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DEVELOPMENT STUDY OF MAGISTRAL COSMETIC FORMULATIONS CONTAINING 5% CAFFEINE

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ABSTRACT

This article refers to an approach to the development of semi-solid formulations containing 5% caffeine for the cosmetic treatment of cellulite. In a bench analysis proposal, five formulations were developed, three emulsions and two base gels that demonstrated when incorporating caffeine, the gels showed turbidity and to correct this problem it was necessary to add cosolvent. The samples were tested in the centrifuge test in a preliminary stability study, evaluating organoleptic characteristics, pH, microbiological control and viscosity determination at time zero and at the end of four weeks, using a commercially available sample as a control group. The parameters pH and average weight were statistically analyzed by the Tukey test at 5% significance. Considering the results obtained, it was concluded that the proposed emulsions and gels proved to be able to incorporate 5% caffeine under the conditions of this study. These formulations demonstrated the maintenance of physicochemical characteristics, with quality similar to the standard emulsion. This is a preliminary stability study, and should be complemented with other stability studies under conditions determined by current legislation, in order to prove the effectiveness of the developed formulations.

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INTRODUCTION

Brazilian magistral pharmacies are considered reference worldwide. The sector currently has a well-organized entity Anfarmag – National Association of Magistral Pharmacists, according to data from Panorama 2020, in Brazil there are 8057 companies and they have been gaining this recognition for being extremely important for the Brazilian health system, mainly due to the expansion in the search for personalized treatments, which include medications and products specifically tailored for each patient, considering their individual needs. In this context, there is considerable interest in the development of dermocosmetic formulations, with the prescriptions of dermatologists being the main production line in the sector. However, stability studies are scarce and demonstrate that the development and production phases must be cautious.

Many factors can destabilize the formulation in a short period of time, causing physicochemical and microbiological changes, which compromise the development and quality of the final manipulated product (VOGEL E.M. 2020). Gynoid lipodystrophy, popularly known as cellulite, is a pathological condition of the adipose tissue, which causes irregularities in the surface of the epidermis, providing an orange peel effect. This pathology is predominantly present in females, affecting about 80 to 90% of women and the cause is related to hormonal and anatomical factors. Another factor of paramount importance for the development of cellulite is an unbalanced diet and a sedentary lifestyle, which leads to an increase in adipocytes its proliferation. Therefore, this disorder has a multifactorial cause that includes hormonal, hereditary and lifestyle factors (TANO; VELASCO, 2003; SADICK, 2018). Currently, there are physical and dermatological treatments to treat this dysfunction. Physical treatments, performed in aesthetic centres, are for example

electromagnetic radiation, aerohydrotherapy, lymphatic drainage, carboxytherapy, among others. The other strand of therapy is a topical treatment, which uses cosmetic products containing actives with anti-inflammatory, vasoprotective, stimulating peripheral microcirculation and lipolytic agents. Retinol (0.3%), centella asiatica (2 to 5%) and ginkgo biloba (5 to 10% of the glycolic extract; 0.2 to 2% of the dry extract) are examples of actives widely used in cosmetics indicated for the treatment of cellulite (KLIGMAN; PANONI; STOUDEMAYER, 1999; HEXSEL; SOIREFMANN, 2011). In addition to these conventional assets, it is observed that in the last decade, there has been a significant increase in studies showing the lipolytic action of caffeine and also new products for this purpose based on caffeine have arrived on the market (LUO; LANE, 2015, RODRIGUES *et al*., 2017, LIS *et al* 2019, VOGEL EM 2020). Caffeine has had its pharmacological activity elucidated for some time now, being classified as a potent stimulant of the central nervous system, also acting on the cardiovascular system and calcium homeostasis (RANG DALE 2012; DE MARIA; GOMIDE, 2019). It is also reported that caffeine has several molecular mechanisms with lipolytic action, among them it inhibits phosphodiesterase, increasing the cyclic AMP messenger of lipolysis (HERMAN; HERMAN, 2013). In this context, there is considerable interest in the development of cosmetic formulations with caffeine in different types of magistral formulations. However, studies on the stability of caffeine-containing cosmetics demonstrate that the development and production phases must be cautious. Many factors can destabilize the formulation in a short period, causing physicochemical and microbiological changes, which compromises the expiration date. Specifically, in magistral formulations, factors such as the use of cosolvent, the type of cosmetic base used, the influence of the storage temperature and the characteristic of the various caffeine-based assets available on the market can influence the shelf life of the finished product (TANO; VELASCO, 2003, CHORILLI, 2007, FERNANDES *et al* 2015, LIS *et al* 2019, VOGEL IN 2020). Thus, the objective of this study is to develop and evaluate the physicochemical stability of different semi-solid magistral formulations containing 5% caffeine.

