Conjecturas

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# Quality control of dentin biomodifiers based on Copaiba oil

## Controle de qualidade de biomodificadores dentinários à base de óleo de Copaíba

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### ABSTRACT

This study aimed to evaluate in vitro the pharmacological stability of the dentin biomodifiers emulsions based on copaiba oil X, at 0, 3, 6, 9, 12, 18, and 24 months, and copaiba oil Y, at 0, 6, and 12 months. The emulsions were stored in different environments and analyzed through centrifugation, pH, and density tests, as well as their organoleptic and microbiological characters were investigated. Emulsion X did not show phase separation at 0 and 6 months in the freezer and fridge and showed cleavage in all environments after 12 months. The Y emulsion did not exhibit phase separation at 0 and 6 months in the stove, fridge, room temperature protected, and exposed to light. Still, after 18 and 24 months, phase separation occurred in all analyzed environments. The emulsions X and Y did not show contamination at 12 months. In the organoleptic test, the main change observed was color. The emulsion X presented the slightest deviation of pH in the room temperature protected from light, air conditioning, and fridge while the Y emulsion at 6 months presented a smaller variation in the freezer and fridge, and at 12 months, freezer, stove, and air conditioning. Regarding density, emulsion X at 24 months showed a very slight deviation, and emulsion Y remained stable in all environments at 12 months. The emulsions tested showed stability for 12 months, with the best storage environment being the fridge. The analysis at 18 and 24 months reinforced the fridge as an ideal environment for storage.

**Keywords**: Copaifera; Emulsions; Quality control; Phytotherapy; Dental materials.

### RESUMO

Este estudo objetivou avaliar *in vitro* a estabilidade farmacológica de emulsões biomodificadoras dentinárias à base dos óleos de copaíba X, nos tempos 0, 3, 6, 9, 12, 18 e 24 meses, e Y, nos tempos 0,6 e 12 meses. As emulsões foram armazenadas em diferentes ambientes, analisadas por meio dos testes de centrifugação, pH e densidade, e investigadas quanto aos caracteres organolépticos e microbiológicos. A emulsão X não apresentou separação de fases nos tempos 0 e 6 meses nos ambientes freezer e geladeira, e apresentou separação em todos os ambientes após 12 meses. A emulsão Y não apresentou separação de fases nos tempos 0 e 6 meses nos ambientes estufa, geladeira, temperatura ambiente ao abrigo ou não de luz, mas após 18 e 24 meses ocorreu separação de fases em todos os ambientes analisados. As emulsões X e Y não apresentaram contaminação em 12 meses. No teste organoléptico, a principal alteração sofrida foi a de cor. A emulsão X sofreu menor variação de pH em temperatura ambiente sem exposição à luz, ar condicionado e geladeira, enquanto a emulsão Y no tempo de 6 meses apresentou uma menor variação no freezer e geladeira, e aos 12 meses, freezer, estufa e ar condicionado.Quanto à densidade, a emulsão X em 24 meses apresentou uma variação muito leve e a Y permaneceu estável em todos os ambientes em 12 meses de análise. Conclui-se que as emulsões testadas apresentaram estabilidade no período de 12 meses, sendo o melhor meio de armazenamento a geladeira. A análise da emulsão X em 18 e 24 meses reforçou o ambiente geladeira como ideal para armazenamento.

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**Palavras-chave:** Copaifera; Emulsões; Controle de qualidade; Fitoterapia; Materiais dentários.

## INTRODUÇÃO

The technological development of herbal medicines from Brazilian biodiversity can be the alternative for access to safe, effective, and quality medicine, as it happens from the cultivation of plants, sustainable management, research, development, and innovation (RD&I), production, with the correct form of presentation and dosage, distribution and use (HASENCLEVER et al., 2017).

Quality control is an essential step for the product to meet the required standards, and its main advantages are the optimization of processes, from collection to product acquisition, the reduction of time and waste, the standardization of procedures and the quality of environments, inputs used and final products (ROCHA; GALENDE, 2014).

