NOVA SCHOOL OF SCIENCE & TECHNOLOGY

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BSc in Biology

Skin-friendly oncosmetics – specific cosmetics for people undergoing cancer treatment

MASTER IN BIOCHEMISTRY

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" Sê todo em cada coisa. Põe quanto és

No mínimo que fazes. "

(Fernando Pessoa)

Abstract

The incidence of cancer in Portugal has been increasing, causing concern at a national level. The aggressive treatments used in cancer treatment can result in physical and psychological challenges for diagnosed patients, including skin problems such as dryness, redness, itching, and irritation. These skin conditions not only cause discomfort but also bring pain and distress to patients, in addition to negatively impacting physical appearance and self-esteem, affecting the quality of life. Therefore, it is urgent to find effective and safe solutions to mitigate these effects and improve the well-being and comfort of patients throughout the cancer treatment process. Cosmetic products can be used to address some of these effects and improve the quality of life.

This master's project aimed to develop and characterize a cosmetic product suitable for sensitized and compromised skin, such as that of an oncology patient.

Thus, in the first phase, a literature review was carried out with the objective of selecting cosmetic ingredients with a more suitable toxicity and efficacy profile for sensitive skin. Subsequently, oil-in-water emulsions were developed consisting of carefully selected ingredients with the aim of strengthening the skin barrier, such as ceramides, niacinamide, hyaluronic acid, and vegetable oils rich in linoleic acid. All formulations were characterized regarding their organoleptic characteristics, pH value, rheology, and droplet size distribution. With this work, it was possible to develop stable emulsions with suitable pharmaceutical properties for topical application.

Keywords: Cancer, Emulsions, Skin barrier, Skin-Restoring, Skin health

RESUMO

A incidência de cancro em Portugal tem aumentado, causando preocupação a nível nacional. Os tratamentos agressivos utilizados no combate ao cancro podem resultar em desafios físicos e psicológicos para os pacientes diagnosticados, incluindo problemas de pele como secura, vermelhidão, comichão e irritação. Essas condições cutâneas não apenas causam desconforto, mas também provocam dor e angústia nos pacientes, além de terem um impacto negativo na aparência física e autoestima, afetando a qualidade de vida. Portanto, é urgente encontrar soluções eficazes e seguras para mitigar esses efeitos e melhorar o bem-estar e conforto dos pacientes durante todo o processo de tratamento do cancro. Os produtos cosméticos podem ser utilizados para contornar alguns destes efeitos e melhorar a qualidade de vida.

Este projeto de mestrado teve como objetivo desenvolver e caracterizar um produto cosmético adequado a uma pele sensibilizada e comprometida, como é a pele de um doente oncológico.

Assim, numa primeira fase foi efetuada uma revisão da literatura com o objetivo de selecionar os ingredientes cosméticos com um perfil de toxicidade e eficácia mais adequado para uma pele sensível. Posteriormente foram desenvolvidas emulsões óleo-em-água constituídas por ingredientes criteriosamente selecionados com o objetivo de reforçar a barreira cutânea, como as ceramidas, niacinamida, ácido hialurónico e óleos vegetais ricos em ácido linoleico. Todas as formulações foram caracterizadas relativamente às suas características organoléticas, valor de pH, reologia e distribuição do tamanho da gotícula. Com este trabalho foi possível desenvolver emulsões estáveis e com propriedades farmacotécnicas adequadas para aplicação tópica.

Palavras chave: Cancro, Emulsões, Barreira cutânea, Restauração cutânea, Saúde da pele

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GLOSSARY

13-HODE – 13-hydroxyoctadecadienoic acid
AHA – Alpha hydroxy acids
BM – Bone marrow
CERs – Ceramides
CHOL - Cholesterol
CoF - Coefficient of friction
dAEs – Dermatologic adverse events
DNA - Deoxyribonucleic acid
FA - Formaldehyde
FFAs – Free fatty acids
FLG – Filaggrin protein
GAG - Glycosaminoglycan
IL - Interleukin
ISO – International Organization for Standardization
LA – Linoleic acid
LCs -Langerhans cells
NMF – Natural moisturizing factors
OA – Oleic acid
O/W – Oil-in-water
O/W/O -Oil-in-water-in-oil
PASs - Potentially allergenic substances
ROS - Reactive oxygen species
SB – *Stratum basale*
SC – *Stratum corneum*
SD – Standard deviation
SPSS – Software Package for social sciences
TEWL – Transepidermal water loss
TI – Thixotropic index
UV - Ultraviolet
UVA – Ultraviolet A
VEGF – Vascular endothelial growth factor
W/O – Water-in-oil
W/O/W – Water-in-oil-in-water

1 INTRODUCTION

Cancer is a disease that has been significantly increasing in terms of incidence, causing great concern worldwide (1). Once diagnosed, patients undergo aggressive treatments that result in a range of physical and psychological issues. This research project aims to address the skin pathologies that arise as a result of these treatments, with the objective of alleviating the symptoms experienced by patients.

The main purpose of this thesis is to develop a highly effective product that can minimize the damage caused by the treatments, promoting the restoration and recovery of the patient's skin health, ultimately leading to an improvement in their overall quality of life.

To ensure the success of this project, an extensive review of relevant literature was conducted to identify the most suitable product type and identify the key ingredients necessary to achieve the desired outcome of revitalizing the skin. This comprehensive analysis is documented in Chapter One - Theoretical Support. To provide a comprehensive understanding of cancer in Portugal and worldwide, this section will present statistical data related to the disease. It will also discuss the different types of cancer treatment, providing valuable insights into the topic. Furthermore, it will examine the characteristics of healthy skin in contrast to skin damaged by oncological treatments, emphasizing the importance of proper skincare. The concept of cosmetics will be defined, along with references to relevant legislation. Additionally, the section will analyze the types of cosmetics to consider in order to achieve the proposed objective. It will introduce essential ingredients for the product under development and highlight controversial ingredients to avoid in this format. Finally, it will discuss the relevance of the skin microbiome. By addressing these points, the section aims to deliver a comprehensive overview and valuable information.

Following the selection of essential ingredients and the determination of the final product type, several emulsions were prepared and characterize to identify the most optimal formulation. Chapter 2 - Materials and Methods provides a detailed account of the entire

manufacturing process, along with the presentation of the characterization tests and stability assessment of the final product. In this section, it will be provided a detailed presentation of the formulation development, including its manufacturing process and all the necessary steps involved. Additionally, it will be presented a comprehensive market study to gather valuable insights and ensure the viability of the product. Moreover, it was also conducted a thorough proof of concept to validate the effectiveness and feasibility of our approach.

Subsequently, a thorough analysis of the development process leading to the final product will be presented, accompanied by the detailed results obtained from various tests such as droplet size analysis, microscopic analysis, rheology tests (including viscosity flow behavior, oscillatory and tribology analysis), and texturometer tests. Based on these extensive evaluations, the most suitable formulation will be chosen. Additionally, stability tests will be conducted to ensure the long-term viability of the final product. All these crucial findings and discussions can be found in Chapter 3 - Results and Discussion.

Finally, the opinions and preferences of the target audience for the product were sought through a comprehensive questionnaire. This feedback was instrumental in understanding the participants' major concerns, desired ingredients, and preferences. Chapter 4 - Questionnaire provides an in-depth analysis and summary of the responses received.

By undertaking this comprehensive research and development process, this thesis aims to contribute to the improvement of cancer patients' lives by providing an effective and reliable solution to mitigate the adverse effects of treatments on their skin.

2 THEORETICAL SUPPORT

2.1 Cancer statistics and Introduction

According to the latest report by GLOBOCAN 2020, there were approximately 19.3 million cancer patients worldwide in 2020, 4.4 million were from Europe and 60,467 were from Portugal. The numbers are expected to increase significantly by 2040, with a projected number of 28.9 million cancer patients worldwide (1). It is alarming to note that cancer is one of the leading causes of death worldwide, and this number is only expected to rise in the coming years.

Cancer is a complex disease that can take many forms and affect various parts of the body. It can begin as a small abnormality in a single cell, but over time, it can grow and spread throughout the body, constituting trillions of cells. While there are many risk factors associated with cancer, including genetics, lifestyle, and environmental factors, the exact causes of cancer remain largely unknown. Cells normally grow and multiply through a process called cell division, which replaces old or damaged cells. However, if this process is disrupted, abnormal cells can emerge and continue to grow uncontrollably, potentially leading to the formation of tumors. Tumors can be either cancerous or noncancerous, also known as benign tumors. If the tumor cells are cancerous, they can spread to other tissues and organs through the bloodstream or lymphatic system, a process known as metastasis. Once the cancer cells have spread to other areas of the body, they can develop into new tumors and cause further damage to healthy tissues. In fact, cancer can be particularly dangerous because it can spread quickly and is often difficult to detect in its early stages. Cancer at its core, cancer is indeed a genetic disease, which means that it is caused by changes in the genes that control cell growth and division. These changes, however, can be influenced by a variety of factors and triggers, which include errors during cell division, inherited genetic mutations, and exposure to harmful substances such as tobacco smoke, obesity, and radiation (2,3).

Cancer continues to be a significant health concern worldwide, with the number of cases on the rise. This disease not only affects patients physically but also emotionally and psychologically. The impact of cancer on patients and their loved ones cannot be overstated. Cancer treatments can be lengthy and arduous, often involving surgeries, chemotherapy, and

radiation, which can take a toll on patients' bodies and minds. Self-esteem is an essential component of human welfare as it plays a significant role in shaping an individual's thoughts, feelings, and behaviors. It can greatly affect how we perceive and interact with the world around us. Inadequate self-esteem can lead to several negative consequences such as depression, anxiety, and even suicidal thoughts. Therefore, it is crucial to enhance one's self-esteem to promote a healthy and fulfilling life. Furthermore, with the advancement of early detection and the development of quality treatment, the survival rate for various illnesses and diseases is increasing. This is especially true for cancer, where survivorship care has significantly improved over the years. By providing better support and care for survivors, we can improve their quality of life and promote a faster recovery (3,4).

According to the National Cancer Institute, there are several cancer treatments available at present. The type of treatment a patient receives depends on the type and stage of cancer. In most cases, patients receive a combination of treatments, although there are cases where only one treatment is adopted (5).

Chemotherapy is a type of treatment that involves the use of drugs that have the ability to kill cells, cytotoxic chemicals. The primary objective of chemotherapy is to eradicate tumors, although in some cases it may only be possible to reduce their size. Over time, oncological therapies have been adapting to the use of new and improved chemotherapeutic agents. These newer drugs are designed to be more selective and have lower levels of systemic toxicity. This is because of their higher specificity, which allows them to target cancer cells more precisely. Although these new protocols have been shown to increase the survival rates of cancer patients, they have also led to an increased frequency of cutaneous side effects. These side effects can cause a deterioration in the quality of life for patients and can even result in the interruption of the treatment. Some of the cutaneous side effects of chemotherapy include skin rash, xerosis, pruritus, paronychia, hair abnormality, and mucositis (6,7).

Radiotherapy, also known as radiation therapy, is a commonly used cancer treatment. This type of therapy uses high doses of radiation to target and kill cancer cells. The radiation damages the deoxyribonucleic acid (DNA) in the cancer cells, making it impossible for the cells to divide or even survive, allowing the body to eliminate them. This process is known to continue even after the radiation therapy has been completed. While radiotherapy is an effective cancer treatment, it can have significant side effects. Similarly, to chemotherapy, one of the most common side effects of radiotherapy is skin damage. The skin can become red and irritated, and may even blister, peel, or become scaly. In some cases, the skin may also develop erosions or ulcers. Other side effects of radiotherapy to the skin include itching, hair loss, and

changes in skin color. In addition to skin damage, radiotherapy can also increase the risk of infection. When the skin is damaged, it becomes more susceptible to bacterial and fungal infections (8,9).

Hormone therapy to treat cancer, also known as endocrine therapy, is a type of systemic therapy that blocks hormones that control the activity of other cells. For example, if we consider breast cancer, the doctor may use endocrine therapy to block the estrogen receptor. By doing so, this could prevent cancer growth and metastasis. However, it is important to note that endocrine therapy is not always effective, and some cancer cells may still grow despite the treatment. In addition, targeted therapies often come associated with dermatologic adverse events (dAEs) as a result of signaling pathways that are associated with malignant comportment or signaling normal equilibrium functions of the epidermis. These types of treatments are associated with the induction of maculopapular rash, eczema-like, or even psoriatic injuries, lichenoid dermatitis along with pruritus and xerosis. It is important to inform patients about these potential side effects so that they may be prepared and to ensure that they report any adverse events to their healthcare provider (10,11).

2.2 The Skin

The skin is the largest organ in the human body, and its primary function is to provide protection. It is important to understand the structure of the skin so that we can appreciate the challenges it faces. The skin is responsible for protecting the body from various harmful stimuli, such as microorganisms, allergens, ultraviolet radiation (UV), toxic chemicals, and mechanical trauma. However, the skin is not only a barrier against external threats, it is also an immunologically active and sensory organ, and plays a crucial role in regulating body temperature and excretion (12,13).

The skin, being the largest organ of the human body, is composed of three primary layers: epidermis, dermis, and underlying subcutaneous tissue. Each layer plays a vital role in maintaining the health and protection of the body. The outermost layer, the epidermis, has four distinct sublayers, namely the *stratum basale* (basal cell layer) (SB), *stratum spinosum*, *stratum granulosum*, and *stratum corneum* (SC) (14).

The dermis, located between epidermis and subcutaneous tissue, is composed of collagen, elastin, and other proteins that provide the skin with elasticity and strength. Its main component is collagen, which is a protein that provides strength and solidity to the skin. The collagen in the dermis is classified into three main types: type I collagen, type III collagen, and

type XII collagen. type I collagen is abundant in the skin, and it plays a crucial role in the structural support of the skin due to its highly organized fibers and fibrils. It consists of three chains: two identical α-1(I) chains and a single α-2(I) chain. Type III collagen is the most abundant collagen type in the skin, and it constitutes approximately 10-20% of total collagen. It is composed of three identical α-1(III) chains, which have higher levels of hydroxyproline and lower levels of hydroxylysine. Type III collagen is associated with tissue extensibility and plays a crucial role in maintaining the elasticity of the skin. Type XII collagen is also present in the skin and consists of three identical α-1(XII) chains, each with two triple-helical domains. This type of collagen is less abundant than type I and type III collagen, but it is still important for the structural support and elasticity of the skin. It is also home to hair follicles, sweat glands, and blood vessels that play crucial roles in regulating body temperature and maintaining homeostasis. Finally, the subcutaneous tissue is the deepest layer of the skin and is composed of adipose tissue and connective tissue. It serves as a storehouse for fat, which provides insulation and energy for the body, and also helps to cushion and protect internal organs (14).

In summary, the skin is a complex organ that serves to protect the body and regulate internal processes. It consists of three layers: the epidermis, dermis, and subcutaneous tissue, which work together to ensure its effectiveness. The dermis, primarily composed of collagen, maintains the strength, structure, and elasticity of the skin.

