200 mg/mL MMF suspension (Roche LTD) is commercially available but its high cost limits its availability in Brazil. Therefore, the use of this dosage form needs to be judicially approved for government financing. The aim of this study was to evaluate the physical and chemical stability of 10 mg/mL MMF formulation for use in tube administration at 20ºC-25ºC and 2ºC-8ºC, prepared with a sugar free vehicle developed in the Pharmacotechnical Laboratory.

2 MATERIALS AND METHODS

2.1 Materials

MMF tablets 500 mg were donated by Walter Cantidio University Hospital. The standard MMF was obtained from the European Pharmacopoeia Reference Standard. The excipients for the vehicle were obtained from a local distributor (Cequimica, Fortaleza, Ceará) along with other reagents (methanol, phosphoric acid, ultrapure water) for HPLC, and other analysis. In filtration process, nylon membrane 0,45 µm was used (Unifil, Cequimica, Fortaleza, Ceará).

2.2 Equipment

The method was developed using a High Performance Liquid Chromatography system (Fortaleza, Ceará) with the following components: Varian Star Workstation management system version 6.41, Dynamax Rainin Model SD-200 pump (Mettler Toledo, Ohio, United States), 20 µL Rheodyne loop hand injector (Idex Corporation, Illinois, United States), Shimadzu DGU-14A (Shimadzu, Kyoto, Japan) degasser, and Varian ProStar UV/vis (Mettler Toledo, Ohio, United States) detector with photodiode array detectors (PAD).

2.3 Development of chromatographic conditions

To obtain MMF crystals, a 500 mg drug tablet was pulverized, with a mortar and pestle in circular motions to a powder comprising tablets components and the coating. The powder was subsequently transferred to a 50 mL volumetric flask, filled to volume with methanol, and then sonicated for 10 minutes to solubilize the drug. Vacuum filtration was performed to remove impurities from the solution using a nylon membrane filter. The liquid was then transferred to a petri dish, following addition of 50 ml of distilled water, afterwards it was placed in an oven at 60ºC for 24 hours for evaporation. The sample acquired was evaluated for microscopic and macroscopic aspects, and identified using High Performance Liquid Chromatography (HPLC).

The analysis method used was established after, testing mobile phases to determine the MMF content obtained from the tablets. For the MMF - SQR analysis, two mobile phases were compared (MP): (1) methanol:H3PO4 (55:45) and (2) acetonitrile:triethylamine 0,3% (35:65) (Adapted from Brasil, 2019 and Costa, 2009). The conditions were established according to the previous evaluations in bibliographical references and adapted accordingly. The analysis used the C18 column (250x4mm; 5µm) with a flow rate of 1.5 mL min-1. The detection was performed at 250 nm and 45ºC. The experiments employed mobile phases available in Brasil (2019), Costa (2009) and meeting compliance specifications such as capacity factor, and resolution for the high-performance liquid chromatography methodological system.

An aliquot of the solution 1 was tested using a diluent (methanol and water 55:45) at a concentration equal to 100 µg/mL in a chromatogram with MP2 and made the comparison with the MP1. Chromatograms were evaluated at different flow rates and run times in order to show which ones had the best quality criteria attributes such as retention times, tailing factor, theoretical plates and resolution. The selected mobile phase was also used for the same procedure described in solution 2, for comparison purposes. After choosing the mobile phase, quality tests were carried out in relation to the critical process parameters: precision, linearity, selectivity, limit of detection, and limit of quantification with the chosen mobile phase (ICH, 2005).

2.4 Preparation of the samples and the standard

Two solutions were prepared to carry out the identification of the active ingredient. Solution 1 contained 20 mg of the powder obtained from the extraction process of the tablets diluted in 10 mL of methanol. Solution 2 contained MMF – Chemical Reference Substance (CRS) also diluted in 10 mL of methanol. Both solutions were sonicated for 10 minutes after preparation to achieve solubilization, resulting in concentration of 2 mg mL-1.

Following transfer of 1 mL to volumetric flask (VF) to prepare aliquots with concentrations equal to 0.2 mg mL-1, using methanol. A final solution was obtained with theoretical concentration equal to 100 µg mL-1, prepared

using the diluent composed of methanol and water (55:45), according to Brazilian Pharmacopoeia (2019).