The stability study of herbal medicine directly interferes with the quality of pharmaceutical products. It aims to accelerate chemical degradation and/or physical changes in forced storage conditions, being carried out by packaging samples of the drug in its primary packaging. The stability study determines the shelf life and recommends the appropriate storage conditions after physical, chemical, biological, and micrological analyzes during the entire shelf life that has been defined, and, optionally, after that period, carried out within 24 months (BRAZIL, 2005; BRAZIL, 2019a).

Dental products produced from natural substances have good prospects in the market (FRANCISCO, 2010). The dentin biomodifier based on Copaifera multijuga oil developed to be used in the restorative process demonstrated antibacterial, anti-inflammatory, and metalloproteinase inhibitory activity, which can assist in the adhesion of restorative materials to the dental structure, with perspectives of preventing the degradation of the adhesive interface, reducing or eliminating marginal nanoleakage, properties that researchers around the world have pursued for years, and still not achieved (DE BARI et al. , 2010; BANDEIRA et al., 2020; MEIRA et al., 2020; ARAÚJO et al., 2020; ARAÚJO et al., 2021, MOURA et al., 2021).

Thus, this study aimed to characterize the physical-chemical, organoleptic, and microbiological aspects of copaiba (Copaifera multijuga Hayne) emulsion X in periods 0, 3, 6, 9, 12, 18, and 24 months and of emulsion Y in times 0, 6, 12 and 18 months,

following the guidelines for standardization and norms of good manufacturing practices for emulsions from the Brazilian Pharmacopoeia and the National Health Surveillance Agency (ANVISA).

## METODOLOGIA

This study was carried out at the Laboratory of Phytotherapy in Dentistry (LABFITO) of the Federal University of Amazonas. The quality and safety of medicines followed the regulations recommended by ANVISA, defined by RDC no 17, of April 16, 2010, RDC no 31, of August 21, 2019, RE no 1, of July 29, 2005, and in the RDC no. 318, of November 6, 2019, which establish criteria for carrying out stability studies of pharmaceutical ingredients (BRAZIL, 2005; BRAZIL, 2019a; BRAZIL, 2010a; BRAZIL, 2019b). The emulsion based on the oil-resin of *Copaifera multijuga* Hayne was formulated, following the guidelines of the Brazilian Pharmacopoeia (BRAZIL, 2010b) and the proportions proposed by De Bari et al. (2010).

### Physical-chemical quality control tests

To carry out the quality control study of the emulsions based on copaiba oil, the emulsion X was analyzed at times 0, 3, 6, 9, 12, 18, and 24 months and the emulsion Y was analyzed at times 0, 6, and 12 months, being stored under different conditions of temperature and humidity, according to the environments described in Table 1. All bottles were coded and dated.

**Table 1** - Storage environments for X and Y emulsions of copaiba oil.

| Environments | Storage Environments | Temperature | Humidity |
|---|---|---|---|
| **A** | Stove | 37ºC | 58% |
| **B** | *Freezer* | -12ºC | 10% |
| **C** | Fridge | 8ºC | 67% |
| **D** | Room temperature protected from light | 28,2ºC | 49% |
| **E** | Air conditioning | 24,2ºC | 42% |
| **F** | Room temperature with exposure to light | 25,9ºC | 52% |

### Centrifuge test

In this preliminary stability test, 5 mL of each prepared copaiba oil-based formulation were placed in previously sterilized Falcon tubes and subsequently centrifuged (5804R, Eppendorf, São Paulo, SP, Brazil) at 3000 rpm for 30 minutes, at room temperature, to observe a possible cremation or separation of the emulsion phases. The test was performed in triplicate (BRAZIL, 2010b).

### pH test

The pH was determined using a potentiometer (TEC 2, TECNAL, São Paulo, SP, Brazil). The electrodes were coupled to the potentiometer and calibrated with pH 7.0 and 4.0 standard solutions (Dinâmica Química Contemporânea, Manaus, AM, Brazil) at 25oC, allowing linearity in the responses concerning the observed potential changes. The results corresponded to the average of three successive determinations (BRAZIL, 2010b).