The dermis is made up of two layers: the papillary and the reticular. The papillary layer is located at the top and is composed of loose areolar connective tissue. Meanwhile, the reticular layer is the deeper layer and is made up of dense irregular connective tissue. This layer of the skin also contains lipocytes, which are small portions of fat cells. The thickness of the dermis varies depending on its location in the body. For instance, the eyelid has the thinnest dermis layer, measuring only 0.1mm in thickness, while the palms and soles have the thickest parts of the dermis, measuring up to 1.5mm in thickness. It is worth noting that the dermis plays a crucial role in the regulation of body temperature, sensation, and protection against external factors. For instance, the dermis is responsible for regulating body temperature by dilating and constricting blood vessels and producing sweat. Additionally, the dermis contains sensory receptors that aid in touch, pressure, and temperature detection. Finally, the dermis protects the body against external factors such as UV radiation and mechanical stress by providing a thick layer of connective tissue. In summary, the dermis is a critical component of the skin that provides numerous protective functions and plays a role in maintaining homeostasis in the body (15).

The skin is made up of several layers, including the SB, also known as the basal layer. This layer is located at the bottom, adjacent to the basement membrane. It is made up of either columnar or cuboidal cells, which serve as the foundation for the other layers. The cells in this layer are primarily keratinocytes, which are responsible for constantly reproducing and pushing upward to regenerate the epidermal cells above. One of the most important layers of the skin is the SC, which serves as the primary barrier to the external environment. In addition to its protective function, this layer also has biosensor properties, allowing it to respond to changes in external factors such as humidity, pH, or water content. For example, when the external environment becomes too dry, the SC will become more compact in order to prevent water loss (16).

The main cellular component of the epidermis is keratinocytes. These sublayers are composed of keratinocytes, which are responsible for producing keratin and keratohyalin, two proteins that provide the skin with structure and strength. Keratinocytes begin their journey in the basal layer of the epidermis and eventually migrate to the surface of the skin as they mature. During this process, they undergo numerous changes, including the formation of bundles with elastic fibrils, which help to elongate and strengthen the cells. Additionally, keratinocytes contain lipids that help to form a barrier to prevent water loss and protect the skin from external factors such as UV radiation and harmful chemicals. In addition to these, there are other components such as melanocytes, Merkel cells, gamma delta T-lymphocytes, and Langerhans cells (LCs) (13).

Keratinocytes differentiate into corneocytes beyond the granular layer and play a crucial role in the overall structure and function of the SC. These cells go through a complex process of differentiation as they move from the basal layer to the outermost layer of the epidermis. Once they reach the SC, these corneocytes become an integral part of the skin barrier, helping to prevent water loss and protect against environmental stressors such as UV radiation and pollutants. Moreover, corneocytes also contribute to the overall texture and appearance of the skin, with abnormalities in their formation or function leading to various skin disorders such as psoriasis and eczema (13).

Melanocytes are a diverse group of cells located throughout the human body. In addition to their presence in the epidermis, iris, and hair, they can also be found in unexpected locations such as the inner ear and nervous system. Within the skin, they are primarily located in the basal layer of the epidermis, though they may occasionally be present in the dermis as well. These specialized cells originate from embryonic cells called neural crest cells and play a vital role in melanin synthesis. Melanocytes have a wide range of functions, but their primary

responsibility is the production and delivery of melanin to keratinocytes. This process is achieved through the use of dendritic processes that connect the melanocytes with neighboring keratinocytes. The melanin produced by melanocytes provides skin pigmentation, which helps to prevent sun-induced skin damage, including the development of skin cancer. In addition to their phenotypic role, therefore, melanocytes also play a vital protective role against radiation. It's worth noting that melanocytes interact with other cells in the skin to perform their functions. They also play a role in immune responses and inflammatory reactions in the skin. Overall, melanocytes are a fascinating and complex group of cells with many important functions in the body (17,18).

Merkel cells are not numerous neuroendocrine cutaneous cells dispersed along the epidermis, they are fundamentally localized in epidermis basal layer, usually concentrated in touch-sensitive areas, these cells are postmitotic cells, they are correlated with the development of the endings of the sensory nerve furthermore the number of peptides they can secrete. Data suggests that Merkel cell's features give a significative contribution to skin homeostasis along with development of cutaneous nerve (19).

Gamma delta T lymphocytes ($\gamma\ \delta$ T) are a diverse group of immune cells that play an important role in both innate and adaptive immunity. These cells differ in function depending on their subtype, with some specializing in attacking cancer cells and others in fighting infections. In the skin tissue, the predominant subtype of $\gamma\ \delta$ T cells is the V δ 1+ T lymphocyte, which has been shown to have a crucial role in maintaining the skin's barrier function and protecting against skin infections. In addition to their role in the skin, $\gamma\ \delta$ T cells are also found in other tissues such as the gut, where they help to regulate the immune response to intestinal pathogens (20).

Langerhans cells (LCs) are a specialized type of dendritic cell that originate from the bone marrow (BM) and reside in the epidermis, where they form a network of resident cells. These cells have the unique ability to migrate to nearby lymph nodes, where they present antigens to T cells and contribute to the establishment of immune responses. In addition to their role as antigen-presenting cells, LCs also serve as an important immunologic barrier between the body and the external environment. This barrier function is critical in defending against pathogens, toxins, and other harmful substances that may come into contact with the skin. Therefore, it is important to understand the functions of LCs in order to develop effective strategies for maintaining skin health and preventing disease (21).

Stratum corneum structure consists of multiple layers of corneocytes, these cells are Keratin-filled dead cells without organelles, these cells are connected by corneodesmosomes,

these cells are surrounded by a lipid-enriched extracellular matrix, phospholipids, cholesterol (CHOL), and glucosylceramide are included. This structure can be effortlessly comprehended by imagine a model of “bricks and mortar” (22–24).

Maintaining moisture homeostasis is critical for preserving the skin's protective function and flexibility. The lipids that form the SC matrix are present in the following percentages: free fatty acids (FFAs) at 20%, CHOL at 20%, and ceramides (CERs) at 60%. These lipids are arranged in organized layers, forming the SC's lamellar phase. Ensuring lipid homeostasis is essential for an effective skin barrier that prevents transepidermal water loss (TEWL). Corneocytes contain numerous natural moisturizing factors (NMF), such as lactic acid, amino acids, urea, glycosaminoglycans, and breakdown products from surface filaggrin (FLG) protein. These factors help maintain SC moisture, pH stability, and flexibility. When the SC becomes dehydrated, corneocyte water content decreases, and barrier repair enzymes are activated. These enzymes degrade FLG proteins, which are then incorporated into the lipid layer to provide NMFs and rebuild the skin barrier (25).

The NMF acts as a basal skin humectant. It is mainly composed of hygroscopic amino acids that absorb moisture from the environment, maintaining water on the corneocytes. NMF is derived from FLG, which accumulates keratin in the final stages of epidermal differentiation. After internal reorganization, FLG is no longer bound to the keratin of the keratinocyte. At this stage, FLG is capable of protease activity and is therefore hydrolyzed into amino acids (26). As mentioned, NMF acts as a highly efficient humectant by not only absorbing atmospheric water but also by providing its own hydration mechanism. NMF allows the SC to remain hydrated, and corneocytes with a higher concentration of NMF can retain more water and become more swollen. NMF is also associated with the regulation of biochemical events (22).

In summary, the skin undergoes constant changes and maintaining a healthy skin barrier is important. Methods to repair the skin barrier include supplying hydration through humectants and preventing water loss through occlusive agents. Cosmetic products also capable of improving skin elasticity, reducing fine lines and wrinkles, and protecting against UV rays and environmental stressors.

2.2.1 Skin conditions

Cancer treatment can impact the condition of the skin, hair, and nails, resulting in various skin-related issues. While these problems are typically not severe, they can still cause discomfort and be noticeable. Some individuals may find it challenging to manage the visible changes or symptoms caused by these skin conditions. It's important to note that while these conditions

may improve over time, complete resolution is not always guaranteed. The most common skin reactions associated with chemotherapy and targeted therapies include the papulopustular eruption and skin rash. This condition is characterized by the development of red follicular papules that can turn into pustules, often occurring in areas with seborrheic skin. Facial redness and superficial skin shedding may also be present. Another condition is skin xerosis, which is characterized by dry, scaly, and itchy skin, particularly in areas affected by the papulopustular eruption. In some cases, it can progress to chronic asteatotic eczema. Photosensitivity and pigmentation disorders are potential side effects of cancer treatment. Photosensitivity refers to an increased sensitivity to sunlight or artificial light, which can lead to skin reactions such as rashes or sunburn. Pigmentation disorders involve changes in the skin's color, such as darkening or lightening in specific areas (27).

The general consensus among specialists is that moisturizing the skin is highly advisable. This will not only alleviate the symptoms of the disease but also prevent the onset of complications like bacterial infections and chronic post inflammatory hyperpigmentation. It is strongly recommended to incorporate a regular moisturizing routine for the skin, even prior to initiating any specific treatment. In order to effectively maintain skin health, it is highly recommended to apply creams or lotions frequently to prevent dryness and provide relief from itching. Moreover, it is of utmost importance to protect the skin from the detrimental effects of the sun's rays by consistently utilizing sunscreen and lip balm that offer adequate sun protection properties (23,24,28,29).

2.3 Cosmetics

As people become more aware of the importance of maintaining healthy skin and the benefits of improving their skin health, the demand for cosmetic products has significantly increased. This growth has not only promoted the development of the industry and its technology, but also led to the emergence of new trends and innovations in the field of skincare. Many companies are now focusing on developing products that not only enhance the appearance of the skin but also provide long-term benefits, such as protection against environmental factors and aging (30).

The cosmetic industry, particularly the skin care sector, is expected to see a significant increase in growth over the next few years. According to the latest statistics, the industry is predicted to grow by approximately 4.7% annually, with a projected value of USD 130.83 billion in 2022 (31).

2.3.1 Regulation

A cosmetic product is defined, according to Article 2 of Regulation (EC) No 1223/2009 of the European Parliament and of the Council, "cosmetic product means any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours;". In other words, cosmetic products are substances or mixtures that are designed to enhance and maintain the appearance and hygiene of the body. The regulation also specifies that a cosmetic product must not be intended for medicinal purposes, such as treating or preventing a disease or medical condition. This is an important distinction, as cosmetic products are subject to different regulations than medicinal products (32).

Cosmetic products have become an essential part of our daily lives. They are used by people of all ages and genders to enhance their appearance and boost their confidence. From basic skincare products to more complex beauty treatments, cosmetics have become an integral part of our daily routines. However, with the increasing demand for cosmetic products, it is important to regulate and control their production to ensure the safety and efficacy of these products. The Food, Drug, and Cosmetic Act of 1938 was the first oversight method for various cosmetics. It established a regulatory framework for the production, labeling, and marketing of cosmetic products in the United States. This act made it mandatory for cosmetic manufacturers to disclose their ingredients on their product labels, and it prohibited the use of harmful substances in cosmetics. In 1960, the Food, Drug, and Cosmetic Act was reviewed and modified to focus on creating awareness of potential carcinogenic ingredients. This led to the establishment of the Cosmetic Ingredient Review (CIR) panel, which evaluates the safety of cosmetic ingredients and publishes its findings in the International Journal of Toxicology. This panel has played a crucial role in ensuring the safety of cosmetic products and protecting consumers from potential harm (30).

2.3.2 Galenic forms

Cosmetic products designed for dry skin, like oncological patients develop, can be found in various galenic forms, such as sprays, lotions, creams, or ointments. These products are typically emulsions with different proportions of oil and water. The viscosity of these formulations can vary, serving different purposes. These emulsions can be classified into two groups: water-

in-oil (W/O) or oil-in-water (O/W). The upcoming subchapter will delve further into this topic. However, it is worth noting that these two groups elicit different perceptions from users, for example, O/W emulsions are easily absorbed, while W/O emulsions may leave an oily sensation on the skin, especially for those with normal skin (33).

2.3.3 Emulsions

Emulsions refer of two immiscible fluids that are brought together through a process of shearing. During this process, one of the fluids is fragmented and dispersed in the other fluid, forming droplets. This dispersed phase is commonly referred to as the dispersed phase while the fluid it is dispersed in is called the continuous phase. Due to the nature of emulsions, they are considered as examples of metastable colloids. This means that the droplets of dispersed phase in the emulsion display behaviors commonly associated with metastable colloids, such as Brownian motion and reversible phase transitions. Brownian motion is the continuous random movement of particles suspended in a fluid, while reversible phase transitions refer to the ability of particles in a system to transition between different phases under varying conditions (34,35).

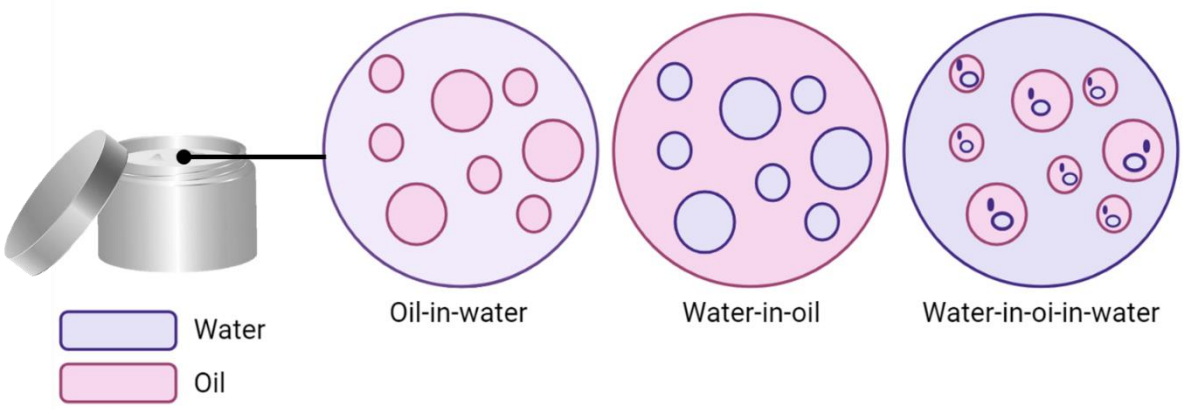


Figure 1 Representation of the droplet formation in different pes of formulation: Oil-in-water; Water-in-oil and Water-in-oil-in-water. Created with BioRender.com.

Emulsions, which are a mixture of two immiscible liquids, are thermodynamically unstable. To prevent separation, an emulsifier is added to stabilize the system. This emulsifier surrounds droplets of the dispersed phase, forming a thin coat. One common type of emulsion is the O/W emulsion, which is a mixture of an aqueous phase with an oil phase, where the oil droplets are dispersed in the water phase (Figure 1). Another type is the W/O emulsion, where the water droplets are dispersed in the oil phase (Figure 1). Emulsions can also be complex systems, such as the oil-in-water-in-oil (O/W/O) emulsion, which consists of small oil droplets

dispersed in water globules of a W/O emulsion. Similarly, the water-in-oil-in-water (W/O/W) emulsion consists of small water droplets dispersed in oil globules of an O/W emulsion (Figure 1) (34).

2.4 Emulsion Ingredients

2.4.1 Emollients

Emollients have been used in cosmetic products since ancient times. In fact, they were derived from naturally occurring animal fats and vegetable oils. These emollients have been known to offer smoothing action to the skin, making it appear more supple and healthy. Furthermore, they help to create a protective barrier on the skin, thereby retaining the moisture and preventing dryness. With time, the use of emollients has evolved, and now synthetic emollients are also available that offer even better results. These emollients are more stable and have a longer shelf life, making them ideal for use in a wide variety of cosmetic products, from lotions to lip balms (36).

2.4.1.1 Butters

Mango butter, for example, is an exotic fat its natural lipids have strong oxidative resistance together with its biocompatibility. These types of fats exhibit improvement on skin elasticity, on natural skin. Exotic fats are known to restore kin lipids and elasticity, promoting natural regeneration and improving skin hydration (37).