2.5 Method evaluation

Evaluation studies were conducted following ICH guidelines (ICH, 2005) to establish optimized assay conditions, adapted from methods mentioned in Brazilian Pharmacopoeia (Brasil, 2019). The method was evaluated for specificity, linearity, limit of detection (LOD), limit of quantification (LOQ), accuracy, and precision.

2.5.1 Specificity

Using solution 1, the selectivity of the method was evaluated by injecting the solution into different degradation media and heating at 60ºC in a water bath for a time interval of 1 to 3 hours. In a test tube, 2 mL of MMF solution was mixed with 2 mL of 1M HCl (acid solution), 1M NaOH (basic solution), 3% H2O2 (oxidative solution) and H2O (aqueous solution). The aqueous samples were kept at room temperature, later they were evaluated by chromatography in triplicate to analyze the degradation within 1, 2 and 3 hours.

2.5.2 Linearity

Using solution 1, aliquots were taken to verify the linearity of the method and make its calibration curve with the same diluent as the samples. Samples were prepared at concentrations of 50, 75, 100, 125, 150 and 175 µg/mL, ranging from 50 to 175% of the concentration intended for the assay. For solution 2, e calibration curve was made using concentrations ranging from 6.25 to 100 µg/mL. All injections were performed in HPLC in triplicate.

2.5.3 Detection and quantification limits

The limits of quantification (LQ) and detection (LD) were calculated based on the slope from the standard deviation of the intercept, obtained from the analytical curve with the equations described below (ICH, 2005).

LD= 3,3 S/a and LQ= 10 S/a, where LD = detection limit, LQ = quantification limit, S = standard deviation of the intercept, a= slope of the analytical curve.

2.5.4 Accuracy and precision

Aliquots were prepared for HPLC injections of solution 1 and 2 from the obtained powder and the SQR, both at equal theoretical concentrations (100 µg/mL). These injections were performed on different days analyzed in triplicate under the same analytic conditions. Six determinations were conducted, evaluating the precision and accuracy by repeatability analysis. The results were expressed as the relative standard deviation (RSD%) and the accuracy as percentage (%) deviation in relative to the mean concentrations observed in relation to the nominal value of the concentrations used.

2.6 Mycophenolate mofetil dispersion preparation

MMF suspension (10 mg/mL) was prepared in a laminar flow hood. For this purpose, 27 tablets (500 mg each) were triturated in a mortar after the average weight was done and then mixed in a mechanical stirrer with 67,5g from the vehicle named GUTE, prepared in the laboratory with 1.350 mL from distilled water. The contents were transferred into 14 amber bottles with 100 mL. Four bottles were maintained at 2º to 8ºC for 63 days and eight bottles at ambient temperature (25ºC, approximately) at the same period and one bottle was used on the day that the formulation was made to the tests. The samples were exposed to room light only when the tests were done, but were used amber bottles.

2.7 Formulation physicochemical stability study

The evaluation was made during a period of 63 days, with the amount available. Macroscopy conditions like visual appearance, color, odor and other tests as pH, drug amount, density and viscosity were analyzed according to Brazilian Pharmacopoeia (2019) and ICH (2005). Before initiating the analyses with the suspensions, it was vigorously shaken with hand for 1 minute. The pH was verified in every sample and determined at room

temperature with a calibrated pHmeter (Digimed – DM20®, Fortaleza, Ceará). The smell was evaluated in a beaker, as a visual analysis of resuspension and sedimentation. The density was analyzed using a clean and dry pycnometer verifying its weight and comparing with the weight after the formulation add and applying the equation d=M/V in all formulations. The viscosity was evaluated for rheological properties over time in all the samples using a viscometer (Haake Viscotester® 6L, Fortaleza, Ceará) and with spindle L1 the results was transcribed in a spreadsheet with the information of rotations per minute (RPM) in centipoise (cP).

The dosing test was realized in HPLC with a C18 column, 250 x 4,4mm; 5µm at 250 nm ultraviolet detector at 45ºC with mobile phase flow of 1,5 mL/minute. The mobile phase used, methanol: phosphoric acid (55:35 v/v), this information was adapted from Brazilian Pharmacopoeia (2019) to adjust the retention time and avoid interferences in analysis. The 2g (about 20 mg MMF) formulation was weighed into a 10 mL volumetric flask and put to sonicated for 10 minutes. Samples were then prepared at a concentration of 100 µg/mL for each formulation and subjected to HPLC analysis (Brasil, 2019; Sousa, A. et. al., 2014). Each sample was passed through microscopy analysis in order to identify the presence of the crystals in the suspension. Optical microscopy was used and images were captured and processed using a computer photograph program. The shelf life was calculated by the arrhenius equation comparing in zero, one and two orders using the drug amount result.

