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Evaluation of the physico-chemical stability of the adapted oral pharmaceutical form of mycophenolate mofetil

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Abstract

Objective: To evaluate the physicochemical stability of the adapted oral suspension of mycophenolate mofetil tablets developed by a university hospital in Paraná, in order to determine the concentration of the active ingredient present in the oral suspension over time, assess the homogeneity of the drug concentration during the administration of the doses and establish a shelf life consistent with the stability of the adapted pharmaceutical form. **Method:** Mycophenolate mofetil tablets were used to make suspensions in two different concentrations- 50 mg/mL and 100 mg/mL- using sorbitol and water as vehicles (1:1) and adding a flavoring agent. The chromatographic analysis of the samples was carried out at times (T): T0h, T24h, T48h, T120h and T168h. The chromatographic conditions used for high-performance liquid chromatography were adapted from the United States Pharmacopeia. **Results:** The average relative standard deviation of the three batches analyzed at each time and concentration ranged from 6 to 18%, establishing an acceptable variability in the data obtained, but signaling the inhomogeneity of the active in the suspension. In the chromatographic analysis, the drug concentration values obtained in the formulations were satisfactory for all the times analyzed, with the values for T0h, T24h, T48h, T120h and T168h being 100%, 99.3%, 97.2%, 106.6% and 96.8% respectively. No physical changes were observed during the analysis period. The formulation showed physicochemical stability in an amber glass bottle, protected from light and at room temperature for 7 days. **Conclusion:** It was possible to validate the stability of the proposed formulations for seven days at room temperature and in an amber glass bottle. It is important to develop further studies on oral liquid formulations adapted from mycophenolate mofetil tablets.

Keywords: mycophenolate, oral suspension, stability, liquid chromatography.

Avaliação da estabilidade físico-química da forma farmacêutica adaptada de uso oral do micofenolato de mofetila

Resumo

Objetivo: Avaliar a estabilidade físico-química da suspensão oral adaptada de comprimidos de micofenolato de mofetila desenvolvida por um hospital universitário no Paraná, a fim de determinar a concentração de princípio ativo presente na suspensão oral no decorrer do tempo, avaliar a homogeneidade da concentração do fármaco durante a administração das doses e estabelecer um prazo de validade condizente com a estabilidade da forma farmacêutica adaptada. **Método:** Utilizou-se comprimidos de micofenolato de mofetila para manipular suspensões em duas concentrações diferentes- 50 mg/mL e 100 mg/mL – utilizando-se sorbitol e água como veículos (1:1) e adicionando um flavorizante. A análise cromatográfica das amostras foi realizada nos tempos (T): T0h, T24h, T48h, T120h e T168h. As condições cromatográficas utilizadas para a cromatografia líquida de alta eficiência foram adaptadas da United States Pharmacopeia. **Resultados:** O desvio padrão relativo médio dos três lotes analisados em cada tempo e concentração teve uma variação de 6 a 18%, estabelecendo uma variabilidade aceitável nos dados obtidos, mas sinalizando a não homogeneidade do ati;vo na suspensão. Na análise cromatográfica, os valores de concentração do fármaco obtidos nas formulações foram satisfatórios para todos os tempos analisados, sendo os valores do T0h, T24h, T48h, T120h e T168h, respectivamente, 100%, 99.3%, 97.2%, 106.6% e 96,8%. Não foram observadas alterações físicas durante o período analisado. A formulação apresentou estabilidade físico-química em frasco de vidro âmbar, ao abrigo da luz e em temperatura ambiente por 7 dias. **Conclusão:** Foi possível a validação da estabilidade das formulações propostas de sete dias em temperatura ambiente e em frasco de vidro âmbar. Destaca-se a relevância do desenvolvimento de mais estudos acerca de formulações líquidas orais adaptadas a partir dos comprimidos de micofenolato de mofetila.

Palavras-chave: micofenolato, suspensão oral, estabilidade, cromatografia líquida.

Introduction

Mycophenolate mofetil (MMF) is a prodrug belonging to the class of immunosuppressive drugs, widely used in the prophylaxis of organ rejection in post-transplant treatments[1].