2.4.1.2 Vegetable oils

Vegetable oils are naturally produced by plants as a source of energy. They play a crucial role in providing the necessary nutrients and fats required for the growth and development of plants. The parts of the plant with the highest concentration of oils, such as the seeds and fruits, are essential for the survival and reproduction of the plant species. Vegetable oils are primarily composed of triglycerides, which are a type of lipid molecule consisting of three fatty acid chains linked to a glycerol molecule. These triglycerides serve as a major energy reserve for the plants, providing them with the fuel needed for various metabolic processes. In addition to triglycerides, vegetable oils also contain smaller amounts of monoglycerides and diglycerides. These compounds contribute to the overall composition and functionality of the oils. The fatty acids present in vegetable oils can be categorized into two types: saturated and

unsaturated fatty acids. Saturated fatty acids are typically found in higher concentrations in oils such as coconut oil and palm oil. On the other hand, oils like sunflower oil and olive oil are more abundant in unsaturated fatty acids, such as linoleic acid (LA) and oleic acid (OA). These unsaturated fatty acids are considered to be healthier options due to their potential benefits for cardiovascular health. In addition to triglycerides and fatty acids, vegetable oils may also contain other substances in smaller quantities. These include glycolipids, which are important for cell membrane structure and function, as well as waxes, which provide a protective barrier for the plants. Some vegetable oils may even contain pigments that contribute to their distinct colors and flavors. It is important to note that vegetable oils should not be confused with essential oils. While both oils are derived from plants, they have different properties and uses. The use of oil offers several advantages. It acts as a beneficial hydrating agent, nourishing and moisturizing delicate skin. Additionally, oils have been found to enhance the absorption of nutrients by the developing skin, which improves nourishment and strengthens the skin barrier. Moreover, oils have shown the capacity to improve the performance of the skin barrier and

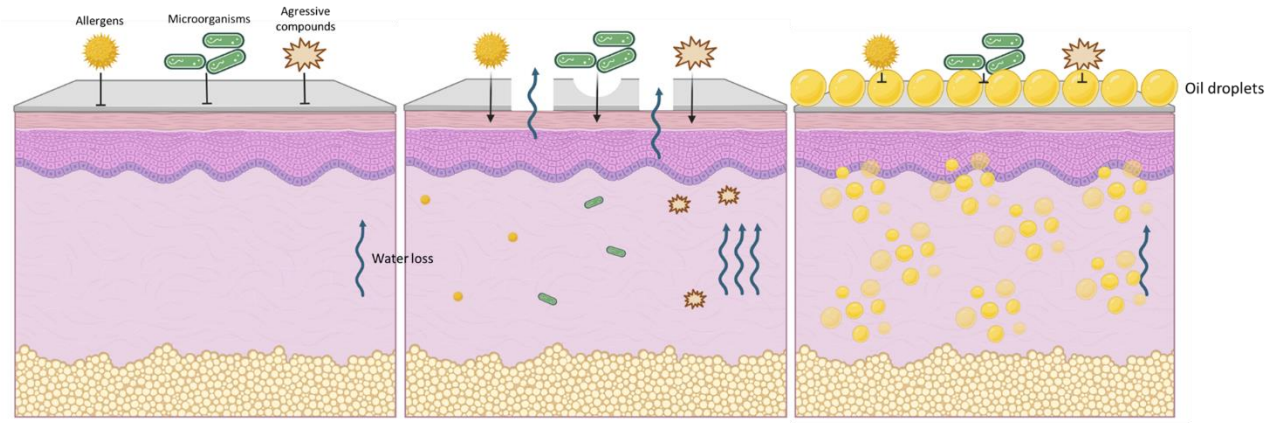


Figure 2 Skin-barrier repair using natural oils. Created with BioRender.com.

enhance its ability to regulate temperature (38).

Vegetable oils have a wide range of applications in the field of dermatology, particularly in the care of neonatal and infant skin (Figure 2). These oils are utilized as a treatment method for various conditions including atopic dermatitis, xerosis, and psoriasis, among others. Moreover, vegetable oils are known for their antimicrobial properties, making them a valuable asset in combating certain infections. In addition to their medicinal uses, these oils are also utilized in alternative therapies for rejuvenating treatments. Recently, there has been a surge in the popularity of incorporating these oils into hair and skincare routines, like, for example, argan oil. For instance, coconut oil, a well-known traditional moisturizer, has gained significant

attention in the beauty industry. It is worth noting that the versatility and efficacy of vegetable oils make them a staple in the field of dermatology and beyond (38).

2.4.1.2.1 Linoleic acid and Oleic acid

Oleic acid 18:1(n-9) (OA) is a monounsaturated fatty acid and is one of the most abundant fatty acids found in adipose tissue. This fatty acid belongs to the omega-9 family of fatty acids which are known to have several health benefits. However, when applied directly to keratinocytes, OA has been shown to have some undesirable effects. For instance, it has been found to be toxic and can cause skin irritation, characterized by redness, itching, and other mild symptoms. Additionally, OA increases the production of inflammatory molecules like interleukin (IL)-1α and other cytokines, which can further damage the skin. The increased production of these molecules is accompanied by heightened circulation of inflammatory cells, exacerbating inflammation and causing more severe skin damage. OA also leads to barrier disruption and can damage the lipid structure of the skin barrier, resulting in increased TEWL and decreased skin hydration. This can lead to dryness, itchiness, and inflammation, ultimately resulting in dermatitis. Therefore, it is important to be cautious when using oils with higher levels of irritating OA to avoid detrimental effects on the skin barrier (39).

Linoleic acid 18:2(n6) (LA) is an essential fatty acid that plays a crucial role in maintaining the health of the skin's outermost layer, known as the SC. This fatty acid is abundant in the SC and helps retain moisture by reducing TEWL when combined with water molecules. Decreased levels of LA in the skin have been associated with various skin diseases. Therefore, it is important to ensure that the skin has sufficient levels of LA to maintain its healthy function and appearance. This acid is metabolized in the skin and forms 13-hydroxyoctadecadienoic acid (13-HODE). The production of LA derivatives in the skin is facilitated by endogenous enzymes. These derivatives of LA have been found to have several beneficial effects, including the regulation of inflammation in the vascular wall. Moreover, 13-HODE plays a crucial role in preventing endothelial cell adhesion, which is vital for the proper functioning of the skin. It is worth noting that the skin's water permeability barrier is responsible for preventing water loss from the skin, especially from exposure to various environmental factors that can cause damage and dehydration. Therefore, the presence of LA and its derivatives, such as 13-HODE, is vital for the proper functioning and overall health of the skin. By ensuring that the skin's water permeability barrier is intact, one can prevent issues such as dryness, irritation, and inflammation, which can lead to more severe problems in the long run (13,40).

A study conducted an in-depth analysis of the differences in skin structure and function across different ethnic groups, concluded that while it is well-known that ethnicity influences pigmentation, such as the quantity of melanin, the melanosome content, and exposure to UV light, there are many other factors at play. Genetics, for instance, can also play a role in determining skin structure and function. The study found that there are also differences in the structure of the SC - the outermost layer of the skin - as well as the levels of TEWL and gland pore size. These differences can have significant implications for the health and appearance of the skin, and may require tailored approaches to skincare and treatment depending on a person's ethnicity. Understanding these differences is an important step towards developing more effective and personalized skincare regimens for people of all ethnic backgrounds (13).

Utilizing different proportions of essential fatty acids can be determinant for the repair of the skin's natural oil barrier. Research has shown that oils with a higher percentage of LA to OA ratio have better results at skin-barrier repair. However, it is important to note that oils with higher levels of irritating OA could lead to the detriment of the skin-barrier. Therefore, it is essential to carefully consider the composition of the oils used in skin care products to ensure that they are beneficial to the skin's natural barrier functions and do not cause any negative effects (25).

Plant oils with fortified FFA have been shown to act as penetration enhancers (40).

Other components such as flavonoids, carotenoids, and phenolic acids, among others, have high potential for antioxidant activity. They protect against reactive oxygen species (ROS). Triterpenes have been shown to improve tissue repair by reducing the time required for wound closure (13).

2.4.1.2.2 Vegetable oils of interest

In the following subsection, a detailed analysis will be conducted of several vegetable oils that are of great interest in the cosmetic industry. This analysis aims to provide a comprehensive understanding of the various ways these oils are currently being used and explore their potential applications. By delving into the intricacies of their properties, benefits, and suitability for different cosmetic products, it is possible to gain valuable insights that will contribute to the overall objectives of this study.

Sunflower Seed Oil is a highly beneficial oil that is extracted from the seeds of *Helianthus annus*. The oil has several important components, including OA and LA, with LA being present in a higher concentration than OA. In fact, LA makes up 60% of the oil. This acid is essential to maintaining the barrier function of skin, making sunflower seed oil ideal for use in skin products. In addition to OA and LA, sunflower seed oil also contains palmitic acid, stearic acid, and

linolenic acid. These components work together to not only preserve the integrity of the skin's SC, but also enhance hydration without inducing erythema. LA also serves as a peroxisome proliferator-activated receptor-alpha (PPAR-α) agonist, which intensifies Keratinocyte proliferation and lipid synthesis, ultimately improving skin barrier repair. Apart from all these skin benefits, sunflower seed oil has also been shown to have chemopreventive effects. One of the oil's constituents, sesamol, has been found to have this particular advantage. Additionally, the oil has demonstrated the ability to accelerate wound healing, making it an even more valuable ingredient in skin care products. With all of these benefits, it's clear that sunflower seed oil is an excellent choice for anyone looking to improve their skin's health and appearance (13,41,42).

Sunflower seed oil has been compared to olive oil in terms of their respective effects on the skin's SC. A study was conducted to investigate the effects of treatment with olive oil and sunflower seed oil on the SC over a period of 4 weeks. The results showed that treatment with olive oil not only reduced SC integrity but also caused a mild erythema in the volunteers. On the other hand, treatment with sunflower seed oil preserved the integrity of the SC in the same volunteers, indicating that it may be a more effective treatment for maintaining healthy skin (43).

Grape Seed Oil is a highly beneficial oil that is derived from the seeds of *Vitis vinifera*. With its high concentration of FFAs, vitamins, and phenolic compounds, Grape Seed Oil has become a popular choice for a wide range of applications. One of the key benefits of Grape Seed Oil is its high percentage of LA, which is typically between 65% to 72%. However, Grape Seed Oil also contains other beneficial fatty acids such as OA, palmitic acid, and stearic acid. This unique combination of fatty acids makes Grape Seed Oil a valuable ingredient in various formulations. In addition to its fatty acid profile, Grape Seed Oil also boasts high stability and resistance to oxidation. This is due to the fact that the oil has elevated concentration of tannins, which act as natural antioxidants (44).

Several studies have been conducted to determine the effectiveness of grape oil in the treatment of wounds in animals. The results of these studies have shown that the animals that were treated with grape oil had significantly higher values of hydroxyproline in the granulation tissue, which is an important factor in wound healing. Moreover, grape seed proanthocyanidin extract, a flavonoid that is extracted from the seeds of grapes, has been found to contain resveratrol. This compound has been shown to accelerate wound contraction and improve the synthesis of vascular endothelial growth factor (VEGF), which plays a crucial role in wound healing. Additionally, it has been found to enhance the deposition of connective tissue, which

is vital in the process of skin regeneration. Furthermore, resveratrol has been found to exhibit antimicrobial activity, which makes it a potentially effective treatment for wounds that are susceptible to infection. In addition, the oil has a high value of LA, which is an omega-6 fatty acid that has been found to aid with skin smoothness and TEWL (13,45).

Evening Primrose oil, extracted from the *Oenothera biennis* (L.) plant, is known for its unique composition. One of its most interesting characteristics is its high concentration of essential fatty acids, including α-linoleic acid (18:2 n-6; ALA) and γ-linolenic acid (18:3 n-6; GLA). These fatty acids are important for maintaining healthy skin and hair, as well as supporting overall health. In addition, Evening Primrose oil is also rich in β- sitosterol, making up approximately 64% of its composition. β-sitosterol is a plant sterol that has been shown to have potential health benefits, such as reducing inflammation and improving CHOL levels. Furthermore, Evening Primrose oil is a substantial source of vitamin E, a powerful antioxidant that helps protect the body from damage caused by free radicals. Vitamin E is also important for maintaining healthy skin and hair, as well as supporting immune function (13,46).

The use of oil in treating skin dryness and TEWL has been widely documented. In addition to its beneficial effects in this regard, recent research has also demonstrated its ability to stabilize the skin's SC barrier. However, it is important to note that the effectiveness of the oil in achieving these outcomes is highly dependent on the vehicle of administration. Specifically, research has shown that W/O emulsions are most effective. Furthermore, Evening primrose has been found to possess impressive antioxidant properties. Studies have also shown that it exhibits strong antibacterial and anti-inflammatory activity, making it a promising ingredient in a variety of skin care products. By incorporating Evening primrose into skin care formulations, it may be possible to enhance the overall efficacy of these products and provide users with a range of benefits beyond those traditionally associated with skin care (47).

Sweet almond oil is an unsaturated oil rich in OA, with a range of 40%-80%. It is a main source of vitamin E, and tocopherols play a significant part in ensuring the almond oil quality, protecting the oil from lipid oxidation. Studies have shown that almond oil can prevent damage caused by UV irradiation, including structural damage, and it has demonstrated abilities to partially inhibit histologic damage related to photoaging in mice skin. Historically, almond oil has been used in traditional medicine to maintain skin elasticity and improve skin conditions such as psoriasis or eczema. The oil is considered safe for human use, including topical application, since it is used in various cosmetic products as an emollient and emulsifier. Sweet almond oil has proven to be effective in reducing itchiness of striae and uremic pruritus. It has also been studied in preterm infants, with a randomized controlled trial showing improvement

in the hydration of the SC. In addition to its other benefits, sweet almond oil is proposed to act as a penetration enhancer for pharmaceutical drugs, with the quality of being a natural vehicle. However, more studies are necessary to fully understand the action mechanisms of the oil in terms of dermatologic effects, as there are divergent reports. One study using confocal Raman microspectroscopy *in vivo* showed that the almond oil only penetrated the outermost layer of the SC in infants and adults alike, while another study concluded that the oils penetrated deep into the SC, using laser scanning microscopy *in vivo* (48).

2.4.2 Humectant

Humectants are ingredients that have the ability to attract and retain moisture on the skin. They work by drawing water from the environment and binding it to the skin's surface. However, it's important to note that if the skin's barrier function is compromised or damaged, these humectants can actually exacerbate dryness rather than improve it. On the other hand, occlusives are substances that help to create a protective barrier on the skin, preventing moisture loss and promoting the healing process of the skin barrier. They work by forming a seal on the skin's surface, effectively trapping the moisture in and preventing it from evaporating. When it comes to choosing an effective moisturizer, it's essential to find a product that combines both humectants and occlusives. This combination ensures that the skin is not only hydrated but also protected from further dryness and damage. By attracting and retaining moisture while also preventing its loss, such a moisturizer can help to improve the overall health and condition of the skin (49,50).

In summary, the key to an ideal moisturizer lies in its formulation. By incorporating both humectants and occlusives, it can effectively address dryness and support the healing process of the skin barrier.