### Density determination

Density was obtained using an analytical balance (Shimadzu, Barueri, SP, Brazil) and a clean and dry glass pycnometer, with a capacity of 5 mL, previously calibrated, by determining the mass of the empty pycnometer and the mass of its content with distilled water. The sample was transferred to the pycnometer and weighed; the sample weight was determined through the mass difference of the full and empty pycnometer. Density

was calculated by the ratio between the mass of the liquid sample and the mass of water. The result was obtained through the average of three successive determinations (BRAZIL, 2010b).

### Microbiological evaluation for research of contaminants - Microbiological control of the emulsion of *Copaifera multijulga* Hayne

The microbiological control of the *Copaifera multijuga* Hayne emulsion was determined by the total number of aerobic microorganisms and by researching yeast,

*Escherichia coli*, *Pseudomonas aeruginosae*, *Staphylococcus aureus*, as recommended in the Brazilian Pharmacopeia (BRAZIL, 2010b).

To investigate the total number of microorganisms, the emulsions were prepared in a 1:10 ratio, using 100 µL of the emulsion and 900 µL of peptone water (Acumedia, Lansing, MI, USA). Then, the emulsions were diluted and homogenized in proportions 1:100, 1:1000, and 1:10000.

For plate counting of microorganisms, an aliquot of 10 µL of each serial dilution was seeded, in triplicate, in Petri dishes containing culture media soy-casein agar (Acumedia, Lansing, MI, USA) and Sabouraud-dextrose agar ( DifcoSa, Saint-Ferréol, France), separately. The plates were incubated at 35oC for 24 and 48 hours for determination of total aerobic microorganisms, in Casein-soy agar culture medium (Acumedia, Lansing, MI, USA) and at 25oC, for 5 to 7 days, for the determination of filamentous fungi and 54 yeasts, in Sabouraud-dextrose agar culture medium.

To search for *Pseudomonas aeruginosa*, 100 µL of Copaifera multijuga emulsion was used for 900 µL of casein-soybean broth (Acumedia, Lansing, MI, USA). Then, it was homogenized and incubated at 35oC for 18-24 hours. After this period, a 10µL aliquot of the subculture was seeded, in triplicate, on Cetrimide agar (Acumedia, Lansing, MI, USA) and incubated at 35oC for 18-72 hours.

For evaluating *Staphylococcus aureus* count, 100 µL of Copaiferamultiuga emulsion was used for 900 µL of casein-soy broth (Acumedia, Lansing, MI, USA). Then, it was homogenized and incubated at 35oC for 18 to 24 hours. After this period, a 10µL aliquot of the subculture was seeded, in triplicate, on Sal Mannitol agar (Himedia, Mumbai, India) and incubated at 35oC for 18-72 hours.

## Evaluation of organoleptic characters

The evaluation of the organoleptic characters was based on the change in color, odor, brightness and consistency, verifying the most suitable place for the storage of the copaiba test emulsion, without changing its characteristics (BRAZIL, 2013). Color and brightness were analyzed in daylight. The consistency was assessed by touch, observing the presence or absence of granules.

A small sample of the emulsion was placed in the hand and inhaled slowly and repeatedly to determine the intensity of the odor: none, weak, distinct or strong; and then the sensation caused by that odor: aromatic, fruity, musty, rancid, or woody.

## RESULTS

In the centrifugation test, the emulsion X did not show phase separation in 6 months in the refrigerator and freezer environments; in the other environments analyzed, phase separation was present. At 9 months, only the emulsions stored in the fridge and air conditioning did not undergo phase separation. At 12 months, the emulsion stored in the fridge did not undergo phase separation. After 18 and 24 months of analysis, all environments showed phase separation. The Y emulsion did not exhibit phase separation at times 0 and 6 months in the environments stove, fridge, room temperature protected from light and room temperature with exposure to light, showing changes in the environments freezer and air conditioning, and after 12 months of the analysis showed phase separation in all environments.