MATERIALS AND METHODS

This work was developed in partnership with Farmácia Herbanário, a magistral pharmacy established in the city of Poços de Caldas, MG, B since 1991. For the preparation of cosmetic bases, raw materials purchased from qualified suppliers by Farmácia Herbanário were used, according to RDC 67. The entire development process took place following Good Manufacturing Practices to avoid contamination, following RDC 48. As a reference, we used a cosmetic with caffeine, from the brand Nívea ®, in the form of an emulsion, obtained in a local market. Studying its composition, it was verified that it is an emulsion that uses secondary emulgents such as carbopol and hydroxyethylcellulose, which are important to increase the stability of emulsions. From this information, it was decided to develop three emulsions with different self-emulsified bases, associating the secondary emulsifiers and two gels, using cosolvent, based on the consulted literature (ANSEL; POPOVICH; ALLEN JR, 2000, COSTA 2012, FERREIRA 2011). The purified water used was reverse osmosis water following the ANVISA purified water guide (ANSEL; POPOVICH; ALLEN JR, 2000, COSTA 2012, FERREIRA 2011). For the preparation of the emulsions, the aqueous phase and the oil phase were heated separately, in a heating plate at a temperature between 70 and 80 ° C, to guarantee the fusion of the components of the oil phase. Both phases were heated to the same temperature. The aqueous phase was added to the oil phase, shaking vigorously on a mechanical stirrer, until a creamy emulsion was formed. The agitation was maintained until the formulation cooled down. We used a Fisaton stirrer at a speed of 1000 rpm. Emulsions were developed with different self-propelled bases in association with secondary emulsifiers and we used 0.6% of Conserv TM NE preservative, composed of (2-Methyl-4-isothiazolin-3-one and Phenoxyethanol), according to the list of preservative substances allowed for cosmetics by Anvisa RDC 29. Gels were prepared using cold carbopol and hydroxyethylcellulose with heating, using glycerin as a humectant (FERREIRA 2011). The carbopol gel preparation technique was cold, weighing the carbopol and adding the required amount of water. It is important to note that carbopol requires prior contact with water to occur dispersion. The homogeneous consistency was the result of using the Fisaton shaker, at a speed of 1000 rpm, performing 3 successive shakes of 5 minutes each, with an interval of 2 hours between each shaking. After this period, the carbopol was in contact with the purified water for 24 hours. After this time, another stirring occurred, followed by neutralization with AMP sq (sufficient amount) until a gel with pH 6 -7 was obtained. The hydroxyethylcellulose gel was prepared with heating using a hot plate and manual stirring until the lumps were completely dissolved. Conserv TM NE 0.6% was used as a preservative and the purified water used was from the same source as the water mentioned above, obtained by reverse osmosis.