2.4.2.1 Glycerin, Sorbitol and Propilenoglicol

Glycerin, Sorbitol and Propilenoglicol are a common ingredient in cosmetics. They used as a humectant, which means that it helps to retain moisture in the skin. This can be particularly beneficial for individuals with dry skin, as it can help to keep the skin hydrated and prevent flakiness and cracking (50,51).

Glycerin, besides its properties as a humectant, possesses the ability to enhance the consistency of beauty products, resulting in a smoother and more effortless application. It also serves as a solvent, promoting the dissolution and blending of other components within the cosmetic formulation. In general, glycerin holds great versatility and value within the realm of

cosmetics. It expedites the process of barrier restoration and enhances the condition of parched and flaking skin. Glycerin contains three functional hydroxyl groups that have the potential to bind with water, thereby influencing the moisture dynamics of products when applied and used (51–54).

Sorbitol, a widely used food substance, is deemed safe for human consumption. In addition to its food applications, sorbitol also finds extensive use in the cosmetic industry. This is primarily attributed to its humectant properties, which help to retain moisture in the skin, its ability to condition the skin, and its thickening properties. Sorbitol belongs to the category of sugar alcohols and is composed of six carbon atoms. It occurs naturally in various sources, including vegetables, fruits, tobacco, and seaweed. When considering its safety, Sorbitol rarely causes contact dermatitis (50,55–57).

Propylene glycol, also referred to as 1,2-propanediol, is an alcohol that has the unique ability to effectively absorb moisture and effortlessly blend with water and a wide range of organic solvents. In addition to its versatile nature, propylene glycol serves multiple functions such as acting as a humectant to retain moisture, stabilizing emulsions, and reducing viscosity. It is worth mentioning, however, that propylene glycol has been associated with a noticeable occurrence of allergic contact dermatitis, although it is important to note that the prevalence of such cases is relatively low (58).

2.4.3 Other beneficial Ingredients

2.4.3.1 Essential oils

Essential oils are a complex mixture of volatile aromatic and aliphatic compounds that are arranged in a unique way at the molecular level. This unique arrangement leads to the delocalization of electrons within the molecules, resulting in better molecular stability (59).

Essential oils are widely utilized in cosmetics due to their generally safe nature. It is important to note, however, that there is a potential for adverse effects to occur as a result of their usage, particularly in individuals with allergies. It is worth mentioning that the risk of experiencing skin sensitization increases with higher concentrations of essential oils. Some common negative reactions that may arise include contact dermatitis, skin reactions, and photosensitivity. Despite the presence of allergens, it is generally believed that the use of essential oils in cosmetics is safe for the majority of individuals. On the other hand, vegetable oils, considering their extensive usage by a wide range of individuals, have been found to have an extremely low incidence of contact dermatitis or allergic reactions. Certain essential oils have

a higher likelihood of causing a reaction compared to others. This is because of the concentration and type of allergens present in the oils. If a powerful allergen is present, it can potentially result in allergic contact dermatitis. Therefore, it is advisable to avoid using these oils on sensitive or damaged skin (38,59,60).

Essential oils are highly concentrated extracts from plants, known for their aromatic properties and therapeutic benefits. Essential oils are typically volatile at room temperature and are used in aromatherapy, skincare products, and natural remedies (38).

2.4.3.2 Oats

Colloidal oatmeal is a natural and safe treatment for various skin conditions. Its antioxidant, anti-inflammatory, and anti-irritant properties make it highly effective in treating different skin problems. The oatmeal is rich in phenols, particularly Avenanthramides, which give it its unique therapeutic properties. The composition of colloidal oatmeal includes around 65%-85% starch, roughly 15%-20% proteins, and 3%-11% lipids, as well as fiber and beta-glucans, each around 5%. This composition allows colloidal oatmeal to target various biological processes in the skin, such as decreasing arachidonic acid and phospholipase A2, and reducing tumor necrosis factor-alpha (TNF-alpha). Moreover, oatmeal extract can inhibit factor kappaB in keratinocytes, which is essential in the treatment of inflammatory dermatoses. It also inhibits proinflammatory cytokines and histamine release, which are all related mechanisms in the pathophysiology of skin inflammation. Colloidal oatmeal has been used to relieve itchiness in many xerotic dermatoses. It has also been shown to be an excellent skin protectant against ultraviolet A (UVA), as the flavonoids in oats can absorb a wide spectrum of UV radiation, ranging from 320nm to 370 nm (61).

2.4.3.3 Hyaluronic acid

Hyaluronic Acid (HA) is a type of glycosaminoglycan (GAG) that is found in various parts of the body, including the skin, eyes, and joints. It has unique properties that depend on factors such as size, salt concentration, pH, and associated cations. HA serves as a lubricant and shock absorber in joints, is involved in tissue repair and regeneration, and plays a role in cell proliferation and migration. Additionally, unlike other GAGs, HA can form aggregates with proteoglycans, which are important for maintaining the integrity and elasticity of tissues. HA is also used in skincare products to improve the appearance and texture of the skin due to its high viscosity and ability to maintain hydration in the skin and other tissues. The skin's hydration depends on a molecule called HA, which binds water in the dermis and vital area of the

epidermis. This binding process helps to maintain the skin's moisture levels, keeping it looking healthy and radiant. One crucial part of the skin responsible for maintaining hydration is the stratum granulosum. This layer of the skin plays a critical role in producing the skin's NMF, which helps to preserve the skin's hydration levels. When the stratum granulosum is damaged, as is often the case in burn patients, it can lead to extensive loss of moisture and dehydration. This, in turn, can cause various clinical problems, such as itching, flaking, and cracking of the skin (62).

2.4.3.4 Niacinamide

Niacinamide, a form of vitamin B3, is a highly sought-after ingredient in skincare products. its popularity stems from its various uses, including improving skin texture, reducing inflammation, and brightening skin tone. In recent studies, it has been found that applying a moisturizer that contains niacinamide can not only reduce the appearance of wrinkles and fine lines, but also rejuvenate the skin. Furthermore, clinical studies have indicated that niacinamide can also be effective in decreasing the appearance of hyperpigmentation, particularly hyperpigmented spots. This has made niacinamide a popular ingredient in cosmetic skincare products, as it can provide visible benefits to facial appearance. In some cases, niacinamide has also been used as a dermatological treatment for acne. Additionally, it has been found to help rosacea patients in improving their skin appearance while supplementing topical retinoids in skincare. All in all, the benefits of niacinamide make it a popular ingredient in many skincare products, and its effectiveness continues to be studied in order to provide better solutions for skincare concerns (63).

2.4.3.5 Collagen

Collagen is a crucial protein that forms connective tissues throughout the human body, including the skin, joints, and bones. It is highly abundant in all living organisms and plays a vital role in maintaining the structural integrity of biological tissues. Due to its abundance, strength, and correlation with skin aging, collagen has become an increasingly important topic of interest for the cosmetic industry. Recent studies have focused on the effects of collagen on skin aging, revealing that collagen fibers tend to lose thickness and strength over time, which is directly associated with the aging process. Moreover, in cases of skin damage, such as in burn patients, the collagen fibers in the affected area can become thinner and weaker, leading to a loss of elasticity and firmness in the skin. This can result in clinical problems, such as itching, flaking, and cracking of the skin (64).

2.4.3.6 Ceramides

The structure of CERs, which binds the corneocytes and contributes to the integrity of the skin, plays a vital role in maintaining the skin's barrier function. The arrangement of lipids forms a protective barrier in the SC, preventing water loss and enhancing impermeability. Any changes in the quantity and arrangement of CERs in the SC can result in skin disorders characterized by compromised barrier function. Variations in the levels and distribution of CERs within the SC can lead to different skin conditions associated with barrier defects. For example, atopic dermatitis is characterized by reduced levels of CERs I and III, while ichthyosis and psoriasis also show abnormalities in the composition of CERs. Acne is also affected by CERs levels, with lower CERs potentially worsening symptoms. Researchers have investigated the use of topical CERs applications as a possible treatment approach for these skin disorders (65).

2.4.4 Controversial ingredients

2.4.4.1 Preservatives

Microorganisms play a crucial role in the decomposition and recycling of organic matter, ensuring the sustainability of ecosystems. However, their presence can also pose risks, as they have the potential to contaminate and spoil various products. In order to mitigate these risks, preservatives are commonly used to prevent excessive microbial growth and chemical deterioration. The ideal preservative should not only exhibit stability, are inexpensive and have a long shelf life but also be non-toxic and non-irritating, ensuring consumer safety. However, it is important to note that only a limited number of preservatives meet these stringent requirements, as some have been found to trigger allergic reactions. This is particularly relevant in the case of cosmetics, which have been known to be highly susceptible to causing allergic contact dermatitis, a condition that affects many individuals (66,67).

2.4.4.1.1 Parabens

Parabens have been used as an effective preservative in the cosmetic industry for decades. However, due to controversies surrounding their use, many consumers now avoid products containing parabens. The compound is derived from p-hydroxybenzoic acid and is not only used in cosmetics but also in food products. Parabens are preferred over other alternatives due to their effectiveness and lower cost, and have been used since the 1930s. They are found in a wide range of products, from soaps to dental products, with methyl and propyl parabens being the most commonly used derivatives. Lipsticks contain them in concentrations ranging from 1.15% to 1%, while pharmaceutical products can contain up to 20%. Formulas containing

parabens are generally considered safe and non-carcinogenic. However, they may cause allergic reactions, specifically allergic dermatitis, when applied to the skin. This is dependent on the formulation of the cosmetic product and the derivative used (68).

Despite being considered safe, regulatory agencies have restricted the usage of parabens in cosmetics due to the potential health risks associated with their absorption into the human body from the products that contain them (69).

In conclusion, parabens have been widely used in the cosmetic industry for several decades. While they are effective and preferred over other alternatives, their usage has been restricted due to potential health risks. Despite being generally considered safe, they may cause allergic reactions when applied to the skin and have led many consumers to avoid products containing them.

2.4.4.1.2 Formaldehyde

Formaldehyde (FA) is a colorless gas with a pungent odor that has various applications, including use as a disinfectant, in resins, and in cosmetics. However, its use in cosmetics has decreased due to potential carcinogenic effects. Despite this, it can still be found in some hair-care products and nail hardeners. FA is considered an irritant and sensitizer. It is important to note that FA can be a hidden ingredient in cosmetics labeled as "FA-free" because FA levels in cosmetics are regulated. The recommendations state that the levels of free FA should not exceed 0.2%. As FA is a known allergen and irritant, with potential respiratory carcinogenic properties, some argue that all cosmetics containing any amount of FA should be labeled accordingly (66,67).

2.4.4.2 Alpha hydroxy acids

Alpha hydroxy acids (AHA) are a group of cosmetic ingredients that have been widely used in various skin care products. Though their mechanism of action is not yet fully understood, there is a widely accepted hypothesis that AHA alters the concentration of calcium ions in the epidermis by reducing its abundance. This, in turn, leads to the removal of ions from the cell's adherence through chelation, further resulting in desquamation. One of the significant benefits of AHA is the skin rejuvenation it provides by lowering the concentration of calcium ions, thus leading to growth and cell differentiation. Apart from this, AHA also aids in reducing the corneal layer and thickening of the epidermal and dermal layer, which in turn, improves lines and wrinkles. However, it is important to note that AHA can be quite controversial when used in higher concentrations, which are typically used in chemical peeling to exfoliate the SC. This procedure permits cellular renewal and results in a stainless and smooth skin. However,

this often leads to erythema and flaking that increase with the concentration of AHA. Moreover, AHA has also been correlated with photosensitivity, which means that it can make the skin more sensitive to sunlight and result in skin damage. Therefore, it is recommended to use AHA-containing products with caution and follow the instructions diligently to avoid any adverse effects. Despite the controversies surrounding AHA, it is an excellent ingredient in many skin care products, providing various benefits to the skin (70).

2.4.4.3 Perfumes

Odors play a crucial role in influencing human behavior. While pleasant smells have a soothing effect, unpleasant scents can have a detrimental impact on mood, leading to feelings of anxiety and discomfort. When it comes to perfumes, they can be broadly categorized into natural and synthetic variants based on their origins. Natural perfumes are derived from plants or animals, whereas synthetic perfumes are meticulously crafted in laboratories to replicate natural fragrances or create entirely new and distinctive scents (71).

In Europe, approximately 16% of individuals with eczema are sensitized to fragrance ingredients, and an estimated 1-3% of the population suffers from allergies to fragrance components. Fragrances are the primary culprits behind allergic contact dermatitis cases related to cosmetic usage, accounting for more than 30% of reported incidents. Identifying specific fragrance allergies poses a challenge due to the intricate compositions of perfumes. Notable allergens commonly found in fragrances include Citronellol, d-Limonene, and Linalool (71–73).

It is now obligatory to disclose the presence of any of these PASs on product labels if they exceed certain concentrations (72,73).

2.5 Skin microbiome

The skin is not just a physical barrier that protects us from the outside environment, it is also a complex ecosystem that hosts a diverse array of microorganisms collectively known as the microbiota. This microbiota is comprised of a wide variety of bacteria and fungi, which work together to maintain the skin's health and integrity. It is also worth noting that the composition of this microbiota can vary depending on factors such as age, diet, and overall health, and disruptions to this delicate balance can lead to a range of skin conditions and diseases. Therefore, it is important to understand and study the skin microbiota in order to develop effective treatments and therapies for these conditions (74).

The skin microbiome, much like other microbiota in the human body, performs crucial functions such as protection against pathogen invasion, breakdown of natural products, and communication with the immune system to maintain a healthy balance. However, disruptions to the skin microbiome can lead to skin diseases and even systemic diseases. There are several factors that can cause such disruptions, including an imbalance between pathogens and commensals or physical trauma to the skin barrier. Given that the skin covers the entire body and varies in characteristics depending on the site, microorganisms also have a diverse range of species coexisting in the skin. Skin sites can be classified according to their physiological characteristics and grouped into three categories: sebaceous, dry, or moist. As such, understanding the complexity of the skin microbiome and its impact on overall health requires a comprehensive approach that takes into account the unique characteristics of each skin site (75).

Bacteria are microorganisms that can be found in various sites of the body, with the genera Staphylococcus and Corynebacterium commonly found in moist sites, while Propionibacterium is often found in sebaceous sites. Probiotics, microorganisms associated with positive and beneficial results in animals and humans, have been found to have various functions, including the treatment of gastrointestinal diseases. Interestingly, probiotics have also been found to have the ability to treat skin diseases, such as psoriasis and atopic dermatitis. This is due to their ability to produce particular cytokine analogs that can inhibit the growth of pathogenic bacteria. With this in mind, the possibility of using probiotics as a treatment option for skin diseases is an exciting area of research that warrants further investigation and exploration. In the future, it may be possible to develop probiotic-based treatments that can provide a safe and effective means of managing a variety of skin conditions, ultimately improving the lives of many individuals (74).

2.5.1 Probiotics and prebiotics

A simple way to understand the difference between prebiotics and probiotics is that the former increases the population of bacteria that already reside in the medium, while the latter incorporate exogenous bacteria, providing new bacterial strains (76).

Inulin is a polysaccharide without branches that belongs to the fructans class. Its components are fructose (30-35 units), and the units are linked by β-1,2-glycosidic bonds. Inulin is used in the cosmetic industry due to its prebiotic benefits, such as antimicrobial activity. Another positive aspect of inulin is that it is extracted from plants, making it a renewable source. In addition to the aforementioned benefits, inulin can also be used as an emulsion stabilizer

and detergent. It is a nutritious component that does not cause any type of irritation on the skin, as it does not form unsafe active ingredients on the surface. The concentration used in O/W emulsions tends to be lower, around 0.2% to 1% (76,77).