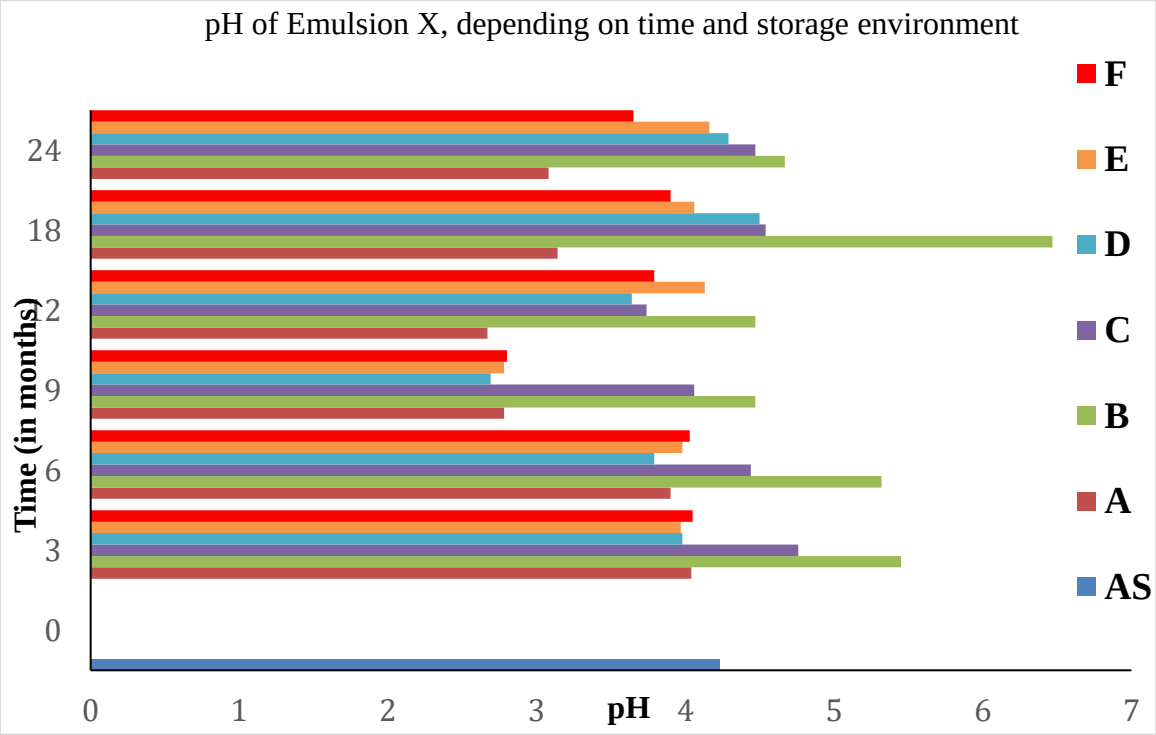
Regarding the pH test, emulsion X initially presented an average value of 4.23. During the 24 months of analysis, there were changes in the average pH when compared to the initial value, with the stove and room temperature environment exposed to light being those that suffered the greatest pH variations; room temperature protected from light, air conditioning and fridge environments showed the lowest pH variation (Table 2 and Figure 1).

| **Time (months)** | **Environments** | | | | | | |
|---|---|---|---|---|---|---|---|
| | AS | A | B | C | D | E | F |
| | Media±SD | Media±SD | Media±SD | Media±SD | Media±SD | Media±SD | Media±SD |
| 0 | 4.23±0.04 | - | - | - | - | - | - |
| 3 | - | 4.04±0.01 | 5.45±0.15 | 4.76±0.01 | 3.98±0.05 | 3.97±0.05 | 4.05±0.03 |
| 6 | - | 3.90±0.04 | 5.32±0.11 | 4.44±0.09 | 3.79±0.16 | 3.98±0.03 | 4.03±0.10 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 9 | - | 2.78±0.03 | 4.47±0.02 | 4.06±0.02 | 2.69±0.01 | 2.78±0.03 | 2.80±0.01 |
| 12 | - | 2.67±0.02 | 4.47±0.03 | 3.74±0.03 | 3.64±0.03 | 4.13±0.01 | 3.79±0.04 |
| 18 | - | 3.14±0.05 | 6.47±2.46 | 4.54±0.03 | 4.50±0.01 | 4.06±0.05 | 3.90±0.07 |
| 24 | - | 3.08±0.01 | 4.67±0.02 | 4.47±0.02 | 4.29±0.01 | 4.16±0.01 | 3.65±0.09 |

**Table 2** - Mean and Standard Deviation of the pH values of Emulsion X, according to time and storage environment. AS - no environment; A - stove; B - freezer; C -fridge ; D – room temperature protected from light; E – air conditioning; F – room temperature with exposure to light.