After the development of semi-solid cosmetic bases according to good manufacturing practices, RDC 48, caffeine was incorporated using the levigation with ethanol method for solubilization, later, cosmetic bases were added, using grade and pistil (CHORILLI *et al*., 2007, FERREIRA; BRANDÃO, 2011, FERNANDES *et al*., 2015). The caffeine used was of synthetic origin, anhydrous manufactured by Cspc Innovation Pharmaceutical Co., Ltda / China, imported by Industria Química Anastásio S.A./ Brazil and distributed by the supplier Infinity Pharma ® lot 18H16-B009-036864 and valid 01/03/2022. The concentration of caffeine is following the guidance from Technical Opinion No. 1, of January 29, 2002, which establishes the maximum value of 8% of the caffeine in cosmetics. After stabilization, the formulations were packed in individual packages, being plastic pots with lids, previously labelled and left to stand at room temperature for 48 hours before the start of their characterization and use. The stowage in this pot was maintained throughout the testing period. To carry out stability studies, extreme temperature conditions were used to accelerate possible reactions between its components and the appearance of signs that were observed and analyzed according to the specific characteristics of each type of pharmaceutical form and as well as assisting in the screening of the substance's formulations (BRASIL, 2004). The formulations were subjected to cycles of 24 hours, at 40 ± 2 ° C and 4 ± 2 ° C, for four weeks. The physicochemical control of the semi-solid cosmetic bases containing caffeine was carried out on day zero of the cycle and at the end of the cycle, according to the methodology described in the Brazilian Pharmacopeia, with some adaptations, based on Resolution RDC nº 481 (BRASIL, 1999). Centrifuge tests and preliminary stability tests were performed analyzing organoleptic parameters, pH verification and average weight. In the centrifuge test, formulations were centrifuged at 3,000 rpm for 30 minutes. Then, visual analysis was carried out regarding the separation of the phases and formation of a precipitate (BRASIL, 2004). The organoleptic characteristics, colour and the physical appearance of semi-solid cosmetic bases were evaluated by observing the colour and appearance of them in a well-lit place (white light) against a white background (FERREIRA; BRANDÃO, 2011).

Weight determination: The weight determination was performed in the primary packaging using an analytical balance, the weight of the packaging with a lid was noted and subsequently added 20 g of sample of each semi-solid cosmetic base with 5% caffeine. This parameter can be used to analyze the compatibility with the stowage material (BRASIL, 2004).

pH determination: The pH was determined by a direct method using the BEL W3B digital peagameter, that is, through the introduction of the electrode in the formulations because they showed viscosity for this type of methodology (FERREIRA; BRANDÃO, 2011).

Dertermination of Viscosity: For the evaluation of viscosity, we used a viscometer (BROOKFIELD®, model: DEV Viscometer). Approximately 100 g of sample was used, enough to keep the "Helipath" system immersed in the sample, at room temperature 25°C +/- 1°C and spindle 63 was standardized at a speed of 1.5 rpm and three 5-min readings were carried out. Obtained product viscosity in

cP (centipoises). The determination of viscosity was according to the Brazilian Pharmacopoeia (BRASIL, 2010c), at the beginning of the cycle (day zero) and at the end of the cycle.

Microbiological control: Microbiological control of cosmetic semi-solid bases containing caffeine was performed during the preliminary stability test on day zero of the cycle and at the end of the cycle. These tests were carried out at the Quality Control Center of Unifal-MG, according to the methodology described in the 5th edition of the Brazilian Pharmacopoeia, with adaptations, based on Resolution RDC nº 67. Aliquots of each formulation were dissolved in a solution of sterile peptoned water added with tween 80 at a concentration of 1% (p/v). These were diluted 1:10 and 1:100 in peptoned water and then applied in petry dishes. Subsequently, inoculations were performed in the plates by the technique of sowing in depth, with a duplicate for each dilution. For the total count of viable bacteria, it was used the culture of Agar Casein-Soy, while Sabouraud dextrose 2% agar was used for the total count of fungi and yeasts. The non-selective enrichment was carried out in infused brain and heart broth, better known as BHI broth, and the investigations of Peseudomonas aeruginosa, Staphylococcus aureus and Escherichia coli were carried out in Cetrimide Agar, Mannitol Salt Agar and Eosin Methylene Blue Agar (EBM), respectively.