This prodrug is also used in Hematopoietic Stem Cell Transplantation (HSCT), which involves replacing diseased or deficient bone marrow with healthy bone marrow cells to restore hematopoiesis[2]. Due to the intense immunosuppression caused by chemotherapeutic agents during the conditioning phase, transplanted patients experience bone marrow aplasia, characterized by significant immune deficiency, making them susceptible to infectious complications such as viral, bacterial, fungal, and parasitic infections, as well as non-infectious complications such as hepatic veno-occlusive disease (VOD), mucositis, pulmonary injury, and graft-versus-host disease (GVHD), the latter being the most severe and potentially fatal complication in allogeneic transplants[3].

In this context, the main groups of immunosuppressive agents include glucocorticoids, calcineurin inhibitors, antiproliferative agents, mTOR inhibitors, and biological therapies. To maintain immunosuppression, a combination of a calcineurin inhibitor (e.g., cyclosporine or tacrolimus), glucocorticoids, and an antimetabolite (e.g., azathioprine or mycophenolate mofetil[3,1]) is generally used. The active metabolite of mycophenolate mofetil, mycophenolic acid, is a potent, selective, non-competitive, and reversible inhibitor of the inosine monophosphate dehydrogenase (IMPDH) enzyme. This enzyme plays a crucial role in purine synthesis, especially in the formation of guanosine nucleotides, essential for RNA and DNA synthesis. B and T lymphocytes heavily depend on this pathway for their cellular proliferation, whereas other cell types can utilize alternative pathways. For this reason, mycophenolic acid selectively inhibits the proliferation and functions of lymphocytes, including antibody production, cellular adhesion, and migration[1,4].

For oral administration, MMF is available in Brazil only in the form of 500 mg tablets. The suspension form, 200 mg/mL (Roche Products Ltd, United Kingdom), is not available and is not manufactured in the country[5].

The absence of commercially available liquid oral forms is a common concern in various clinical settings. To address this challenge, adapting pharmaceutical forms has become a common practice in hospital environments, especially for pediatric patients, patients with feeding tubes (nasogastric, nasoenteric, or gastrostomy), patients with swallowing difficulties, and others facing limitations in conventional medication administration[6].

Adapting a pharmaceutical form means modifying it to make it suitable for administration, considering the needs of the patient and the multidisciplinary team. The practice of "adaptive pharmaceutics" is a highly complex and responsible activity assigned to the pharmacist and their team. It requires specific infrastructure that complies with good compounding practices[6].

The preparation of liquid oral formulations poses various risks, such as formulation failure, microbial contamination, calculation errors, raw material quality issues, patient acceptability, health safety risks, and specific clinical risk factors depending on the preparation site. However, the risks associated with preparation tend to decrease when liquid oral formulations are prepared by pharmacists in compounding pharmacies[7].

Despite this scenario, challenges persist in masking the unpleasant taste of the solution and ensuring dose uniformity to guarantee the correct drug dosage. Additionally, the literature offers limited[7] information on the stability, storage conditions, packaging, and handling techniques for the preparation of extemporaneous formulations.

This study evaluated the physicochemical stability of the oral suspension adapted from mycophenolate mofetil tablets developed by a university hospital in Paraná using an adapted high-performance liquid chromatography (HPLC) method. The objectives were to determine the concentration of the active pharmaceutical ingredient in this adapted oral suspension over time, assess the homogeneity of mycophenolate mofetil concentration during dose administration, and establish a shelf life consistent with the stability of the adapted pharmaceutical form.

Methods

Preparation of Samples

The adapted oral suspensions used as samples were prepared in the pharmaceutics sector of the Hospital de Clínicas Complex of UFPR. Mycophenolate mofetil 500 mg tablets from three different batches and expiration dates (Table 1), all from the Accord brand, were used. Suspensions were compounded from each batch at concentrations of 50 mg/mL and 100 mg/mL, commonly prescribed for routine patient care. The preparation of the suspensions followed the same methodology: for the first concentration, one 500 mg tablet was used, and for the second, two 500 mg MMF tablets and water q.s. to 10 mL. The tablets were individually placed in a mortar, crushed with a pestle, moistened with a small amount of water, and left to stand for 15 minutes. They were then ground with the pestle until a paste-like consistency was achieved. The contents of each mortar were completely transferred to a beaker, where the volume was adjusted with the remaining water, and sorbitol was added in a 1:1 ratio. Three drops of cherry-flavored flavoring were added to mask the taste. The suspensions were then transferred and stored in amber glass bottles with dropper caps. The samples were kept at room temperature (20°C ± 5) and protected from light. This process resulted in six suspensions with the following concentrations: Batch 1 50 mg/mL, Batch 1 100 mg/mL, Batch 2 50 mg/mL, Batch 2 100 mg/mL, Batch 3 50 mg/mL, and Batch 3 100 mg/mL, enabling triplicate analysis at two distinct concentrations routinely used at the institution.