2.8 Nasoenteral and nasogastric tube administration test

To evaluate the substance's loss in tube, a simulation was made for administration using nasoenteral and nasogastric tubes. First the tubes were washed with ultrapure water. Then, using a syringe, each tube was filled with the MMF formulation (10 mg/mL) to the 50 mL volumetric flask. Subsequently, 10 mL of ultrapure water was added to wash the tube again and the rest of the capacity was completed with methanol and agitated. Then an aliquot of 5 mL was retired and to a 10 mL volumetric flask and sonicated for 10 minutes, after that an aliquot with the supernatant of 100

µg/mL was made with diluent methanol: ultrapure water (55:45) and subjected for HPLC analysis for each tube.

3 RESULTS AND DISCUSSION

3.1 Development and optimization of analytical method

In the optimization methods studies, using the MP1, the peak in the chromatogram showed better standards according to the quality criteria attributes. The peak observed in the chromatogram under the analysis conditions of MP2 showed asymmetric peaks with retention time above 10 minutes and additional peaks were visible, compared to the baseline. Further tests were made using C8 columns and variant concentrations of acetonitrile and triethylamine. However, these experiments did not have symmetrical identification or a precision identification. Therefore, MP1 was selected for the tests in this study. The MP1 method demonstrated reproducible retention time and better efficiency compared to MP2. Moreover, the suitability parameters for MP1 were considered satisfactory, with tailing factor 1,44, number of theoretical plates 53.424 and capacity factor 1,26. While, MP2 shows the following results: tailing factor 0,6, number of theoretical plates 38.248 and capacity factor 0,4.

In MMF suspensions tests, it was shown that there were overlapping peaks with the use of the mobile phase concentration (A) 55:45 methanol and 0.05% phosphoric acid, so the adjustment was made to a concentration (B) 65:35 methanol and 0.05% phosphoric acid to facilitate the identification of the drug peak. Resolution calculations were also performed to verify the impact of changing the mobile phase on this parameter. The concentration (A) resolution result was equal to 7,86 after the changes to concentration (B) resolution had increased to 17,7.

The use of MMF solutions in alkaline, acidic, oxidative and aqueous media did not show perceptible macroscopic changes over time in degradation, but the formation of degradation products was noticeable in HPLC and it did not interfere in the drug peak. With the chromatograms generated by the forced degradation test, it can be seen that the greater degradation

tendency is concentrated in alkaline and oxidative environments. The acidic sample demonstrates degradation, but a lesser extent than the other sample. The unheated aqueous medium served as a comparison parameter for the other analyses and the tests showed that the method has specificity to separate the degradation products from the drug.

The method showed linearity (r2=0,9985) across standard solutions concentrations ranging from 6.25 to 100 µg/mL. The slope and the intercept were 14,454 and 14,379, respectively. The method demonstrated high sensitivity, with LOD and LOQ values of 0.099 and 0.299, respectively. MMF determinations were carried out within the established using solution 1, derived from powder pills extraction, and solution 2 prepared with the SQR. Six samples were taken, with a nominal concentration of 100.3, which were evaluated for repeatability on the same day. The results showed accuracy of 100.3%, a standard deviation of 1, and a coefficient of variation of 0.070%, meeting pharmacopeial requirements (Brasil, 2019).

3.2 Physicochemical stability study

Mycophenolate mofetil formed a bright pink, translucent suspension, the color presented is because of the revestment from the pill. No changes in color or smell in the entire period were analyzed despite the presence of dispersed white particles. All formulations showed satisfactory redispersion when agitation was made. None degradation was verified for gasses production when a film paper sealed the beaker in 14 days. In all microscope's analysis, cylindrical crystalline forms from MMF were present.

The initial percentage of MMF in suspensions and the remaining substance were measured over several days at controlled temperatures (room temperature and refrigerated). The expressed value was obtained as the mean of three injections with a maximum of 2% relative standard deviation (Table 1).