Statistical analysis: The pH and weight values of the formulations were prepared using the Analysis of Variance (ANOVA) in a completely randomized design (DIC) and 2x6 factorial scheme, between moments (initial and final) and formulations (carbopol, Hydroxyethylcellulose (HEC), emulsion, anionic emulsion, non-ionic emulsion, anionic emulsion with 2 secondary emulgents), with three repetitions. Multiple comparisons between the averages were performed using the ExpDes.pt package (Ferreira, Cavalcanti and Nogueira, 2020) from the software R (R Core Team, 2020), using the Tukey test. All tests were performed at a 5% significance level.

RESULTS AND DICUSSION

Development of semi-solid cosmetic bases: For the development of semi-solid bases, a previous study was carried out, referring to formulations that were studied by several authors (CHORILLI, 2007, FERNANDES *et al* 2015, LIS *et al* 2019, VOGEL E. M. 2020). The reference cosmetic product was Nivea Pernas Renovadas® which contains caffeine in its formulation, analyzing its composition in the information available on the manufacturer's website. This information guided the selection of raw materials for the development of semi-solid cosmetic bases. It is known that semi-solid cosmetic bases are widely used in the cosmetic industry due to factors such as moisturizing properties, optimization in the incorporation of various assets and meeting consumer demand (COSTA, 2012; TOPAN 2012). The entire development process took place following RDC 48 Good Manufacturing Practices. Based on data from the literature, five different formulations were developed, as recorded in Table 1. Analyzing the data in Table 1, it was observed three emulsions developed using oily components and secondary emulgents (carbopol and hydroxyethylcellulose) and two gels, one of carbopol and the other of hydroxyethyl cellulose and its respective pH before adding caffeine. Table 1 also shows the development of the anionic and non-ionic emulsion that used secondary emulgent and selected hydroxyethylcellulose based on the stability results of other authors (CHORILLI, 2007, FERNANDES *et al* 2015, LIS *et al* 2019, VOGEL EM 2020).

All formulations developed contain glycerin, which has a moisturizing action on the skin (CORREA, 2012). In addition, it changes the hydrogen bond between water, solvent and polymer, which contributes to stability (CHU *et al*., 1992; HURLER *et al*., 2011; ISLAM *et al*., 2004; SOARES *et al* 2020). The preservative was added to the formulations to guarantee the microbiological quality of the preparation. The preservative CONSERV ™ NE was selected, consisting of (2-Methyl-4-isothiazolin-3-one and Phenoxyethanol), according to the list of preservative substances allowed for cosmetics by Anvisa RDC 29. A chelator (EDTA) and antioxidant (BHT) were also added to avoid oxidation reactions, which are very common in cosmetic bases (COSTA 2012). All developed emulsions presented a homogeneous and shiny aspect,as shown in Figure 1,which indicates that the emulsification process was satisfactory. Factors such as proportion between the phases, agitation and temperature are in accordance with the literature (ANSEL; POPOVICH; ALLEN JR, 2000, FERREIRA, BRANDÃO 2011). In this context, it was also evidenced the importance of the correct choice of the components of an emulsion, liquid petroleum jelly has an important role in the formation of the skin barrier and vegetable oils are widely used in cosmetics as active or components of the formulation, as is the case of coconut oil, which has an emollient action (COSTA, 2012). After the development of the cosmetic bases, caffeine was incorporated. The incorporation technique was based on the levigation of caffeine in ethanol and subsequent mixing with the respective bases (FERREIRA; BRANDÃO, 2011). Various concentrations of ethanol were tested during this initial phase. When ethanol sq (sufficient quantity) was used in the levigation to solubilize the caffeine, the turbidity of the gels occurred. In the case of the emulsions, there was no change in organoleptic properties after incorporation. This change in the transparency of the gels is associated with the solubility of caffeine (GASPARI, 2015), which may be an indication of instability. These results differ from those found for a caffeine gel at 5% in the carbopol gel during which remained transparent at the stability study (LIS *et al* 2019). In the study using carbopol gel and papain, sensory changes were also observed, which were associated with the low solubility of the asset in water. Caffeine also has low water solubility, which may have contributed to the observed change (MIURA 2017). In the present study, it was noted that when using gels as a cosmetic base for caffeine incorporation, there was a change in organoleptic properties. Nonetheless, it is important to report that, after several tests, we opted for using 30% ethanol cosolvent for the solubilization of caffeine. This decision was made after analysis in the consulted literature, in which other authors opted for the use of cosolvents (CHORILLI, 2007, FERNANDES *et al* 2015). Vogel 2020, studying different semi-solid cosmetic forms with 5% caffeine, concluded that the choice of cosmetic base is fundamental for its stability.