Table 1. Batch numbers and expiration dates of mycophenolate mofetil tablets.

	Batch 1	Batch 2	Batch 3
Batch Number	M2207	M2300245	M2212394
Expiration Date	30/05/2024	30/04/2025	30/08/2024

Preparation of Standard Solution and Calibration Curve

The experimental analysis was performed in the chromatography laboratory of the Pelé Pequeno Príncipe Research Institute. The standard used was the pharmacopeial reference standard for mycophenolate mofetil 100 mg, produced by Toronto Research Chemicals with 98% purity, Batch 20-X-JZ-32-1. A 50 µg/mL standard solution was prepared using a water and acetonitrile solution (1:2) as solvents and subjected to equipment for active ingredient identification. From the standard solution, a calibration curve was constructed with a concentration range of 1, 10, 25, 50, 75, and 100 µg/mL of mycophenolate mofetil. The curve was

obtained through a graph plotting the proportions of analyte peak areas in the solutions versus analyte concentrations, with analysis by linear regression.

HPLC Method

The presence and concentration of MMF in the adapted oral suspension were determined using an HPLC method adapted from the United States Pharmacopeia (USP)[8] and the study by Seebacher et al. (1999)[9]. The compounds were separated using a Shimadzu Prominence LC-20AT chromatograph equipped with two pumps (one quaternary and one isocratic), an automatic injector, a column oven, and a photodiode array (PDA) detector. An Ascentis® C18 column (15 cm x 4.6 mm, 5 µm) was used, and two mobile phases (MP) were employed: MP A consisted of a water and 0.05% phosphoric acid solution (V/V), and MP B consisted of acetonitrile. The flow rate was set at 0.5 mL/min. The gradient program started with 20% MP A for the first 8 minutes, transitioned to 80% MP B from 8 minutes onward, remained stable until 13 minutes, and then returned to 20% MP A, stabilizing from 15 minutes to the end of the run. The injection volume was 10 µL, with a total run time of 20 minutes. The column oven temperature was 40°C, and the analysis wavelength was 305 nm.

Sample Analysis

Chromatographic analysis of the samples was performed at intervals of 0h, 24h, 48h, 120h, and 168h after the preparation of the adapted suspensions. At each established time point, an aliquot was collected from each of the three batches of both preparations (50 mg/mL and 100 mg/mL) and diluted in an acetonitrile and water solution (2:1) to achieve the working concentrations of 25 µg/mL and 100 µg/mL. This process resulted in 12 preparations (Table 2).

The solutions were filtered using a 0.45 µm filter, transferred to HPLC tubes, and analyzed in triplicate.

Table 2. Preparations Obtained After Dilutions.

Batch	Concentration (mg/mL)	Working concentration (µg/mL)
1	50	25
		100
	100	25
		100
2	50	25
		100
	100	25
		100
3	50	25
		100
	100	25
		100

Organoleptic Analysis of Samples

The organoleptic analysis of the samples was performed based on the Brazilian Pharmacopeia[10]. Changes in color, odor, and appearance were evaluated at 24h, 48h, 120h, and 168h relative to 0h. The organoleptic evaluation of the color and appearance of the suspension was performed visually at room temperature under white ambient light against a white and black background. The odor evaluation was conducted using the human sense of smell.

Results

In the chromatographic analyses of the sample solutions, the main retention peak coincided with the retention time of the standard solution, as shown in Image 1. Therefore, the retention time of the samples, approximately 9.4 minutes, confirmed the presence of MMF in the analyzed solutions.

The calibration curve for MMF, used to evaluate the linearity of the assay method, demonstrated linearity between concentrations of 1 to 100 µg/mL, as shown in Image 2. The method exhibited appropriate linearity with a determination coefficient (R^2) of 0.999.