2.6 Objectives

Oncological treatments can lead to skin changes and undesired effects, such as itching, which can significantly impact the daily lives of patients. However, with adapted care, it is possible to prevent or minimize these effects, thereby improving the overall quality of life.

The objective of this project is to develop and analyze a cosmetic solution specifically tailored for individuals with sensitized and compromised skin, addressing their unique needs and challenges. This is particularly important for those undergoing cancer treatment, as their skin requires extra care and attention. The primary goal of this thesis is to create a formulation that effectively reduces the negative effects caused by oncological treatments, promoting the rejuvenation and revitalization of the patient's skin health. By achieving this objective, we can greatly enhance the individual's overall well-being and quality of life.

To successfully accomplish this goal, a comprehensive analysis will be conducted, utilizing a wide range of tests. These tests will include droplet size analysis, microscopic examination, rheology tests to assess viscosity flow behavior, oscillatory analysis, and tribology analysis. Additionally, texturometer tests will also be conducted to further enhance the accuracy and reliability of the analysis. Furthermore, stability tests have been conducted to ensure the long-term viability and effectiveness of the formulation.

In addition, a questionnaire has been conducted to identify cutaneous side effects experienced during and after cancer treatments, as well as to evaluate suitable cosmetic products for the skin of cancer patients. The findings of this questionnaire will enhance our understanding of skin-related side effects and help identify effective products to alleviate these effects, ultimately benefiting the health and well-being of cancer patients.

3

MATERIALS AND METHODS

3.1 Materials and Methods

3.1.1 Materials

Kahl Vego Jelly 7036 PLUS (Ricinus Communis (Castor) Seed Oil (and) Hydrogenated Rhus Verniciflua Peel Wax (and) Rhus Succedanea Fruit Wax (and) Ascorbyl Palmitate (and) Tocopherol) was obtained from KahlWax (Germany); Kahlwax 7036 (Crambe Abyssinica Seed Oil (and) Euphorbia Cerifera (Candelilla) Wax (and) Hydroxystearic Acid (and) Beta-Sitosterol (and) Rhus Verniciflua Peel Wax (and) Tocopherol (and) Helianthus Annuus (Sunflower) Seed Oil) was obtained from KahlWax (Germany); Kahl Complex 6427 (Crambe Abyssinica Seed Oil (and) Euphorbia Cerifera (Candelilla) Wax (and) Hydroxystearic Acid (and) Beta-Sitosterol (and) Rhus Verniciflua Peel Wax (and) Tocopherol (and) Helianthus Annuus (Sunflower) Seed Oil) was obtained from KahlWax (Germany); Shea butter (Butyrospermum Parkii (Shea) Butter) was obtained from Plena Natura (Portugal); Tegin 4100 Pellets (Glyceryl Stearate) was obtained from Evonik (Germany); Tego Alkanol 1618 (Cetearyl Alcohol) was obtained from Evonik (Germany); Sunflower oil (Helianthus Annuus (Sunflower) Seed Oil) was obtained from Plena Natura (Portugal); Grape seed oil (Vitis Vinifera (Grape) Seed Oil) was obtained from Plena Natura (Portugal); Evening primrose oil (Oenothera Biennis (Evening Primrose) Oil) was obtained from Plena Natura (Portugal); Glycerin (Glycerin); Geogard Ultra (Gluconolactone (and) Sodium Benzoate) was obtained from Lonza (Switzerland); Tego Care CG 90 (Cetearyl Glucoside) was obtained from Evonik (Germany); Citric acid·H_2O (Acidum citricum monohydricum) was obtained from Fagron (Denmark); Sodium citrate·$2H_2O$ (Sodium citrate); Montanov 68 (Cetearyl Alcohol (and) Cetearyl Glucosid) was obtained from Seppic (France); Xanthan gum (Xanthan gum) was obtained from Neimenggu Fufeng Biotecnhologies (China); Sabowax CP MB (Hexadecanoic acid (and) hexadecyl ester) was obtained from SABO S.p.A. (Italy); Deionized water.

3.1.2 Manufacturing process

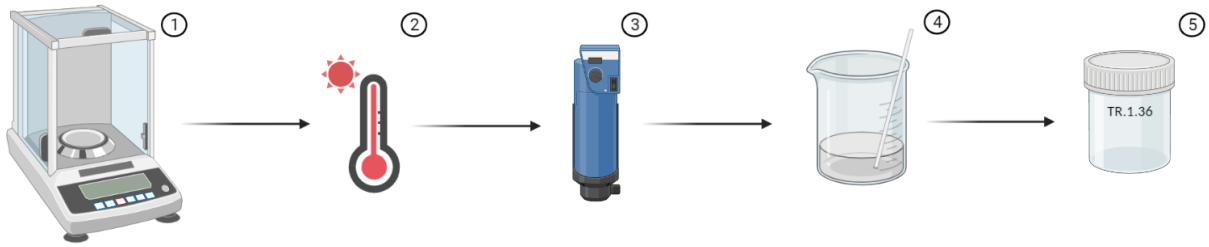


Figure 3 Representation of the protocol followed to create the formulations of this study. Created with BioRender.com.

The process of creating the emulsion began with the precise measurement of all ingredients. A scale was used to weigh each ingredient, ensuring that the correct amount was added to the mixture. The water phase and oil phase were weighed separately. These phases were, then, placed on a warm bath at 75ºC to ensure each component dissolved correctly (Figure 3, Illustration 2). After the components had dissolved, the oil phase was added to the water phase, creating a two-phase formulation. To mix the formulation, an ultraturax was used for 1 minute at a speed of 14500 rpm (Figure 3, Illustration 3). The mixture was then stirred manually until it had cooled down (Figure 3; Illustration 4). At this point, the heat-sensitive compounds were carefully added to the mixture. To complete the process, the emulsion was then transferred to its appropriate container. This step ensured that the emulsion was properly stored and protected until it was ready for use (Figure 3; Illustration 5). As can be seen in Figure 3, this process was carefully monitored and executed to create the perfect emulsion.

3.1.3 Physical and chemical characterization of emulsions

After developing formulations, it is essential to validate their consistency with a sensory method. In this case, several tests were conducted to validate or exclude an emulsion. These tests included macroscopic characterization and spreadability, phase separation test, droplet size analysis, and rheology.

Macroscopic characterization is the visual observation of the emulsion, such as its color, texture, and homogeneity. The spreadability test determines the ability of the emulsion to spread on the skin or other surfaces. Phase separation test assesses the stability of the emulsion by detecting any separation of the oil and water phases. Droplet size analysis measures the size of the droplets within the emulsion, which is essential in understanding the emulsion's

stability and efficacy. Lastly, rheology evaluates the flow properties of the emulsion under different conditions. The validation method used in this study was crucial in determining the effectiveness of the formulations. The subsequent figure 4 demonstrates the validation method

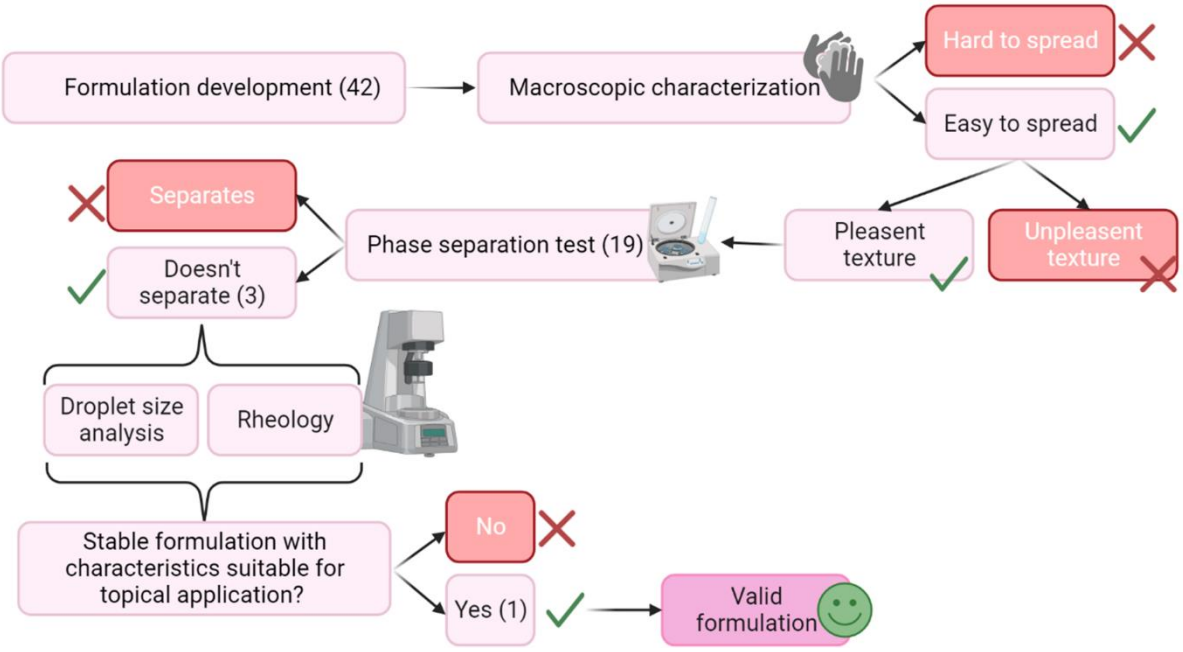


Figure 4 Validation method representation

mentioned.

3.1.3.1 Appearance, pH determination and physical stability

According to the method representation for validation, the nineteen formulations that were previously approved underwent a phase separation test. In order to ensure that the different formulations were clearly separated, the test was designed with the intention of eliminating any that did not meet this criterion. Specifically, 2g of each formulation was transferred to a tube and centrifuged at 4000rpm for 10min. The results of the test revealed that only one formulation separated, which ultimately led to its elimination. When combined with the macroscopic characterization, two more formulations were eliminated, bringing the total number of eliminated formulations to three.

The table presented below (Table 1) shows the base composition of the stable formulations of F1, F2 and F3. These formulations are quite similar, with the only variation being in the emollient used (varying the waxes).

Table 1 Representation of the stable formulations, hence the final formulation

Ingredients	INCI name	Function	Quantity (%)		
			F1	F2	F3
Kahl Vego Jelly 7036 PLUS	Ricinus Communis (Castor) Seed Oil (and) Hydrogenated Rhus Verniciflua Peel Wax (and) Rhus Succedanea Fruit Wax (and) Ascorbyl Palmitate (and) Tocopherol	Emollient	5	X	X
Kahlwax 7036	Crambe Abyssinica Seed Oil (and) Euphorbia Cerifera (Candelilla) Wax (and) Hydroxystearic Acid (and) Beta-Sitosterol (and) Rhus Verniciflua Peel Wax (and) Tocopherol (and) Helianthus Annuus (Sunflower) Seed Oil	Emollient	X	5	X
Kahl Complex 6427	Crambe Abyssinica Seed Oil (and) Euphorbia Cerifera (Candelilla) Wax (and) Hydroxystearic Acid (and) Beta-Sitosterol (and) Rhus Verniciflua Peel Wax (and) Tocopherol (and) Helianthus Annuus (Sunflower) Seed Oil	Emollient	X	X	5
Shea butter	Butyrospermum Parkii (Shea) Butter	Emollient	5	5	5
Tegin 4100 Pellets	Glyceryl Stearate	Stabilizer	2	2	2
Tego Alkanol 16:18	Cetearyl Alcohol	Stabilizer	1	1	1
Sunflower oil	(Helianthus Annuus (Sunflower) Seed Oil	Emollient	3	3	3
Grape seed oil	Vitis Vinifera (Grape) Seed Oil	Emollient	4	4	4
Evening primrose oil	Oenothera Biennis (Evening Primrose) Oil	Emollient	6	6	6
Water	Aqua	Solvent	55.05	55.05	55.05
Glycerin	Glycerin	Humectant	3	3	3
Geogard	Gluconolactone (and) Sodium Benzoate	Preservative	1	1	1
Tego Care CG 90	Cetearyl Glucoside	Emulsifier	3	3	3
D-Panthenol	Panthenol	Vitamin	5	5	5
Sodium citrate $\cdot 2H_2O$	Sodium citrate	Ph stabilizer	0.1	0.1	0.1
Citric acid$\cdot H_2O$	Acidum citricum monohydricum	Ph stabilizer	0.05	0.05	0.05
Vitamine E	Tocopherol	Antioxidant	0.2	0.2	0.2
Allantoin	Allantoin	Wound healing	0.1	0.1	0.1
Niacinamida	Niacinamide	Reducing inflammation	0.5	0.5	0.5

Inulin	Inulin	Prebiotic	0.5	0.5	0.5
Ceramides	Ceramide	Maintaining the skin's barrier function	5	5	5
Hydrolized oats	Hydrolyzed oats	Anti-inflammatory and anti-irritant	0.5	0.5	0.5

3.1.3.2 pH determination

The pH value was determined for each formulation with the pH meter (pH Meter 744 (Metrohm) at room temperature. During the experiment, it was ensured that the values had stabilized before collecting the data. After the stabilization of the values, the pH was adjusted to an interval between 5-6. To achieve this, a solution of sodium hydroxide (NaOH) 40M was used. The use of NaOH to adjust the pH was necessary to ensure that the experiment is conducted under the required conditions. It is important to note that the pH range of 5-6 was specifically chosen for the experiment to ensure that the results obtained are accurate and reliable.

3.1.3.3 Droplet size analysis

To determine the droplet size distribution of the emulsions, a Malvern Mastersizer 2000 instrument was employed, which utilizes light scattering technology. In order to ensure proper obturation, each formulation (0.5g) was diluted in 25mL of distilled water. It was necessary for the sample to reach an obstruction between 10% and 15%, which was achieved by adding approximately 3mL of the diluted sample to the chamber, along with distilled water, using a stirrer at 1750rpm.

The data were expressed in terms of the relative distribution of the volume of droplets and given as diameter values corresponding to percentiles of 10%, 50%, and 90% (mean ± SD; n=6). The measurements were performed 24 hours after the preparation of the emulsions.

Importantly, the measurements were performed 24 hours after the preparation of the emulsions to ensure accurate results.

3.1.3.4 Viscosity test

In this subsection, the relation between shear viscosity and time is demonstrated in the three tests.

During the shear rate test, the measurements were performed at a temperature of 25ºC. The test started with a shear rate of $0.1s^{-1}$ and gradually increased until reaching a final shear rate value of $100s^{-1}$. In order to gather comprehensive data, 10 samples were collected for each decade during the experiment.

In Three step of shear rate test, the first step involves a slow shearing process with a shear rate of $0.100s^{-1}$, lasting for 30s with a 2s sampling interval. This step provides a reference for the sample's behavior at rest. The second step involves quick shearing with a shear rate of 100 s^{-1}, lasting for 30s with a sampling interval of 2 s. The final step, the third step, is the recovery step. It involves a shear rate of $0.1s^{-1}$, lasting for 10min with a sampling interval of 1s, and all steps are performed at a temperature of 25˚C.

The Thixotropic Index (TI) was calculated for each formulation using the following formula:

$$TI = \frac{\eta\, A}{\eta\, B}$$

Where η A Is the viscosity at 2s and η B Is the viscosity at 600s.