Centrifuge test: The centrifugation test is very useful for the formulator as it brings a quick result. There was no phase separation in any formulation studied, indicating preliminary stability. However, the test performed with the carbopol gel and ethanol sq to solubilize the caffeine after 24 hours showed the formation of crystalsfor the carbopol gel. For hydroxyethylcellulose gel, the presence of crystals was verified when the test tube was placed against the light, which indicates instability of the formulation (BRASIL, 2004). As crystals formed after centrifugation of the gels, it was decided to use 30% ethanol as a cosolvent to prepare the gels, the use of cosolvents was also used by other authors (CHORILLI, 2007, FERNANDES *et al* 2015).This crystallization process did not occur when using 30% ethanol to solubilize caffeine during its incorporation in carbopol and hydroxyethylcellulose gels. In the emulsions developed with caffeine solubilized in alcohol sq and submitted to the centrifugation test, there was no phase separation, the same happened for the emulsion used as standard, showing that the formulations remained stable during the Centrifuge test (BRASIL, 2004). Similar results were observed during the development of oil phase emulsions using a non-ionic self-emulsified base with synephrine and caffeine liposome (TERRA R.S., MININ M.M., CHOROLLI M. 2009), as well as an emulsion composed of beeswax, ketoesteryl alcohol, triglycerides caprylic acid with caffeine (OLIVEIRA, 2018).

Preliminary stability test

Organoleptic parameters: appearance and colour: During the cycle, no changes were observed in the colour and aspect of the formulations developed, both for emulsions without caffeine and with 5% caffeine solubilized in alcohol sq., The same result was observed for gels with 5% caffeine solubilized in 30% ethanol.

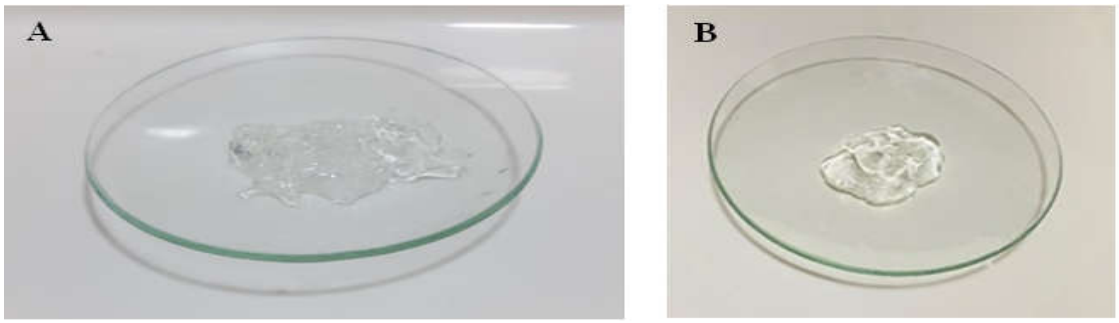
Table 1. Composition of developed semi-solid cosmetic bases and their respective pH

Components of semi-solid cosmetic bases	Percentage – % (p/v) ou % (v/v)				
	Non-ionic emulsion	Anionic emulsion	Anionic emulsion with 2 secondary emulgents	Carbopol Gel	HEC Gel
Non-ionic self-emulsified base	11	-	-	-	-
Anionic selfemulsified base	-	8	3	-	-
Solid petroleum jelly	5	5	5	-	-
Coconut Oil	2	2	2	-	-
Carbopol	-	-	0,1	1	-
Hydroxyethylcellulose (HEC)	0,2	0,2	0,2	-	2
EDTA	0,1	0,1	0,1	0,1	0,1
BHT	0,05	0,05	0,05	0,05	0,05
Preservative NE	0,6	0,6	0,6	0,6	0,6
Vegetable glycerin	5	5	5	5	5
Purified water	q.s.p. 100 mL	q.s.p. 100 mL	q.s.p. 100 mL	q.s.p. 100 mL	q.s.p. 100 mL
pH	5,8	5,9	5,8	6,3	6

Source: From the author (2021).