**Figure 1** - Distribution of the averages of the pH of Emulsion X, according to the time and the storage environment. AS - no storage; A - stove; B - freezer; C -fridge; D – room temperature protected from light; E – air conditioning; F – room temperature with exposure to light.

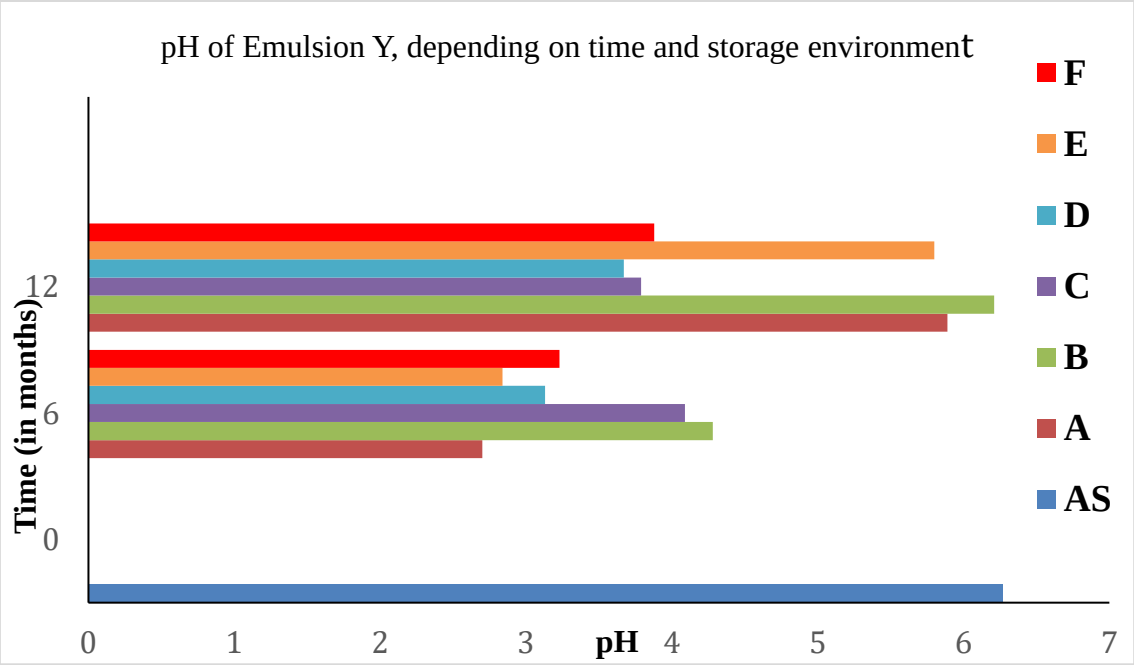



The pH test results for time 0 of the Y copaiba emulsion were 6.28. At the time of 6 months of storage, it was possible to notice that the environments that presented a lower initial pH variation were the freezer and fridge, while after 12 months, the freezer and stove (Table 3) and (Figure 2).

**Table 3** - Mean and Standard Deviation of the pH values of Emulsion Y, according to time and storage environment. AS - no storage; A - stove; B - freezer; C -fridge ; D – room temperature protected from light; E – air conditioning; F – room temperature with exposure to light.

| **Time** | **Environments** | | | | | | |
|---|---|---|---|---|---|---|---|
| **(months)** | AS | A | B | C | D | E | F |
| | Media $\pm SD$ | Media ±SD | Media ±SD | Media ±SD | Media ±SD | Media ±SD | Media ±SD |
| 0 | 6.28±0.04 | - | - | - | - | - | - |
| 6 | - | 2.70±0.00 | 4.28±0.10 | 4.09±0.17 | 3.13±0.02 | 2.84±0.02 | 3.23±0.08 |
| 12 | - | 5.89±0.01 | 6.21±0.04 | 3.80±0.08 | 3.67±0.004 | 5.80±0.09 | 3.88±0.02 |

**Figure 2** - Distribution of the averages of the pH of Emulsion Y, according to the time and the storage environment. AS - no storage; A - stove; B - freezer; C -fridge; D – room temperature protected from light; E – air conditioning; F – room temperature with exposure to light.