To assess variability relative to the mean, the mean relative standard deviation (RSD) of the concentration values obtained from the three analyzed batches at each time point and concentration was calculated. The results showed an RSD ranging from 6% to 18%, with the greatest variation in active ingredient concentration observed in aliquots collected from the 100 mg/mL oral suspension at both working concentrations analyzed (25 and 100 µg/mL) at 24 and 48 hours, as shown in Table 3.

Table 3. Values of relative mean standard deviation and average concentration of samples at 25 µg/mL and 100 µg/mL over time.

Solution 25 µg/mL					
	0h	**24h**	**48h**	**120h**	**168h**
Average µg/mL	25.42	25.32	24.64	26.3	25.4
Average DPR (%)	6.03	12.68	18.10	6.68	6.01
Solution 100 µg/mL					
	0h	**24h**	**48h**	**120h**	**168h**
Average µg/mL	104.57	103.58	100.68	107.2	104.02
Average DPR (%)	6.31	12.45	17.73	6.46	5.54

The stability of the drug concentration in the formulation was evaluated by correlating the mean concentration values obtained from the analyses with the values at T0h, which was considered 100%. The Brazilian Pharmacopeia[10] stipulates that the active ingredient content in the adapted formulation at T0h should be at least 90% and at most 110% of the declared active ingredient content on the label. The values obtained were satisfactory for the analyzed period, with the active ingredient concentration representing 100% at T0h, thus meeting pharmacopeial requirements. For 24h, 48h, 120h, and 168h, the values were 99.3%, 97.2%, 106.6%, and 96.8%, respectively, as detailed in Table 4, demonstrating that the formulations remained chemically stable in terms of active ingredient content during the analyzed period.

Regarding the physical stability of the adapted oral suspensions, no changes in the organoleptic characteristics of the samples were observed, with no alterations in color, odor, or appearance. No crystallization or other changes in the appearance of the analyzed suspensions were detected up to T168h. As expected for a suspension, sedimentation of the solid particles in the formulation occurred; however, redispersion was easily achieved after vigorous manual shaking.

Figure 1. (A) Chromatogram obtained from the standard solution. (B) Chromatogram obtained from the sample solution of 50 mg/mL at a working concentration of 25 µg/mL at T(0).