Source: The author (2021).

Figure 1 – Image of the developed emulsions. A) Anionic emulsion; B) Non-ionic emulsion; C) Anionic emulsion with two secondary emulsifying agents



Source: The author (2021).

Figure 2 – Image of the developed carbopol gel and hydroxyethylcellulose (HEC). A) Carbopol Gel; B) Hydroethylcellulose (HEC) Gel

Table 2. Values of the pH averages of the formulations studied at the beginning and at the end of the cycle.

Formulations	pH at the begginig of the cycle	pH at the end of the cycle
Non-ionic Emulsion	5,23 ± 0,03	5,22± 0,02
Anionic emulsion	5,42 ± 0,03	5,41 ± 0,01
Anionic emulsion with 2 secondary emulgents	5,09 ± 0,04	5,08 ± 0,03
Carbopol Gel	5,66 ± 0,02	5,66 ± 0,01
HEC Gel	5,59 ± 0,04	5,66 ± 0,01
Reference Product	5,57 ± 0,03	5,54 ± 0,03

Table 3. Viscosity of formulations containing caffeine at the beginning and end of the cycle

Formulations	Beginning Viscosity	End Viscosity
Anionic emulsion	63600 ± 26,28	63550 ± 24,55
Non-ionic emulsion	67280 ± 28,99	67260 ± 27,57
Anionic emulsion with 2 secondary emulgents	79600 ± 28,28	79620 ± 25,57
Carbopol Gel	61280 ± 25,78	61255 ± 27,78
Gel de Hydroxyethylcellulose Gel	59200 ± 26,80	59220 ± 28,88
Pattern	70960 ± 28,58	70950 ± 28,28

Note: The viscosity values of the formulations are not statistically different with $p < 0.05$. Analysis performed in triplicate.
Source: The author (2021).

There was no phase separation, showing that the formulations will remain stable during the preliminary stability test (BRASIL, 2004). The stability of the standard emulsion was already expected because it is a product available on the market purchased within the expiration date, that is, it has undergone a stability study. However, it is noteworthy that similar results were obtained with the proposed emulsions. Nonetheless, in another similar study, using different formulations of emulsions and 4% caffeine, the author noted that the stability of the formulation depends on the type of emulsion used for the incorporation of caffeine. Analyzing the components of the oil phase it was concluded that the choice of these components influences the stability (TANO; VELASCO, 2003). Colour changes were also observed using a non-ionic self-emulsifying base (TERRA R.S, MININ M.M., CHOROLLI M. 2009). It was concluded that the composition of the emulsion is a determining factor for its stability. In addition to the standard used as a reference in our study, there are other caffeine emulsions available on the market, for example Zone-5®, containing 3.5% caffeine, which was used in a clinical study by a group of researchers, who proved its effectiveness in the treatment of cellulite (BYUN *et al* 2015). Vogel 2020, studying different semi-solid cosmetic forms with 5% caffeine, concluded that the choice of cosmetic base is fundamental for its stability. The result of the visual analysis of the gels with caffeine solubilized in ethanol sq demonstrated the formation of crystals. The formation of crystals can be associated with the solubility of caffeine in water and the use of cosolvents, such as sodium benzoate, can be used according to The United States Pharmacopeia (2011).