In the test of ramp up and ramp down, the experimental setup involved a sequence of ramp-up and ramp-down procedures at a constant temperature of 25˚C. This sequence, which lasted for 5min, involved the retrieval of a total of 10 samples per decade. The maximum and minimum shear rates obtained were $100s^{-1}$ and $0.1s^{-1}$, respectively.

3.1.3.5 Oscillation test

The test was conducted in the linear viscoelastic region, at a temperature of 25˚C, with the frequency starting at 10Pa and ending at 0.1Pa. A total of 10 samples were collected per decade, allowing for a thorough analysis of the material's viscoelastic behavior. By performing an oscillatory test, we can gain valuable insights into both the viscous and elastic responses of the material. This information is essential in determining the material's suitability for a particular application, as well as in understanding its behavior in different conditions.

3.1.3.6 Adhesion test

In order to evaluate the tackiness and adhesion properties of the material, a pull away test was performed at a temperature of 25ºC. The test was conducted using a plate-plate geometry with a gap of 5.5mm and a velocity of 0.5 mm/s. The test was repeated 6 times (n=6) to ensure statistical significance. Overall, the pull away test is a crucial tool in evaluating the performance of adhesives and other materials that rely on tackiness and adhesion for their functionality.

3.1.3.7 Tribology

To conduct this study, the following parameters were established. The study was conducted at a temperature of 25ºC, which was deemed suitable for the purpose of the study as it is the reference temperature. A three-ball-on-plate geometry was used in the assay. The assay's velocity was varied between $1x10^{-4}$rad/s and 25rad/s to collect a wide range of data. Finally, the normal force was set at 0.5N.

3.1.3.8 Spreadability

The spreadability of the emulsions was evaluated by following a specific protocol. First, 1g of each emulsion was carefully measured using an analytical balance. Next, each emulsion was placed at the center of an acetate sheet. A second acetate sheet, of the same size, was then placed on top of the emulsion. To apply pressure, a weight of 200g was placed on the upper face of the sheet. After 2min, the weight was removed, and the spread area was observed over time. During the test, a photograph was taken every 30s. By using the program ImageJ, the diameter of the spread area (in cm) was calculated from the photographs. These measurements were taken in triplicate (n=3) to ensure accuracy and consistency of results.

3.1.3.9 Microscopy analysis

To gain a more comprehensive understanding of the droplet size distribution, it was conducted an optical microscopic study in addition to the Malvern analysis. The optical study was performed using a trinocular microscope (Y-TV55 lens) equipped with a digital camera (MD-E3-6.3) and connected to a computer (SyncMaster BX2331). The samples were carefully prepared by placing them on slides and covering them with coverslips. It was observed the samples under the microscope with a magnification of 40x, carefully analyzing their morphology and size distribution.

3.1.3.10 Texturometer

To determine the force required to remove the product from its airless tight packaging, a measuring actuation force test was conducted using a hemispherical probe. Additionally, a spreadability test was performed using the TTC Spreadability Fixture.

In the spreadability test, the probe return distance was set to 25mm. The probe gently penetrates the sample to a depth of 2mm above the surfaces of the concave container, causing the probe to move a distance of 23mm. The speed test was set to 3.0mm/s, and the post-test speed was set to 10.0mm/s.

3.1.4 Stability assay

During the stability assay, two different conditions (at 25ºC and at 40ºC±2ºC, 75% RH±5%) were tested in an airless tight container at 25ºC and at 40ºC. The following set of tests were performed to evaluate the emulsion stability: pH, viscosity behavior, oscillation frequency, and droplet size distribution.

The values were obtained on four different occasions: T0 (one week after production); T1(One month after production); T2(Three months after production); T3 (Five months after production).

4
RESULTS AND DISCUSSION

This chapter presents the results of the study, focusing on the selection of the final formulation and stability assay results. The selection process involved testing different formulations and analyzing the results.

4.1 Topical Formulation development

To create a skin-friendly emulsion that repaired and protected the damaged skin, specific compounds were selected for that purpose. Research was conducted in order to build a concrete formulation and from there a several formulations were executed.

4.1.1 Composition of the validated formulation

The following section provides an in-depth analysis of the process of inclusion and exclusion that ultimately led to the final formulation. By examining the various components that were included and excluded throughout the development process, we can gain a deeper understanding of the factors that influenced the final outcome.

4.1.1.1 Process of decision

Considering that, O/W emulsions are commonly used in cosmetic and pharmaceutical products due to their moisturizing properties, skin absorption capacity, and less viscous, often more easier to spread on the skin, this type of emulsion was selected for this project. The chosen ingredients were selected based on their function and potential, taking into consideration what was mentioned in the theoretical support chapter. The vegetable oils chosen were also presented in the theoretical support chapter. These oils were selected based on their high concentration of LA, along with their additional beneficial characteristics.

At the outset of the process, a basic formulation was created using a few key ingredients, including sunflower seed oil, an emulsifier (Hexadecanoic acid (and) hexadecyl ester), a preservative (Gluconolactone (and) Sodium Benzoate), a surfactant (Cetearyl Glucoside), glycerin, and water. However, upon testing through sensorial methods, it was discovered that this mixture contained too much water and was excessively oily. It was clear that the oily component

of the formulation needed to be altered. Given that sunflower oil, which was already being used, is naturally oily, it was deemed essential to incorporate dry oils to improve this aspect. By adding dry oils, it was possible to achieve a more desirable consistency and texture that would be more effective in its intended use.

In the second attempt, the formulation was modified to include two additional oils: grape seed oil and primrose oil. These two oils were chosen for their unique properties as "dry oils," which means that they are quickly absorbed by the skin without leaving a greasy residue. This new oil mixture proved to be effective and was maintained throughout the rest of the testing process, with only slight adjustments made to the percentage of each oil used. The addition of grape seed oil and primrose oil not only improved the texture of the final product, but also added additional nourishing benefits for the skin.

Once the oil components were established, different combinations of ingredients were tested. One example of such components is Shea butter. Not only is it deeply moisturizing, but it also has anti-inflammatory properties that make it a great choice for those with sensitive skin. This ingredient was added during the testing phase and ultimately selected for the final formulation.

The texture was still very fluid, almost watery, so in the next phase another emulsifier (Cetearyl Alcohol (and) Cetearyl Glucosid). In this phase the percentage kept being changed so the ideal combination was obtained.

This emulsifier was chosen due to its ability to stabilize emulsions and improve texture.

Xanthan gum is a polysaccharide that is commonly used as a food additive due to its unique thickening and stabilizing properties. Its application, however, is not limited to the food industry. Xanthan gum is also utilized in the production of cosmetics, pharmaceuticals, and even industrial products. In fact, it has been widely studied and tested for its efficacy in various fields, with promising results. For these reasons, it was conducted an experiment to understand the impact of the mentioned component on the fluidity of the emulsion.

Improvements were observed in the formulations, nevertheless, thickener agents were tested. Three different agents were tested: glyceryl stearate, cetearyl alcohol, and stearic acid. Each agent was tested alone at different percentages to assess its individual effect on the thickness of the formulation. After these individual tests, the agents were then combined in different ratios to determine how they would interact with each other and affect the overall thickness of the formulation. These tests provided a comprehensive understanding of how the different thickener agents can be utilized to optimize the formulation's thickness.

In order to address the issue of formulation texture, natural waxes were added to the product. The chosen waxes were carefully selected to ensure that the desired skin feel was achieved. These waxes (Kahl Vego Jelly 7036 PLUS (Ricinus Communis (Castor) Seed Oil (and) Hydrogenated Rhus Verniciflua Peel Wax (and) Rhus Succedanea Fruit Wax (and) Ascorbyl Palmitate (and) Tocopherol (F1); Kahlwax 7036 (Crambe Abyssinica Seed Oil (and) Euphorbia Cerifera (Candelilla) Wax (and) Hydroxystearic Acid (and) Beta-Sitosterol (and) Rhus Verniciflua Peel Wax (and) Tocopherol (and) Helianthus Annuus (Sunflower) Seed Oil (F2); Kahl Complex 6427 (Crambe Abyssinica Seed Oil (and) Euphorbia Cerifera (Candelilla) Wax (and) Hydroxystearic Acid (and) Beta-Sitosterol (and) Rhus Verniciflua Peel Wax (and) Tocopherol (and) Helianthus Annuus (Sunflower) Seed Oil) (F3)) were added to different formulations, with the same percentage, to analyze the different texture formulations they produced. F1, for instance, is known for its excellent film-forming properties and its ability to provide a smooth, non-greasy feel. F2, on the other hand, is a versatile wax that improves texture and stability. Finally, F3 is a unique blend of natural waxes that enhances the sensory experience of the product. By incorporating these natural waxes into the formulations, the product's texture was significantly improved, resulting in a formulation that not only feels great on the skin but also delivers the desired benefits.

By combining all of the knowledge that had been acquired thus far, six formulations were created, each of which showed promise. To determine which of these formulations were most viable, a phase separation test was conducted, which resulted in the elimination of one of the six. The remaining five formulations were then used to create three final formulations, which involved combining the waxes with the thickeners. These three formulations were then subjected to the phase separation test once again.

Despite their differences, all three of the final formulations had a desirable texture.

4.1.1.2 Final formulations

The three formulations (F1, F2 and F3) that have been chosen to proceed to the next phase of the project seem to have very similar compositions, with the only difference being in the wax used. This section will delve deeper into the composition of the selected formulations, highlighting their unique properties and explaining why they are ideal for fulfilling the objectives of this project.

In addition to the listed ingredients, water is also included in the formulation. It serves as a solvent, diluent, and humectant, among other purposes.

4.1.1.2.1 Waxes

Waxes have been found to be an excellent alternative to synthetic emollients in cosmetic products such as skin creams, lotions, cleansers, and lip care products. They offer a range of benefits such as excellent skin tolerance, protecting properties and broad viscosity options. In addition, waxes are known to provide long-lasting hydration and nourishment to the skin, making it look smooth, supple, and youthful.

However, as with any natural ingredient, the use of waxes may also have some downsides. For example, natural triglycerides can lead to crystallization, unsaturated compounds can cause oxidation, and undesirable colors or odors may develop. Some waxes may also be incompatible with other natural and synthetic ingredients, which can affect the stability of the formulations and lead to product degradation over time. It's important in cosmetic formulators to carefully consider the type and amount of wax used in the products to ensure that it strikes the right balance between benefits and drawbacks (78,79).

4.1.1.2.2 Shea butter

Shea butter is an interesting natural ingredient that has a lot of benefits. It is made up of triglycerides, which are compounds that are composed of glycerol and three fatty acids. The specific fatty acids found in shea butter are OA, stearic, LA, and palmitic acids. These fatty acids have been shown to have many positive effects on the skin, such as moisturizing, anti-inflammatory, and anti-aging properties. In addition to these fatty acids, shea butter also contains unsaponifiable matter, which is a complex mixture of plant sterols and triterpene alcohols that have been found to have antioxidant and soothing properties. Additionally, shea butter has, like it was mentioned, anti-inflammatory properties that can help alleviate skin conditions such as eczema and psoriasis. It was also been found that Shea butter has tocopherol in is composition, cosmetics that contain tocopherol, also known as Vitamin E, have become increasingly popular in recent years. Tocopherol is a fat-soluble antioxidant that helps to protect the skin from damage caused by environmental factors such as pollution, UV radiation, and cigarette smoke. It can also help to improve the overall health and appearance of the skin by reducing the appearance of fine lines and wrinkles, and by promoting the growth of healthy skin cells. As a result, many skincare brands have begun to incorporate tocopherol into their products, making it easier than ever for consumers to benefit from its many advantages. Shea butter is also a natural moisturizer that can soothe dry and cracked skin. In fact, shea butter is a common ingredient in many skincare products because of its nourishing properties (80,81).

4.1.1.2.3 Vegetable oils

The oils that have been selected were previously introduced in this thesis. To summarize what has been mentioned before:

Sunflower seed oil is abundant in essential fatty acids, especially LA, which are essential for maintaining healthy skin, it also possesses hydrating properties. Grape seed oil is a potent antioxidant that contains essential fatty acids and vitamin E, making it beneficial for nourishing and moisturizing the skin. In addition to its high LA content, evening primrose oil has positive effects on treating skin dryness and maintaining the skin's barrier. The product formulation incorporates high concentrations of these oils to deliver the necessary nutrients for healthy and radiant skin.

4.1.1.2.4 Tegin 4100 pellets and Tego alkanol 16:18

Tegin 4100 Pellets (glyceryl stearate) and Tego alkanol 1618 (Cetearyl Alcohol) are emulsifiers that are derived from vegetable raw materials. They are widely used as an emulsifying agent in O/W creams because of their excellent application properties. Additionally, they can improve the texture and feel of creams, leaving a pleasant sensation on the skin (82,83).

4.1.1.2.5 Geogard

Geogard ultra (Gluconolactone (and) Sodium Benzoate) Is a perservative. This product is derived from natural sources and provides broad-spectrum protection. It improves skin moisture levels and has an exceptional toxicity profile, as well as a long history of safe use. It is also non-sensitizing and non-irritating (84).

4.2 Characterization

4.2.1 Droplet size analysis and microscopic analysis

4.2.1.1 Droplet size analysis

In the analysis of formulations F1, F2, and F3, droplet size analysis was conducted to assess stability. This analysis will identify any issues and optimize the formulation process if needed.

The stability of an emulsion is a crucial factor that determines the quality and shelf life of the emulsion-based products. It depends on various parameters such as surfactant type and concentration, water concentration, mixing speed, and temperature, which influence the size and distribution of the dispersed droplets in the emulsion. Emulsions can be stabilized by surfactants due to their ability to reduce the interfacial tension between water and oil phases, which allows the droplets to remain dispersed and prevents their coalescence. The droplet size and its distribution are essential factors that determine the stability of the emulsion. Emulsions are considered stable when the droplet size and its distribution do not change significantly throughout storage. Higher concentrations of emulsifiers can lead to smaller droplets, which in turn leads to greater emulsion stability. This is due to the fact that lower concentrations of emulsifiers do not cover the droplets adequately, causing them to coalesce and form larger droplets. Water concentration is another critical factor that influences the stability of the emulsion. Higher water concentrations correlate with larger droplet size, which can reduce the stability of the emulsion. (85).