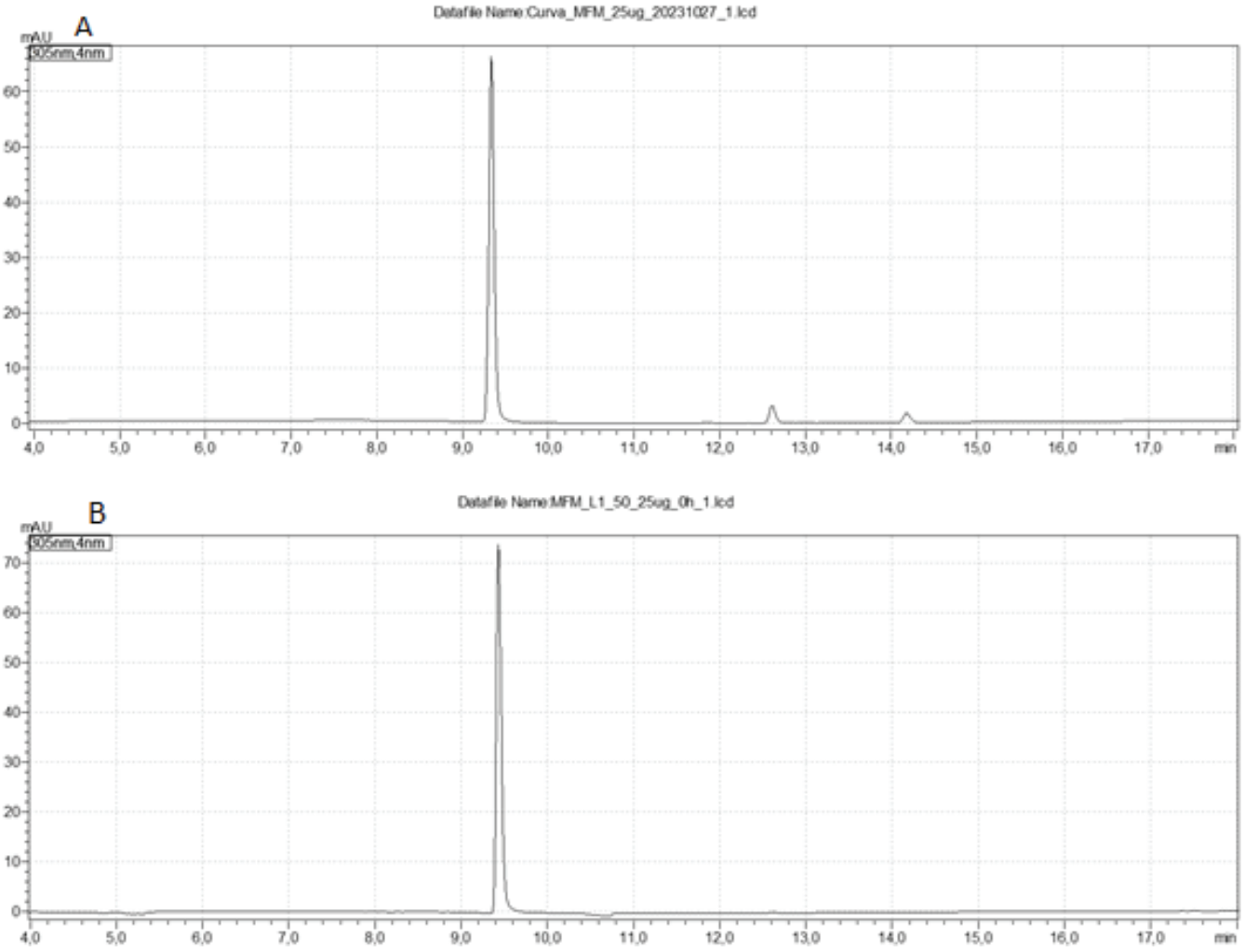
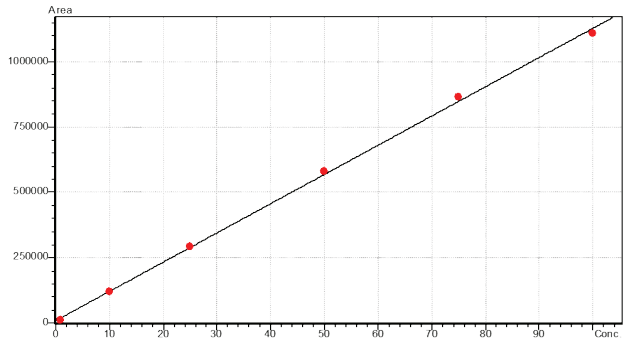


Figure 2. Calibration curve of mycophenolate mofetil.



R^2 = 0.999 y = 11189.2 x + 9329.72.

Discussion

The proposed adapted HPLC method proved efficient for the separation, identification, and quantification of the drug in the samples.

The calculation of the mean relative standard deviation (RSD) revealed variability ranging from 6% to 18%, indicating the non-homogeneity of the active ingredient in the suspension.

The MMF oral suspensions were prepared at two commonly prescribed concentrations, 50 mg/mL and 100 mg/mL. The 100 mg/mL concentration showed greater variability in the active ingredient concentration across aliquots, which can be attributed to the high amount of excipients in the tablets that are insoluble in the vehicles used. This led to a suspension comprising powders of different granulometries, complicating sample homogeneity. Additionally, the water immiscibility of MMF exacerbates the challenge, underscoring the need for a formulation with greater compatibility with the active ingredient.

According to the study by Anaizi et al. (1998)[11], MMF is soluble in methanol, and its solubility in water is pH-dependent, being 43 µg/mL at pH 7.4 and 4.27 mg/mL at pH 3.6. The aim of the study focused on evaluating the stability of MMF in an extemporaneous oral solution prepared from 250 mg capsules in a cherry syrup vehicle at a concentration of 100 mg/mL, adjusted to pH 5.1, stored at room temperature and in a refrigerator for up to 121 days. The analysis of the sample concentrations was carried out using the HPLC method. The results obtained by the authors

Table 4. Correlation between average concentration values and percentage relative to T0h for samples at concentrations of 100 µg/mL and 25 µg/mL.