The density of a substance is characterized by the amount of mass of matter existing in a given volume. The results obtained at time 0 with the emulsion X was 1.00 g/cm. During 24 months of analysis, a very slight deviation in the density average was observed in some environments (Table 4).

| Time (months) | Environments | | | | | | |
|---|---|---|---|---|---|---|---|
| | AS | A | B | C | D | E | F |
| | Media±$SD$ | Media±SD | Media±SD | Media±SD | Media±SD | Media±SD | Media±SD |
| 0 | 1.00±0.00 | - | - | - | - | - | - |
| 3 | - | 0.99±0.00 | 1.00±0.00 | 0.99±0.00 | 1.00±0,00 | 1.00±0.00 | 0.99±0.00 |
| 6 | - | 0.99±0.00 | 1.00±0.00 | 1.00±0.00 | 0.99±0.01 | 1.00±0.00 | 1.00±0.00 |
| 9 | - | 1.00±0.00 | 1.00±0.00 | 1.00±0.00 | 1.00±0.00 | 1.00±000 | 1.00±0.00 |
| 12 | - | 1.00±0.00 | 1.00±0.00 | 0.99±0.00 | 1.00±0.00 | 1.00±0.00 | 1.00±0.00 |
| 18 | - | 0.96±0.00 | 0.98±0.00 | 0.94±0.00 | 0.96±0.00 | 0.96±0.00 | 0.92±0.00 |
| 24 | - | 1.00±0.00 | 1.00±0.00 | 0.99±0.00 | 1.00±0.00 | 0.99±0.00 | 0.99±0.00 |

**Table 4** - Average and Standard Deviation of the density of Emulsion X, according to time and storage environment.AS – no storage; A - stove; B - freezer; C -fridge; D – room temperature protected from light; E – air conditioning; F – room temperature with exposure to light.

At time zero, the Y emulsion of copaiba had a density of 0.99 g/cm³. The results found in the 6 and 12 months evaluation showed that the emulsion density remained stable in all environments (Table 5).

**Table 5 -** Average and Standard Deviation of the density of Emulsion Y, according to time and storage environment.AS – no storage; A - stove; B - freezer; C -fridge; D – room temperature protected from light; E – air conditioning; F – room temperature with exposure to light.

| **Time (months)** | **Environments** | | | | | | |
|---|---|---|---|---|---|---|---|
| | AS | A | B | C | D | E | F |
| | Media$\pm SD$ | Media $\pm SD$ | Media $\pm SD$ | Media $\pm SD$ | Media $\pm SD$ | Media $\pm SD$ | Media $\pm SD$ |
| 0 | 0.99±0.00 | - | - | - | - | - | - |
| 6 | - | 1.00±0.00 | 1.00±0.00 | 0.99±0.00 | 1.00±0.00 | 1.00±0.00 | 1.00±0,00 |
| 12 | - | 0.99±0.00 | 1.00±0.00 | 0.99±0.00 | 1.00±0.00 | 1.00±0.00 | 1.00±0.00 |

The results for emulsion X in time up to 12 months showed the absence of contaminants in all environments tested. After 18 and 24 months, there was no contamination in storage at room temperature with exposure to light. There were no contaminants in the 12 months analyzed regarding the Y emulsion.

The organoleptic characters found in this study described the copaiba emulsion X and Y as having a milky white color, a strong woody odor, in addition to a liquid consistency without granules, with the presence of gloss at time 0. After evaluating 6, 9, 12, 18, and 24 months of emulsion X and evaluating 6 and 12 months of emulsion Y, changes occurred in all environments tested, except in the fridge environment. These changes were mainly related to color, as the emulsions took on more yellowish tones.