In that experiment, the amount of mycophenolate mofetil for suspensions samples in the remaining test at room temperature dropped below 90% after 7 days, while at refrigeration temperature it remained above 90% up to 42 days. In the refrigerated storage conditions, a minor reduction of the

MMF remaining was observed, demonstrating more stability, indicating that temperature has an influence on the drug amount. The difference between the samples in terms of amount can be explained for water evaporation from the bottle, ineffective dispersion of MMF, or potential drug photolysis which was not measured. According to The United States Pharmacopeia (USP-NF, 2015) the acceptable levels of mycophenolate mofetil in tablets are not less than 90,0% and not more than 110,0%, so the drug concentration was considered stable from the initial concentration.

Table 1 – The percentage of initial amount of mycophenolate mofetil remaining, after the storage at room (15°C-30ºC) and refrigerated (2°C-8ºC) temperature

Room Temperature (15°C-30ºC)			Refrigeration Temperature (2°C-8ºC)	
Time (days)	MMF remaining	RSD (%)	MMF remaning	RSD (%)
0	97,24%	1,39	97,24%	1,39
7	86,34%	0,99	-	-
14	83,10%	0,78	90,62%	2,04
21	83,09%	1,07	-	-
28	87,74%	1,55	99,52%	1,46
35	90,14%	0,91	-	-
42	93,51%	0,92	89,97%	1,24
49	117,19%	0,46	-	-
56	78,71%	1,54	86,46%	0,91
63	73,33%	1,68	-	-

Source: prepared by the autors

The pH measurements in formulations at 20ºC-25ºC had similar results over time, starting at 6.81 on day 0 and decreasing to 5.58 in the last sample. In the first two months, the variation was smaller, from 6.81 to 6.15, and in samples stored at 2°C-8ºC, the variation was the smallest, from 6.81 to 6.69. At very basic pH levels, it has been shown that mycophenolate is converted almost entirely in MA, according to chromatography analysis. Even in cases of administration by tubes, it is recommended to change mycophenolate

sodium for mycophenolate mofetil because of the enteric coating present in the former, under the risk of obstruction (Wanden-Berghe *et al*., 2019). In general, all the samples at different conditions had results close to each other with slightly acid values, which are more recommended for oral liquid dosage forms, because the pH tolerated in oral liquids is 2-9 (Attebäck; Hedin; Mattsson, 2022; Foley *et al*., 2021).

The density results were constants in both temperatures analyzed. At 20°C-25ºC had an average equal to 1,0273 (± 0,0021) and at 2°C-8ºC samples with an average equal to 1,0272 (± 0,0016). The density, remained stable throughout the evaluation process and, in addition to the non-formation of gasses, suggest good resistance to the development of fermenting microorganisms. Additionally, it shows that precipitation takes longer than 24 hours and that redispersion is simple, indicating a low likelihood of precipitate leftovers remaining in the tube. This is very significant as remnant can result in agglutination processes and cause obstruction (Zajicek *et al*., 2014).

The viscosity had a smaller drop when stored under refrigeration compared to storage at ambient temperature The relative drop was 9.46% at ambient temperature and 36.86% in refrigerated temperature when compared to the initial viscosity. The fluid showed pseudoplastic flow, similar to others formulations with GUTE (Batista, 2014; Medeiros, 2014; Sousa, E. *et al*., 2014), where viscosity decreases with increasing shear force (speed in rpm). Thus, with the formulation at rest, its viscosity is high with a decrease in the sedimentation of the particles, providing physical stability to the formulation. However, with agitation, it becomes less viscous. Another advantage of this formulation is that it is not syrup based, causing administration through the tube more feasible, as it is a less viscous liquid and does not have high amount of excipients that often cause gastrointestinal disorders (Waitzberg, 2017; Yellepeddi, 2020).

The GUTE vehicle is a liquid developed by the Pharmacotechnical Laboratory of the Federal University of Ceará to facilitate manipulation at an affordable cost. It is being intended for children, but enabling the use of solid dosage forms as extemporaneous formulations for those that lack manufacturing or validation of liquid forms by health agencies in Brazil. Consequently, its use in the administration in probed patients becomes

viable in view of its simple, and safe formulation. It is composed (excipients) of: xanthan gum, mannitol, methyl and propyl parabens, sucralose and purified water (Batista, 2014).

The selection of excipients for this formulation was considered based on several pharmacotechnical criteria, such as the choice of a non-calorigenic sweetener, and avoiding complications that are related to glycemia (Medeiros, 2014; Boullata, 2020). Similarly, polyhydric alcohols with sweeteners were avoided, which are linked to various gastrointestinal disorders, such as diarrhea, colic, abdominal distension, and vomiting when used in tubes, especially sorbitol (Motta *et al*., 2021).