100 µg/mL			
Analyzed Time (h)	**Average Concentration of Prepared Batches at 100 µg/mL**	**% Relative to T0h**	**Compliance with the Brazilian Pharmacopoeia**
0h	104.6±0.04	100	Agreed
24h	103.6±0.02	99.06	Agreed
48h	100.7±0.04	97.2	Agreed
120h	107.2±0.17	106.5	Agreed
168h	104.02±0.18	97	Agreed
25 µg/mL			
Analyzed Time (h)	**Average Concentration of Prepared Batches at 25 µg/mL**	**% Relative to T0h**	**Compliance with the Brazilian Pharmacopoeia**
0h	25.42 ±0.05	100	Agreed
24h	25.32 ±0.04	99.6	Agreed
48h	24.64 ±0.12	97.3	Agreed
120h	26.3 ±0.09	106.7	Agreed
168h	25.4 ±0.02	96.5	Agreed

showed that the initial pH of the oral suspension (6.1) remained stable in both storage conditions, with no differences between them, and no changes were observed in the physical aspects of the suspension. The drug concentration remained above 90% in all samples over the 121 days analyzed, demonstrating the great stability of the proposed formulation.

A stability study of a formulation for extemporaneous use, conducted by Fahimi et al.[12], analyzed the stability of MMF capsules and tablets in oral suspensions using Ora-Plus and simple syrup as vehicles, with pH adjusted between 5 and 6, stored in amber glass bottles. The suspensions were kept at 5, 25, and 40°C for 50 days and exposed to light, with concentration monitored by HPLC. After 50 days, samples stored at 5 and 25°C showed no physical changes, while those stored at 40°C darkened. The suspensions prepared with tablets maintained stable concentrations, while those prepared with capsules showed a significant loss of concentration after 28 days, suggesting that the use should not exceed 14 days.

As shown in the studies presented above, the suspensions remained stable over time. Although the studies were conducted with different bases from the one used in this study and measured the pH, we can use the results as a guide in the research line of MMF suspension stability. Furthermore, analyzing the results of the aforementioned studies, it is noticeable that the solubility of mycophenolate mofetil in water can be increased depending on the pH value, which makes monitoring this parameter in preparations necessary. In the present study, pHmetry was not performed because the institution where the analysis was developed is a public hospital and did not have the necessary equipment for this measurement. Moreover, the feasibility of including this parameter in the routine of preparation is questioned, both due to the availability of resources and equipment for such measurement, and the impact on the agility of the preparation and dispensing of the medication.

Additionally, a formulation with a pH-dependent solubility active ingredient becomes more complex, as it requires the inclusion of acidifying or alkalizing agents to maintain the ideal pH. Therefore, the lack of pH analysis is a limitation of the study and should be addressed in future research.

The HPLC method used in this study to analyze the concentration of the samples over time showed that the concentration of the formulations remained stable and within pharmacopeial standards for a period of 7 days, supporting the possibility of extending the current expiration period at the institution, which is 2 days.

According to the National Formulary of the Brazilian Pharmacopoeia[13], since the manipulated medication is produced in a personalized manner to meet the specific needs of the patient and is used immediately, no expiration date is established, but rather a usage limit date (use period). This period can vary from a few days to months, as the stability of extemporaneous products varies from one formulation to another, which presents a significant challenge.

For formulations already described in the literature, the use period should be determined according to what is established in the compendiums and published studies. In cases where the formula is not found in the literature, it is the responsibility of the pharmacist to develop it based on scientific principles, requiring a careful analysis of: a) the potential degradation of the active ingredient by oxidation, hydrolysis, photolysis, or thermolysis; b) the interactions between the excipients and the active ingredient, especially if tablets or capsules are used as the source of the drug, when it is not available on the market; c) the most suitable packaging to protect the product from environmental factors that may affect its stability; d) the most suitable formulation, balancing stability and the suitability of the dosage form to facilitate administration; e) the storage conditions, conservation, and considerations for assigning a use period to the formulation[13].

The United States Pharmacopeia (USP)[14], through Chapter 795 on non-sterile preparations, provides a table containing the maximum recommended use periods for compounded non-sterile drug preparations that are packaged in light-resistant, airtight containers and stored at controlled room temperature when no specific stability information is available in the literature for the formulation in question. According to the USP table, the oral suspension of MMF analyzed in this study falls under the use period established for oral formulations containing water, which would be a maximum of 14 days stored at controlled cool temperatures.