## DISCUSSION

The microbiological test aimed to investigate the presence of contaminants, such as bacteria and fungi, in copaiba emulsions X and Y. The emulsion based on copaiba oil X was evaluated in the period of 0,3,6,9,12,18 and 24 months, while the emulsion Y

in the period of0, 6 and 12 months using centrifugation, density, pH, organoleptic, microbiological control for research of contaminants.

The emulsions were submitted to the centrifugation test, where initially they should not show phase separation, with the permanence of a homogeneous substance, which offers stability (BRASIL, 2008). The spin test is therefore performed to assess stability; phase separation occurs when there is not good stability and can be seen macroscopically (FIRMINO, 2011) when there is the instability of the formulation, incompatibility, insufficient amounts of reagents, or even evaporation of the water present in the formulation (LANGE; HEBERLÉ; MILAN, 2009). Emulsions A and B did not show phase separation in the first months of analysis, which is in agreement with the findings of Vieira et al. (2019) and Schorro et al. (2020), who, when carrying out studies involving formulations, did not find separations of phases, which demonstrates the maintenance of the components' homogeneity and stability.

The organoleptic characteristics are evaluated to ensure that the senses' possible changes are not perceptible and do not lead to benefits and insecurity (BRASIL, 2008; NAVARRO-OÉREZ et al., 2021). Changes in organoleptic characteristics are caused by destabilization processes (ISAAC et al., 2008; FIGUEIREDO; MARTINI; MICHELIN, 2014). The organoleptic characteristics of the two emulsions remained stable for 24 months in the fridge environment, with no change. When the packaging is adequate, the quality and stability are maintained in packages that promote greater sealing, with no change in color, odor, and aspects (OLIVEIRA; MORAES, 2019).

Another test performed to certify the physical-chemical stability is the pH test, which measures the acidity, alkalinity, or neutrality (BRAZIL, 2004). The pH scale ranges from 1 (acid) to 14 (alkaline) and can detect structural changes such as oxidation and incompatibility (BRAZIL, 2008). The decrease in the pH value as a function of the increase in temperature is related to the oxidation of the oil phase of the formulations (NAVARRO-OÉREZ et al., 2021). Monitoring the pH of emulsions becomes extremely important to assess their stability, since the interactions between the chemical substances present in the formulations lead to a change in pH, compromising the final quality of the product (HOSCHEID et al., 2017; FERNANDES; BOYLAN; SALGADO et al., 2018). Both emulsions X and Y presented pH variation; however, room temperature protected from light, air conditioning and fridge environments showed the lowest pH variation for X after 24 months and the freezer, stove, and air conditioning for Y after 12 months.

Density analysis, used in quality control, may indicate the incorporation of air or the loss of volatile ingredients in the sample (BRAZIL, 2008). The measure for determining the density of a product depends on the characteristics of the components present in the formulation and if there was the incorporation of air during it (PEDRAZZI et al., 2012). In this aspect, this study found favorable results with copaiba emulsions, as there was little value change on density.

The control of microbiological contaminants is essential to guarantee the quality of the product, as materials of plant origin may present the presence of fungi and bacteria, which are present in their microbiota, or which can be inserted at the time of handling. Contamination, when not initially controlled, intensifies and, as a result, compromises the material and, consequently, the user (MIGLIATO et al., 2007; HUBINGER; SALGADO, MOREIRA, 2009).

The evaluation of microbiological contaminants registered that all samples of the two emulsions showed no presence of contaminants, not even in the samples of time 18 and 24 months. The presence of microbiological contaminants, when not controlled, can cause risks to the consumer since many of these can present pathogenic potential. These microorganisms can change the chemical characteristics, reduce the product's effectiveness, and even cause the formation of toxic substances (GONÇALVES et al., 2015; FERNANDES; BOYLAN; SALGADO, 2018).

Quality control is one of the essential steps in manufacturing a drug, as it determines the quality, efficacy, and safety of a drug (CHAN, 2003). This study can assure that the two copaiba emulsions obtained satisfactory results, providing security to the final consumer (CHEN; HSU; LEE, 2019).

## CONCLUSION

Based on the results of this research, the ideal shelf life for the Copaíba X and Y emulsions was 12 months, and the storage place, the fridge.

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