The formation of crystals was also observed when using 5% caffeine in carpopol ultrez gel when storing the formulation at low temperature, the authors associated the formation of crystals with low caffeine solubility (LIS *et al* 2019). The loss of the physical stability of the carbopol gel with caffeine solubilized in ethanol sq was also observed by other authors when they did not use cosolvent for caffeine in 3% in Copolymer gel (FERNANDES *et al* 2015). In the formulation selected for the preliminary study with 30% ethanol, and it was also observed turbidity of the carbopol gel and the hydroxyethylcellulose gel. Despite this turbidity, these formulations were selected for the preliminary stability study, since in the centrifuge test there was no crystal formation or phase separation. During the study, the formation of crystals in the gels was also not observed. Therefore, these results suggest that the use of ethanol as a cosolvent prevents the formation of crystals in the carbopol gel and the hydroxyethylcellulose gel. In another study, in a similar condition, 25% ethanol was also used to solubilize caffeine (Chorilli *et al*, 2007). In this article, a caffeine release study was made using a carbopol gel preparation and it was observed that increasing the carbopol concentration from 1% to 1.5% increased the viscosity, but decreased the caffeine release. A similar result was also reported by Fernandes *et al* (2015), who did not observe precipitate formation when he used a 1/1 hydroalcoholic solution to solubilize the 3% caffeine in the Copolymer gel. In the study in question, it was shown that the use of ethanol also facilitates the measurement of caffeine in the spectrophotometer. Still, it was reported that one of the strategies to increase the stability of caffeine-containing gels was the use of adjuvants such as sodium benzoate and cosolvents such as ethanol (TANO; VELASCO, 2003, CHORILLI, 2007, FERNANDES *et al* 2015).

Physico-chemical parameters

Determination of pH: The determination of pH is essential in the study of the stability of cosmetic formulations. Cosmetic assets have a pH range for stability and effectiveness. In addition, the pH influences the physicochemical properties of the bases, especially gels (BRASIL, 2004, CORREA 2005, COSTA 2012). The pH values of the formulations were determined daily throughout the preliminary study cycle. Table 2 shows the pH values at the beginning and end of the cycle. The pH results obtained in this study are in agreement with other studies that claim that semi-solid cosmetic bases are ideal for topical application and stability of caffeine (FERREIRA; BRANDÃO, 2011, COSTA 2012).

The pH values, present in Table 2, of the cosmetic bases with 5% caffeine are in agreement with the pH values of other formulations with caffeine studied by several authors, who developed formulations with pH in the range of 5 to 7 (TANO ; VELASCO, 2003, CHORILLI, 2007; FERNANDES *et al*., 2015, LIS, 2019). A formulation prepared with copolymer gel and 3% caffeine using a 1/1 proportion of hydroalcoholic solution as a cosolvent obtained a gel with a pH of 5.70, close to the values shown in Table 3, the determination was also carried out directly as in the present study (FERNANDES *et al*., 2015). Lis *et al*. (2019) used carpobol ultrez gel and 5% caffeine during the stability study and the pH values did not change, a result similar to that found in this study. The pH value found was 6.2, showing a difference when compared to our study, however, the authors do not mention whether the determination was carried out directly, which may be responsible for the difference in the result of our pH of 5.66 for the carbopol gel. Another factor that may have caused such a difference was the type of carbopol used. In a similar study, the pH of ionic and non-ionic emulsions with 5% caffeine was analyzed, the values found were 5.4 and 6.4, respectively, and it was shown that the non-ionic emulsion was more stable because their pH values were constant throughout the stability study (VOGEL 2020).

Determination of viscosity: In the present work, the viscosity of the formulations at the beginning and at the end of the cycle was determined, which is shown in Table 3. The viscosity values of the formulations remained stable during the study, indicating stability of the developed formulations. Authors studying the viscosity of carbopol gel with caffeine, the viscosity of the formulations remained stable even at a temperature of 40 degrees (CORREA *et al* 2005). However, other stability studies of gels containing Melissa Officinalis L. at a temperature of 40 degrees showed a reduction in the viscosity of carbopol gels (RECHIA 2010). It is known that one of the factors influencing viscosity is pH (ISLAM *et al*., 2004), pH values remained constant during the study, which contributes to maintaining the viscosity of the formulations. Assessing the viscosity of a chitosan hydrogel with Passiflora Edulis extract during the stability study, the authors observed a result similar to ours, with no change in viscosity at the beginning and end of the cycle (SOARES, *et al* 2018). Analyzing different formulations obtained from master pharmacies containing 5% caffeine, the author observed that non-ionic emulsions had their viscosity maintained, while for anionic emulsions the results were different from our study, as it observed a reduction during the analyzed period, the presence of agents Secondary emulgents used in our formulations may have contributed to our stability results (VOGEL 2020).