Liquid formulations for oral use may present greater complexity when compared to solid forms. This is because it is necessary to

add various components to make the pharmaceutical form more suitable, such as the vehicle, preservatives, suspending agents, viscosity modifiers, among others. Moreover, the excipients in the commercial product can pose a challenge for the compounding pharmacist, as there are potential interactions between the components of the commercial product and those added during compounding, as well as possible solubility incompatibilities[13].

In the present study, sorbitol was used as the vehicle. It is known that poor absorption of this substance can trigger laxative effects (osmotic diarrhea), bloating, and abdominal discomfort in sensitive individuals[15,16,17], which may aggravate one of the most common side effects of MMF use, which is diarrhea. However, there is considerable intra- and inter-subject variability in the threshold for sorbitol intake to induce gastrointestinal symptoms, which seems to be dose-dependent. For example, most tolerant individuals can ingest 10g of sorbitol without experiencing any gastrointestinal symptoms[15].

Considering the above and the fact that sorbitol is the only available vehicle in the institution for oral preparations, being cost-effective and chosen as an adjunctive pharmaceutic vehicle to control the preparation's taste, it was decided to continue the project using this vehicle. Additionally, the preparation being studied has an unpleasant taste, especially for children. When prepared only with water, the taste of the preparation is very poor, causing nausea and vomiting in patients. To improve treatment adherence, sorbitol and flavoring were added. Therefore, the use of sorbitol as a vehicle is a limitation of the study and should be explored for substitution with other cost-effective vehicles in future studies.

The aforementioned immiscibility of MMF in water presents a difficulty not only for performing analytical tests and compounding the formulation but also when the patient or responsible caregiver needs to measure the medication for administration. In the dispensing form established by the institution, a suspension bottle of about 30 to 80 mL is dispensed for the patient to use at home. Usually, the caregiver, the mother, is responsible for withdrawing the medication from the bottle using an oral dispenser, provided along with the medication. At the time of dispensing the medication, it is suggested that the bottle be shaken well before measuring the dose. Another option would be for the institution to dispense the doses in oral dispensers, one dose per dispenser.

This heterogeneity of the suspension leads to deviations in the administered dosage, compromising the drug's plasma level for the patient. These deviations make it difficult to reach the ideal plasma concentration, which would provide better efficacy and fewer side effects. Therefore, based on the data found in this study, it is suggested that the adapted oral MMF formulation be dispensed in oral dispensers measured by the pharmacy professional, who should shake the suspension well before measuring the doses.

Dispensing in unit doses facilitates administration at home and helps ensure the maintenance of the balance in the amount of MMF administered in each dose. The pharmacist's role in this regard is of utmost importance, both in the compounding and research of more accurate formulations and in patient counseling alongside the multidisciplinary team, aiming to monitor and identify possible difficulties in using the medication, ensuring therapeutic safety and efficacy.

Conclusion

It can be concluded that the analytical results indicate that the adapted suspensions remained within the standards established by the Brazilian Pharmacopeia, demonstrating an adequate concentration of mycophenolate mofetil throughout the study period. The observed mean relative standard deviation highlights the need for attention to homogeneity during dose administration. Thus, this study contributes not only to validating the stability of the proposed formulations for seven days at room temperature in amber glass bottles but also emphasizes the relevance of developing a homogeneous liquid pharmaceutical form to meet the needs of the target patients and ensure the safety and therapeutic efficacy of each administered dose. Additionally, this study highlighted the need for further research to evaluate the stability of pharmaceutical forms adapted from mycophenolate mofetil tablets.

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All authors listed participated in the conception, design, data analysis and interpretation, manuscript drafting, and approval of the final version for publication.

Conflict of interest statement:

None to declare.