Fahimi *et al*. (2012) study evaluated a formulation prepared in the hospital environment and concluded that a preparation with the powder present in the drug capsules can be used for 14 days at 5ºC. Venkataraman *et al*. (1998) study MMF suspension with concentration equal to 50 mg/mL, analyzing its stability by HPLC. They obtained a final pH of 6.1, with no color change and without positive microbial cultures and found that it was stable at 5ºC for 121 days. In another study, Swenson *et al*. (1999) formulated a suspension at 100 mg/mL, showing stability at 23 to 25ºC for 120 days, but the flavoring agent used was only stable for 28 days.

These above studies (performed the addition of a syrup in their formulation and did not report tests related to use in tubes. Thus, the formulation developed in this study becomes a crucial option for use in tubes and pediatrics presenting stability of around 15 days at room temperature and 40 days when stored between 2 and 8ºC.

3.3 Study of degradation kinetics and shelf life determination

The pertinent analyzes infer that it corresponds with a better correlation as kinetics of order two, that is, the data are placed inversely of the concentration in relation to time. MMF has a degradation correlation rate equal to (r^2= 0.956) in relation to the content at room temperature, indicating a shelf life of approximately 14 days.

The samples at refrigerated temperature had longer shelf life, but with low correlations when the contents were analyzed, therefore, in a

more sensible way the application of the shelf life should meet the one that obtained the best correlation with the content. But bringing the relevance of other stability tests, it can be understood that the shelf life of 14 days stored at refrigerated temperature tends to be the most appropriate choice to meet the purposes of administering the drug in the idealized formulation.

3.5 Nasoenteral and nasogastric tube administration test

With the results obtained, it is inferred the possibility of administration by suspension with both techniques, but preferably by nasoenteral tube. The material present in the probe may favor the loss of the drug and this may compromise the therapy. With the result remaining greater than 90% (Table 2), it is possible to maintain the appropriate therapeutic dose for the patient using the developed suspension administered via tube.

Table 2 – Values obtained from the experimental comparison experiment of administration the suspension developed by NET (Nasoenteral tube) and NGT (Nasogastric tube); (*) representative of the control concentration of the sample taken for testing

	SUSPENSION			NET			NGT		
Injections	1	2	3	1	2	3	1	2	3
Areas	997	1027	990	963	970	953	897	906	939
Average	1004,67			962			914		
Absolut Concentration	100 µg/mL*			95,75 µg/mL			90,98 µg/mL		
Amount (%)	100%			95,75%			90,98%		

Source: prepared by the autors.

With the analysis of administration in tubes, it was observed that in the nasogastric tube, a greater amount of the active ingredient content was obtained, as well as a better fluidity during the transfer to the volumetric flask. Unlike the nasogastric tube, which showed less fluidity and noticeable traces of the formulation that can be recorded with the naked eye. These results emphasize that using a nasoenteral tube for administrating the formulation can beindicated, as it is commonly occurring in clinical practice., Polyurethane or silicone material are preferred for such tubes due to

their flexibility, malleability and biocompatibility (Pereira *et al*., 2020). The nasogastric tube is generally used for gastric lavage in conditions such as examinations in case of digestive system or surgeries, bleeding stagnation, and for nutritional diet (Waitzberg, 2017).

The limitations of this study included lack of microbiological evaluation. However, the density and pH stability suggest that the formulation was not contaminated with fermenting microorganisms and gas development was not observed. The tube test needs more attention for interactions with coadministred nutrition and evaluation with different sizes and models.

4 CONCLUSIONS

Despite the necessity of the optimization and adaptation of the method, the quality parameters tests using HPLC method to determine mycophenolate mofetil was satisfactorily evaluated. For safe administration, considering the variability in results, especially in the amounting test, the formulation should be used for maximum of 14 days and stored at refrigerated temperature (2°C-8ºC) to ensure stability.

The formulations could serve as an alternative in countries that do not have the MMF suspension and an option for use in hospitalized patients who are unable to use the solid pharmaceutical forms. The physicochemical study results showed the stability for 14 days at refrigerated temperature. The formulation could be incorporated in hospital routines, with careful assessment of dose concentration adjustment and understanding the drug use routine.

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