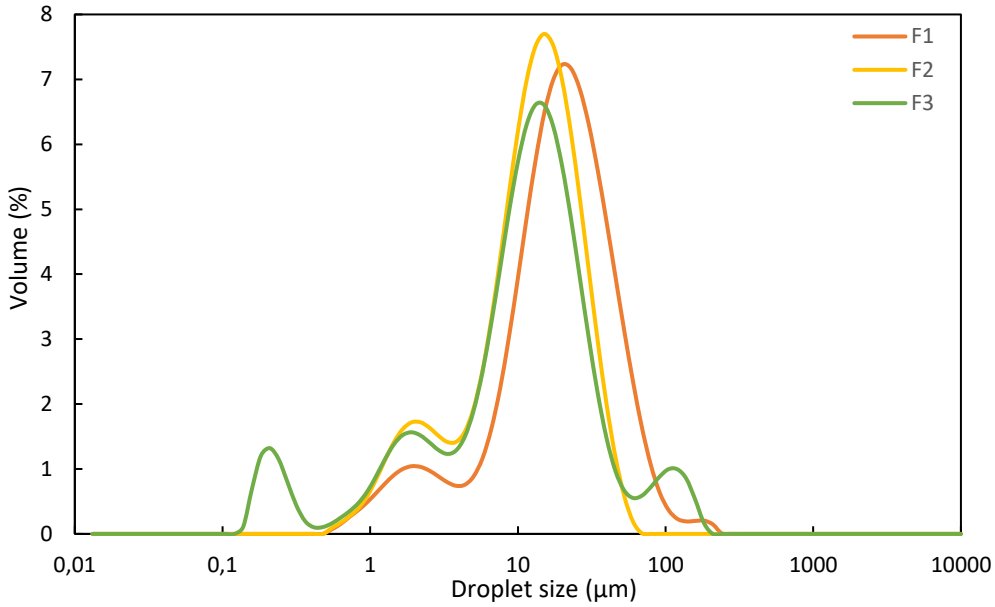


Figure 5 Comparison of droplet size distribution in three emulsions (F1, F2 and F3) (mean, n=6)

Firstly, it is worth noting that formulation F1 and F2 exhibited a bimodal distribution, which means that it had two peaks (Figure 5). This could be an indication of different size droplets within the sample. On the other hand, formulation F3 had a multimodal distribution, with multiple peaks that could suggest the presence of different sizes distribution in the sample. Overall, these differences in distribution patterns provide important insights into the

composition and properties of the samples under investigation. It is worth mentioning that the size distribution of droplets in the pre-emulsion is consistently bimodal. However, once the emulsion undergoes microfluidization, it exhibits a monomodal distribution. Nevertheless, achieving perfectly dispersed emulsions is challenging. A narrower distribution of droplet sizes results in increased viscosity, which improves the physical stability of the emulsion (86,87).

In the following table 2 it is represented the span, this parameter provides an additional information about the uniformity of the droplets, when it is nearer 0 it means that the droplets distribute uniformly and the sample has higher droplet size consistency (88).

The parameter can be calculated by the subsequent expression: $\triangle s=(D_{0.9}-D_{0.1})/D_{0.5}$.

Table 2 Obtained values for 3 size distribution d (10), d (50) e d (90) and span values for three different formulations (F1, F2 and F3), (mean±SD, n=6)

Sample name	Span	d (0.1)	d (0.5)	d (0.9)
F1	2.33±0.08	3.89±0.08	18.11±0.76	45.97±1.16
F2	2.09±0.01	2.20±0.01	11.94±0.02	27.15±0.13
F3	2.88±0.10	1.25±0.03	11.13±0.11	33.27±1.28

After conducting a thorough analysis of the presented data in the table, it can be deduced that the span values range between 2.09 and 3.88. Analyzing the table, it is evident that F1 contains a higher number of droplets with larger sizes, while F2 has a higher number of droplets with the smallest size. Additionally, the formulation exhibits the lowest Span value, indicating a more uniform distribution of droplet sizes and greater consistency in droplet size within the sample.

It is noteworthy to mention that the F3 formulation has the highest span value recorded at 2.88, which is indicative of the fact that this particular sample has a greater number of dispersed droplet sizes, as compared to the other formulations. This can also be observed through the multimodal distribution in this sample.

4.2.1.2 Microscopic analysis

Based on the results of the previous test, it has been observed that the F1 formulation contains larger droplets (Figure 6; illustration 1), which is in line with the initial expectations. It is important to note that the droplet size distribution of F2 and F3 is relatively similar, indicating that these formulations may have similar properties.

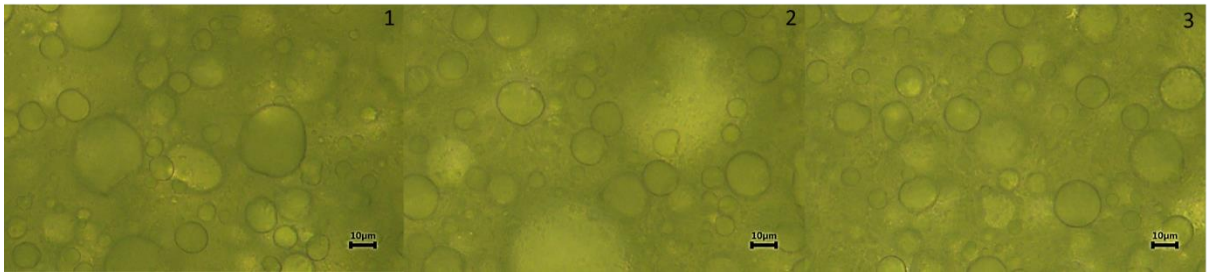


Figure 6 Representation of the droplet size of the formulations in study, (1-F1; 2-F2; 3-F3)

4.2.1.3 Rheology

This following section provides information on the structure analysis of emulsions. Assays such as rotational and dynamic viscosity, oscillation frequency test, and tackiness and adhesion test were conducted to examine the emulsion's physical properties.

4.2.1.3.1 Viscosity flow behavior

Viscosity measurements are essential to understand how a formulation behaves. To obtain a complete understanding, three different tests were performed: table shear rate, three step shear rate, and a sequence of ramp up and ramp down. By performing all of these tests, a better understanding of the formulation's behavior can be obtained. It is crucial to have a complete understanding of the formulation behavior to ensure the final product's quality.

Viscosity is a fundamental concept in fluid mechanics that measures the resistance of a fluid to deformation. It is a property that characterizes the fluid's internal friction, which is related to its flow behavior (89).

Newtonian liquids are those that have a constant viscosity and are independent of strain and strain rate. This means that their viscosity remains the same, regardless of how much they are deformed or how quickly they are deformed. Examples of Newtonian liquids include water, ethanol, and mineral oil. On the other hand, non-Newtonian liquids are those whose viscosity depends on the rate of shear. The viscosity of these liquids changes as the shear rate changes,

which means that they cannot be described by a constant viscosity. Examples of non-Newtonian liquids include ketchup, toothpaste, and blood (89).

This rheological parameter is an important consideration in determining skin feeling, which is a key factor in personal care and cosmetic product development. Skin feeling can be divided into two categories: primary skin feeling and secondary skin feeling. Primary skin feeling refers to the initial physical sensation upon application of a product to the skin, while secondary skin feeling is the physical sensation that occurs after application. This sensation can be affected by the product's viscosity and shear rate. Higher viscosity products may result in a heavier and more dense feeling on the skin, while lower viscosity products may feel lighter and more fluid. Additionally, the shear rate of the product can affect skin feeling, as higher shear rates can result in a more slippery or oily sensation on the skin. Therefore, it is important to carefully consider both the viscosity and shear rate of a product when formulating for optimal skin feeling (90).

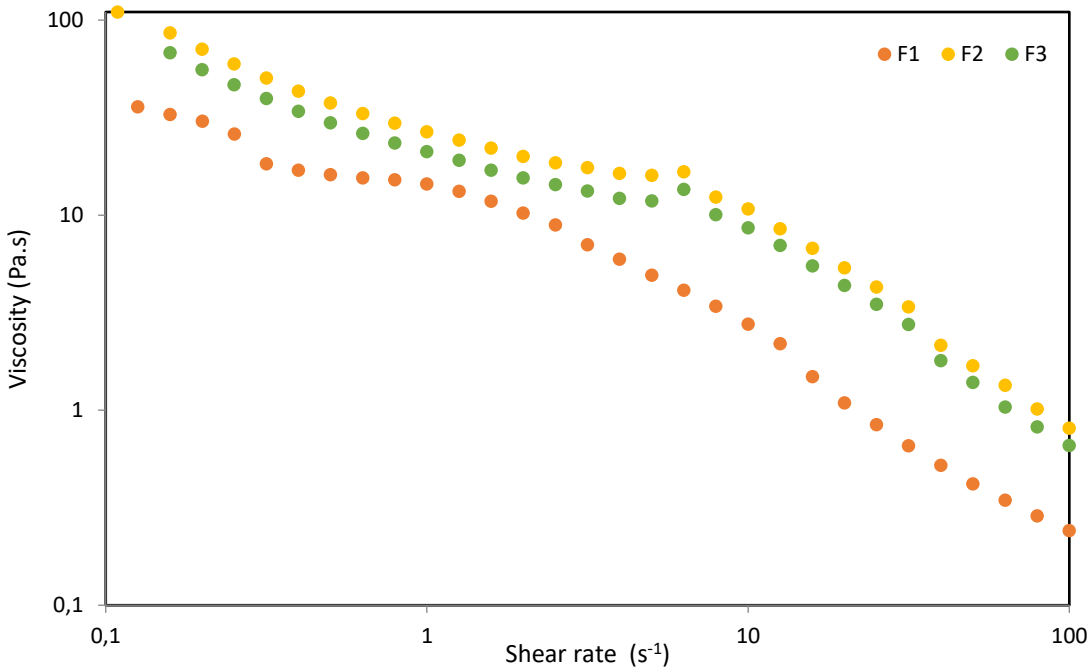


Figure 7 Viscosity flow behavior (viscosity against shear rate) of formulation F1, F2 and F3.

As depicted in figure 7, it is possible to observe that all three formulations exhibit similar flow behavior. It is noteworthy that F2 and F3 have almost identical behavior, which is in line with the expectations based on macroscopic analysis, they present higher viscosity values when compared to F1. By conducting an analysis of the existing literature, it becomes evident that the anticipated outcome aligns with the findings, since the size of the droplets in the emulsion

decreases, there is a noticeable increase in viscosity. This phenomenon can be attributed to the inherent characteristics of smaller droplets, which tend to possess a higher level of rigidity (91).

In figure 8, the relation between shear viscosity and time is demonstrated in the three-step shear rate test, which is a valuable tool for evaluating and quantifying the thixotropy of samples. Through this test, we can observe how a material rebuilds its structure after undergoing a high shear process (92).

Furthermore, it is worth noting that the three-step test mode consists of employing a low shear rate in the first stage. This is followed by progressively increasing the shear rate in the second stage, and finally returning to the initial low shear rate in the third stage. This process allows for a comprehensive assessment of the material's behavior under different shear conditions, providing valuable insights into its rheological properties.

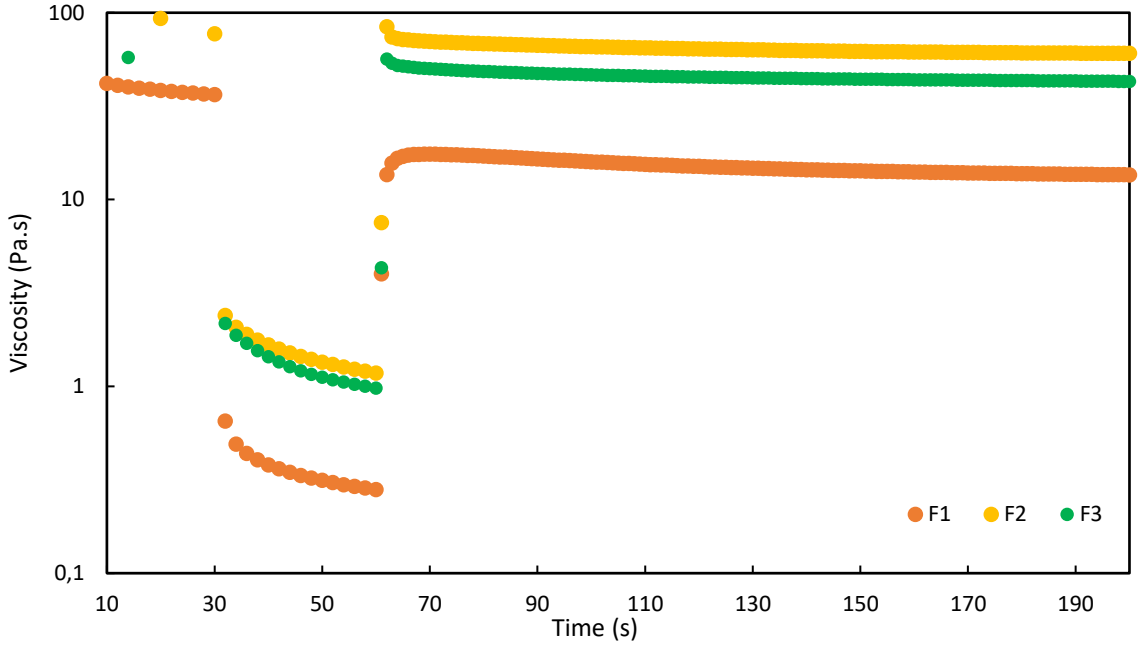


Figure 8 Viscosity flow behavior (Three step of shear rate) of formulation F1, F2 and F3

Many structured materials exhibit shear thinning behavior, which can be reversible or irreversible depending on the microstructure, if it is reversible, the structure rebuilds over time, those are often classified as thixotropic. None of the emulsions achieved complete recovery.

When measuring viscosity, the TI (Thixotropic Index) is determined by comparing viscosity values at different time points while keeping the rotational speed constant. A TI value of 1 indicates flow behavior that is not affected by time, a TI value greater than 1 indicates time-dependent shear-thinning behavior, and a TI value less than 1 indicates time-dependent shear-

thickening behavior. It is important to note that the term "thixotropic index" may be misleading, as it actually measures structural decomposition rather than regeneration (93).

After calculating the value of TI for each formulation, the following results were obtained: F1 (TI=3.70 Pa.s), F2 (TI=3.41 Pa.s), and F3 (TI=1.88 Pa.s). All formulations have TI values greater than 1, indicating shear-thinning behavior.

Following is represented the results from the ramp-up and ramp-down test, by using a sequence of ramp-up and ramp-down, we were able to gain insights into the thixotropic behavior of the material being studied. In this experiment, the structural strength of a thixotropic formulation is reduced by applying a shear rate. During the test, the sample's capacity to regenerate its structure is evaluated. This reversible process involves the decomposition and regeneration of the sample's structure. However, the decomposition of the sample occurs due to the weak interactions between the particles. These interactions are capable of breaking due to the shear flow that leads to the separation of the droplets. To further understand this process, it is important to note that thixotropic formulations are materials that exhibit time-dependent structural changes. This means that they can change their viscosity over time, depending on the amount of stress applied to them. Thixotropic formulations are commonly used in various industries, such as food, cosmetics, and medicine. This is because they have the ability to maintain their structure during storage and transportation, but can easily be applied when needed (94).

In this experiment, the sample's ability to regenerate its structure is crucial. This is because it determines the sample's overall stability and performance. By evaluating the sample's capacity to regenerate its structure, researchers can determine the ideal conditions to optimize its performance.

Figure 9 represents the recovery rate of the various formulations that were tested. It is important to note that all of the formulations demonstrated similar behavior.