Microbiological control: Some aspects when dealing with the microbiological control of non-sterile products, that is, those in which the presence of microbial load is admitted, revolve around two essential parameters: the evaluation of the microbial load (microbial count) and the absence of pathogenic microorganisms according to the limits recommended by the Brazilian Pharmacopoeia 5th edition. For of topical products, Staphylococcus aureus and Pseudomonas aeruginosa must be absent (PINTO; KANEKO; PINTO, 2015). The Good Manufacturing Practices implemented important requirements for the practice of magistral manipulation, establishing quality criteria for facilities, equipment, human resources and procedures, important factors so that all studied cosmetic semisolid bases with caffeine presented the microbial count within the limits recommended by RDC 67/2007. These results are important, as a possible loss of stability during the cycle could lead to a loss of microbial stability (FOX, 2014). Contamination sources are critical points in the manufacture of products and must be monitored in accordance with Good Manufacturing Practices. Thus, the sources of microbial contamination can be classified as: direct, such as raw materials, water, packaging materials; and indirect, such as equipment, environment and operators.In the case of semi-solid cosmetic bases, in which water is thecomponent ir more concentration, its quality is an important factor for the microbiological quality of the final product (PINTO; KANEKO; PINTO, 2015. The data from the reports of the microbiological control of purified water, carried out monthly by the

Herbanário Pharmacy, guarantee its quality. Microbiological evaluations of purified water were carried out in accordance with RDC 67/2007. All reports analyzed presented the microbial count within the limits recommended by the Brazilian Pharmacopeia. The control of the microbial load is important not to compromise its final quality or its safety, in a study on the microbiological control of products handled in master pharmacies, the authors reinforce the importance of Good Manufacturing Practices (VIEIRA 2020). In studies performed with several non-sterile products, the authors found a small percentage of samples outside the parameters of the European Pharmacopeia (RATAJCZAK, *et al* 2015). Evaluating the microbiological parameters of a chitosan hydrogel with Passiflora Edulis extract during the stability study, the authors observed a similar result in microbiological control to that found in the present study, as the parameters were within the limits recommended by the Brazilian Pharmacopeia, at the beginning and at the end of the cycle (SOARES *et al* 2018). A study on the microbiological control of cosmetics from industries in the region of Goiânia identified that some samples were unsatisfactory, with microbial limits outside the parameters established by current legislation (TEODORO 2019).

CONCLUSION

Considering the results obtained, it was concluded that the proposed emulsions and gels proved to be able to incorporate 5% caffeine under the conditions of this study. These formulations demonstrated the maintenance of the physicochemical characteristics, with quality similar to the standard emulsion. Analyzing these results, we clearly observed compliance with the applying legislation. The need to use cosolvents to avoid caffeine crystallization was confirmed when using the semi-solid pharmaceutical form gel, using carbopol or hydroxyethylcellulose. In this case, 30% ethanol proved to be an effective cosolvent. It is important to note that this stability study is a preliminary result, and should be concluded with the analysis of the caffeine content in the finished product and also microbiological analyzes evaluating parameters such as the presence of viable bacteria and specific pathogens. It is concluded that the proposed formulations showed great potential to be used as semi-solid cosmetic bases for incorporating 5% caffeine, with a satisfactory and accessible price to the consumer. However, for these bases to be effectively used in cosmetics, it is suggested that additional studies be carried out, such as an accelerated stability study, a long-term stability study and an efficacy and safety study.

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