References

1. De Oliveira Costa AL. Éster 2-morfolinoetil e sal sódico do ácido micofenólico: desenvolvimento e validação de métodos analíticos para o controle de qualidade de matéria-prima e comprimidos [dissertation]. 2009. Available at: http://hdl.handle.net/1843/FARD-82TLBV. Accessed on December 11, 2023.
2. Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde (CONITEC). Relatório de recomendação- Imunossupressores pós-transplante de medula óssea. Brasília: Ministério da Saúde; 2016. Accessed on February 5, 2024.
3. Da Silva LCF, Martins CL, Tofani AA. Perfil de utilização de imunossupressores para profilaxia de doença enxerto versus hospedeiro em pacientes submetidos ao transplante de células-tronco hematopoiéticas. *Rev Bras Cancerol.* 2019;65(2). doi:10.32635/2176-9745.RBC.2019v65n2.148
4. Ezquer-Garin C, Ferriols-Lisart R, Alós-Almiñana M. Stability of mycophenolate mofetil in polypropylene 5% dextrose in-

fusion bags and chemical compatibility associated with the use of the Equashield® closed-system transfer device. *Biomed Chromatogr.* 2019;33(7):e4529. doi:10.1002/bmc.4529

5. Ministério da Saúde. Nota Técnica nº 304/2013. Micofenolato de mofetila e micofenolato de sódio. Brasília: Ministério da Saúde; 2013. Available at: https://www.gov.br/saude/pt-br/composicao/conjur/demandas-judiciais/notas-tecnicas/notas-tecnicas-medicamentos/notas-tecnicas/m/micofenolato.pdf. Accessed on February 5, 2024.
6. Marinho RNA, Cabral CHK. Estudo de adaptações de formulações farmacêuticas em um hospital universitário pediátrico. *Rev Bras Farm Hosp Serv Saúde.* 2014;3.
7. Silva MR, *et al*. Preparation of extemporaneous oral liquid in the hospital pharmacy. *Braz J Pharm Sci*. 2020;56. doi:10.1590/s2175-97902019000418358
8. United States Pharmacopeia and National Formulary. 35th ed. Vol 2. Rockville: United States Pharmacopeial Convention; 2012. Available at: http://www.usp.org/. Accessed on November 22, 2023.
9. Seebacher G, *et al*. A simple HPLC method for monitoring mycophenolic acid and its glucuronidated metabolite in transplant recipients. *Clin Chem Lab Med*. 1999;37(7):759-764. doi:10.1515/CCLM.1999.067
10. Agência Nacional de Vigilância Sanitária (ANVISA). Farmacopeia Brasileira. 6ª ed. Vol 2. Brasília: ANVISA; 2019. Available at: https://www.gov.br/anvisa/pt-br/assuntos/farmacopeia/farmacopeia-brasileira. Accessed on December 11, 2023.
11. Anaizi NH, Swenson CF, Dentinger PJ. Stability of mycophenolate mofetil in an extemporaneously compounded oral liquid. *Am J Health Syst Pharm*. 1998;55(9):926-929. doi:10.1093/ajhp/55.9.926
12. Fahimi F, *et al*. Physical and chemical stability of mycophenolate mofetil (MMF) suspension prepared at the hospital. *Iran J Pharm Res*. 2012;11(1):171-176.
13. Farmacopeia Brasileira, Coordenação. Formulário nacional da farmacopeia brasileira. 2ª ed. Brasília: ANVISA; 2012. Available at: http://bibliotecadigital.anvisa.ibict.br/jspui/handle/anvisa/834. Accessed on February 9, 2024.
14. United States Pharmacopeia. General Chapter <795>: Pharmaceutical compounding — nonsterile preparations. Rockville, MD: United States Pharmacopeial Convention; 2010.
15. Lenhart A, Chey WD. A systematic review of the effects of polyols on gastrointestinal health and irritable bowel syndrome. Adv Nutr. 2017;8(4):587-596. Available at: https://www.sciencedirect.com/science/article/pii/S2161831322006901. Accessed on October 12, 2024.
16. Fernández-Bañares F, Esteve M, Viver JM. Fructose-sorbitol malabsorption. Curr Gastroenterol Rep. 2009;11(5):368-374. Available at: https://link.springer.com/article/10.1007/s11894-009-0056-9. Accessed on October 12, 2024.
17. Gotfried J. Diarreia. Manual MSD. 2022. Available at: https://www.msdmanuals.com/pt/profissional/dist%C3%BArbios-gastrointestinais/sintomas-dos-dist%C3%BArbios-gastrointestinais/diarreia. Accessed on October 12, 2024.