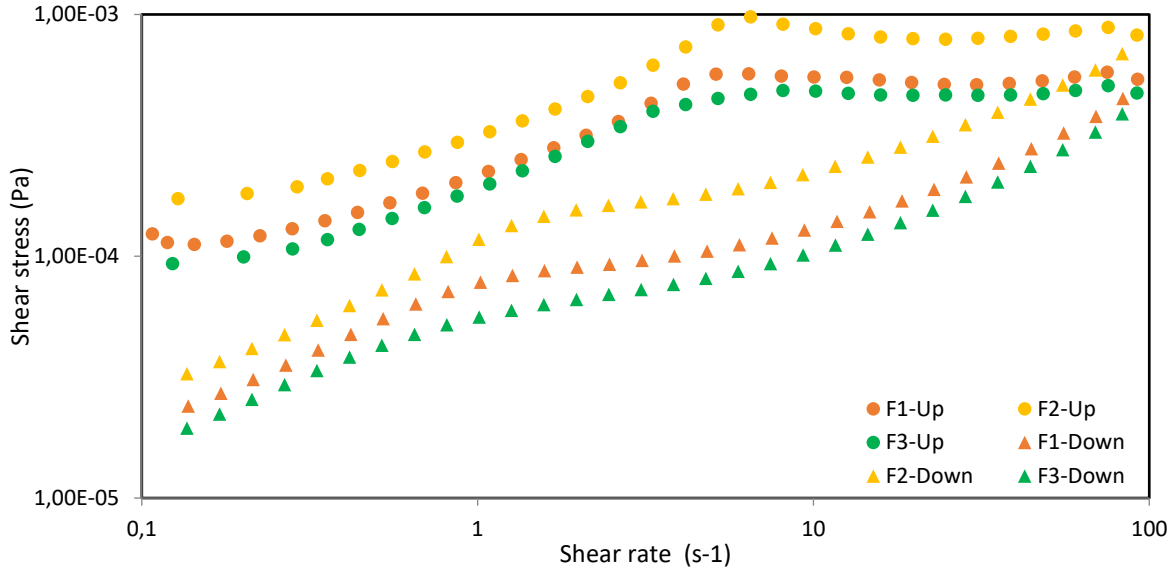


Figure 9 Viscosity flow behavior (ramp-up and ramp-down) of formulation F1, F2 and F3

In comparison F1, F2 and F3 show similar behavior with a high recovery rate. Despite the fact that F1 exhibits better results in terms of recovery, it is worth noting that the behavior of F1 is not significantly different from the other formulations. This suggests that while F1 may be more effective in terms of recovery, it may not necessarily provide distinguished behavior when compared to F2 and F3.

A when a notable difference is observed between the measurements taken during the first ramp up and the subsequent ramp down, It suggests that the shear forces applied during the initial ramp up were strong enough to damage the product structure (95) .

4.2.1.3.2 Oscillatory

The oscillatory shear tests however are associated with the determination of storage modulus, G', and loss modulus, G", as a function of oscillation frequency, temperature or time.

The oscillatory shear tests are an important part of rheology and are used to determine the viscoelastic properties of a material. In these tests, the material is subjected to shear stress that varies sinusoidally over time. The response of the material to this stress is measured by the storage modulus G' and the loss modulus G", which represent the stored and dissipated energy during sample deformation, reflecting the material's "elastic" and "viscous" properties, respectively (96).

Emulsions and gels, commonly used as cosmetic ingredients, often exhibit viscoelastic properties. When assessing these samples using a frequency sweep, two parameters, G' (elastic

modulus) and G'' (viscous modulus), are measured. Emulsions with higher G' values compared to G'' values are considered more stable, as they recover their initial structure faster and more efficiently, making them less susceptible to gravitational forces. This stability is important in preventing coalescence and phase separation. The storage modulus is a key parameter that describes the material's ability to store elastic energy when subjected to external forces. Higher storage modulus indicates better resistance to deformation under load, which is particularly important for materials subjected to repeated stress cycles over time (97,98).

In figure 10, G' represents the elastic modulus, which measures the solid-like behavior of a material. G'' represents the viscous modulus, which measures the liquid-like behavior of a material. Together, G' and G'' make up the complex modulus (G*), which measures the overall stiffness or resistance to deformation of a material. Oscillatory behavior of the formulations in study.

In the formulations F2 and F3, G' is higher than G'', showing that these formulations have a superior elastic module to the viscous module. This provides insights about their suitability for skin application, like mentioned before, G'>G'' (98).

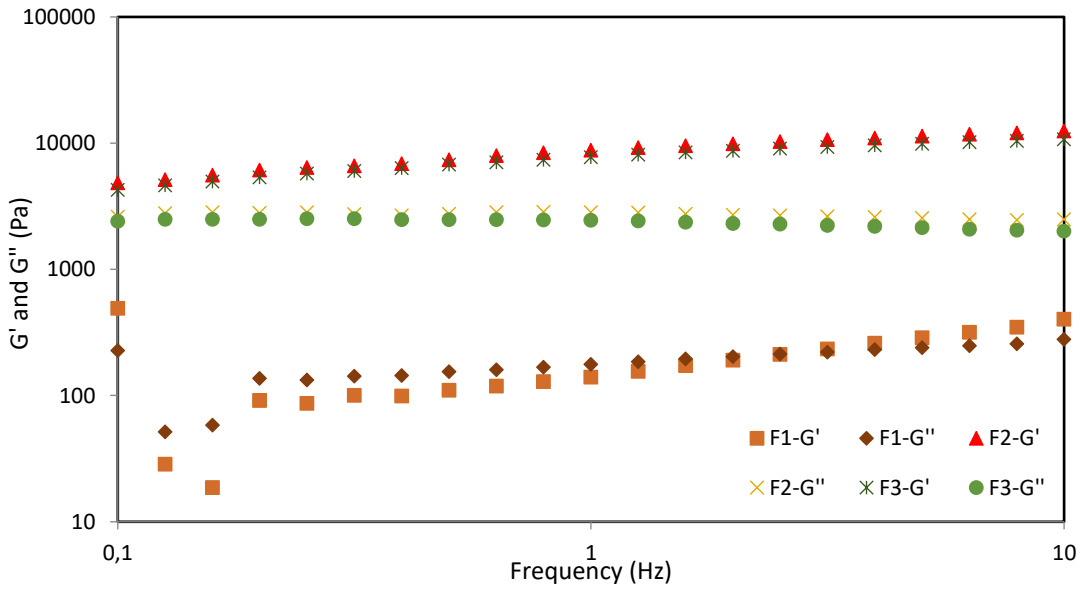


Figure 10 Oscillatory behavior of the formulations in study of formulation F1, F2 and F3.

Formula F1 is the only formulation that has a G'' value higher than its G' value. In contrast, formulations F2 and F3 consistently exhibit a lower G' value, regardless of the frequency. In F1, initially, the viscous modulus (G'') is higher than the elastic modulus (G'), and the material exhibits liquid-like behavior. However, as the frequency of oscillation increases, the elastic

modulus (G') begins to dominate, and the material exhibits solid-like behavior. The point at which G' becomes higher than G'' is called the crossover point, and it indicates the transition from liquid-like to solid-like behavior (99).

4.2.1.4 Tribology

Tribology is the study of friction, wear, and lubrication of surfaces in contact, and it plays a crucial role in understanding the behavior and applications of emulsions. In emulsions, various factors impact tribology. The type of emulsion is particularly important, as different types have distinct tribological properties that affect their performance in different applications. Droplet size and distribution also influence tribology, with smaller droplets increasing the emulsion's surface area and potentially reducing friction and wear. Additionally, the properties of the surfaces in contact, including roughness, chemical composition, and other surface properties, affect the interaction between the surfaces and the emulsion, ultimately influencing tribological properties (100).

The coefficient of friction (CoF) measures the level of friction between two surfaces. A lower CoF means that less force is required for sliding to occur, in contrast to situations with a higher CoF (101).

The CoF values were calculated for each formulation (F1, F2 and F3). F1 had a CoF value of 2.17 ± 2.90, which was the lowest among the three emulsions. On the other hand, F2 had a slightly higher value of 3.59 ± 4.10, while F3 had a value of 3.42 ± 4.83. This indicates that emulsion F1 exhibits a comparatively lower resistance to sliding between surfaces when compared to the other two formulations.

4.2.1.5 Spreadability and Adhesive properties

The spreadability test will complement the results from previous tests, such as tribology. The test involves spreading the emulsion on a surface to determine how easily it spreads and how well it adheres. The spreadability of an emulsion is affected by various factors, such as the type and concentration of emulsifier used, and the viscosity of the oil and water phases.

The degree of adhesion is evaluated through debonding tests, commonly referred to as probe-tack tests. These tests assess the amount of force needed to separate two bonded surfaces over a period of time. In these tests, a small probe is used to apply a gradually (pulling) increasing force to the bonded surfaces. This allows for the measurement of the adhesive strength between the surfaces. Tack or tackiness is an important phenomenon in material behavior, typically associated with stickiness. It may occur due to adhesive forces between two

materials in contact or cohesive forces within a material bridging two substrates. To measure tackiness, the force required to separate two initially stationary parallel plates with a pre-defined volume of material in-between is determined. Tack is a crucial property of adhesives, useful in determining their suitability for a given application. Understanding these properties is essential for selecting the right adhesive for a given application, and ensuring long-term product performance (102,103).

Table 3 Adhesive properties of the formulations F1, F2 and F3 (mean±SD, n=6) and representation of spreadability tests, performed in two different ways. The first two columns (Firmness and spreadability) refer to the spreadability test on the texturometer (mean±SD, n=3), while the last column (Area) refers to the manual method performed (mean±SD, n=3)

Formulation	Peak Normal Force (N)	Time for Force to reduce by 90% of peak (s)	Area under force time curve (N.s)	Firmness	Spredability	Area
F1	0.38 ± 0.02	10.18 ± 1.40	0.18 ± 0.03	1296.47 ± 104.00	343.35 ± 40.90	51.75 ± 3.93
F2	0.34 ± 0.01	7.90 ± 0.64	0.73 ± 0.03	767.08 ± 88.27	139.51 ± 35.38	20.83 ± 3.38
F3	0.34 ± 0.01	5.87 ± 0.19	0.61 ± 0.05	1078.97 ± 95.61	236.40 ± 29.16	22.56 ± 0.82

The table 3 provides data on the adhesive strength of different formulations (F1, F2, and F3) as measured by peak normal force, time for the force to reduce by 90% of the peak, and the area under the force-time curve. Peak normal force (N) represents the maximum force applied during the debonding test, indicating the strength of the bond between the surfaces. Time for force to reduce by 90% of peak (s) measures how long it takes for the force to decrease to 90% of its maximum value, reflecting the bond's resistance against separation over time. The area under the force-time curve (N.s) represents the total work done during the debonding test, indicating the overall energy required to separate the surfaces (102).

Comparing the formulations, F1 exhibits the highest "Peak Normal Force," indicating the strongest adhesive force between the surfaces. In contrast, F2 and F3 demonstrate lower values, suggesting weaker adhesion. Regarding the "time for force to reduce by 90% of peak," F3 displays the shortest time value, indicating a more rapid force decrease compared to F1 and F2. This suggests that F3's adhesion is less resistant to separation over time compared to the

other formulations. F2 exhibits the highest area under the curve value, indicating the greatest amount of work performed during the peel test. This suggests that F2's adhesion is more resistant to separation compared to F1 and F3.

Considering F1, F2, and F3, it seems that F2 is the optimal emulsion formulation. F2 shows the highest "Maximum Normal Force," indicating the strongest adhesive strength between surfaces. Additionally, F2 has the highest "Area under the Force-Time Curve," suggesting it undergoes the most work during the peel test. This implies that F2 has better resistance to separation compared to F1 and F3.

Next, the spreading ability of the emulsions under study will be thoroughly analyzed and evaluated. This analysis will involve examining the emulsions using two different methods: a texturometer and a manual method, as mentioned before.

The table 4 presents the results of different formulations (F1, F2, F3) in terms of firmness and spreading area. Among the three evaluated formulations, the F2 formulation shows a firmness of 767.08 and an area of 139.51. On the other hand, the F3 formulation demonstrates a higher firmness of 1078.97 and a larger spreading area of 236.40. However, it is worth noting that the F1 formulation exhibits the highest spreading capacity (51.75) compared to the other formulations. In addition to that, it also shows a firmness of 1296.47 and a spreading area of 343.35. These results indicate that the tested material possesses greater resistance and spreading capacity. This information is valuable for comparing and evaluating the firmness and spreading capacity characteristics of the different formulations.

The force of action measures the force required to remove the formulation from the container. It provides an indication of the dispensing ease of the emulsion. In this study, formulation F1 required a force of action of 596.00 ± 7.88, while formulation F2 required a force of action of 803.29 ± 98.79, and formulation F3 required a force of action of 1063.39 ± 53.64. Upon careful examination of the presented values, it is evident that formulation F1 requires less force for dispensing, which aligns with the findings from the previous viscosity analysis.

4.3 Stability assay

The analysis of the data indicates that Formulation F1 exhibits favorable characteristics in terms of flow behavior, spreading capacity, friction properties, and ease of dispensing. F1 demonstrates similar flow behavior to F2 and F3 but has lower viscosity values. It also shows the highest spreading capacity, indicating easier application. Additionally, F1 has lower friction coefficients, suggesting less resistance during application, making it suitable for sensitive skin.

Moreover, F1 requires the lowest force of action to dispense from the container compared to F2 and F3. Therefore, Formulation F1 was the selected formulation to continue to the stability phase due to its properties in terms of flow, spreadability, friction, and ease of dispensing.

Over time, the emulsion can undergo changes in its characteristics due to various factors such as temperature, humidity, and exposure to light. One such change is coalescence, which refers to the separation of the phases. This can lead to instability and possible deterioration of the product. In order to ensure the stability of the emulsion, a thorough stability assay was conducted on three batches that were manufactured to ensure reliable results.

These additional tests enabled a more comprehensive evaluation of the emulsion's stability over time and under different conditions. The analysis will include two different temperatures (25ºC and 40ºC). All of the time results will be Included In the annexes (Annex A).

4.3.1 The pH stability

The table 6 presents the pH values for formulations L1, L2, and L3 at four different times (T0, T1, T2, and T3) and two different temperatures (25ºC and 40ºC). We can observe the stability of each emulsion based on these values.

Formulation L1 exhibits a slight variation in pH values over time, at both 25ºC and 40ºC. However, this variation is within a range considered stable. Formulation L2, on the other hand, shows a more significant variation in pH values, particularly at 25ºC. This suggests lower stability compared to the other formulations. Formulation L3 demonstrates a similar variation to L1, with relatively stable pH values over time and temperatures.

Table 4 Stability test results for formulation L1, L2 and L3 during 5 months (T0- one week after production; T1- One month after production; T2-Three months after production; T3-Five months after production) at two different temperatures (25ºC and 40ºC)

Formulation	Time	25ºC	40ºC
L1	T0	5.18	5.18
	T1	5.23	4.73
	T2	5.25	4.87
	T3	5.29	4.98
L2	T0	5.18	5.18
	T1	6.08	5.16
	T2	5.97	5.23
	T3	5.76	5.33
L3	T0	5.15	5.15

T1	5.61	5.02
T2	5.72	5.16
T3	5.71	5.25

In conclusion, formulations L1 and L3 appear to have adequate stability. The stability of an emulsion is heavily influenced by the pH, as it directly impacts the surfactant properties. The values presented are in agreement with the literature (104).

The skin has a slightly acidic pH on its surface, ranging from pH 4.5 to 5.7, this makes the formulation compatible for skin application (105).

4.3.2 Droplet size distribuition

The distribution of droplet sizes is a critical characteristic of emulsions, which can greatly affect their overall stability. By comprehending and managing the droplet size distribution, it is possible to optimize the stability and performance of emulsions, ensuring desirable properties and enhancing their functionality. This distribution plays a vital role in determining various properties of emulsions, including viscosity.

The figure 11 present the results of particle size distribution at time T0 and T3.

It can be observed that at 40ºC, the batches increased the discrepancy between the results, which can be seen through the increase in the second peak of the bimodal distribution. Regarding the ambient temperature (25ºC), there was a shift in the graph towards smaller distribution values.

In the Droplet size distribution test, an increased discrepancy was observed in the results. This can be seen by the increase in the second peak of the bimodal distribution in T3 at 40ºC.

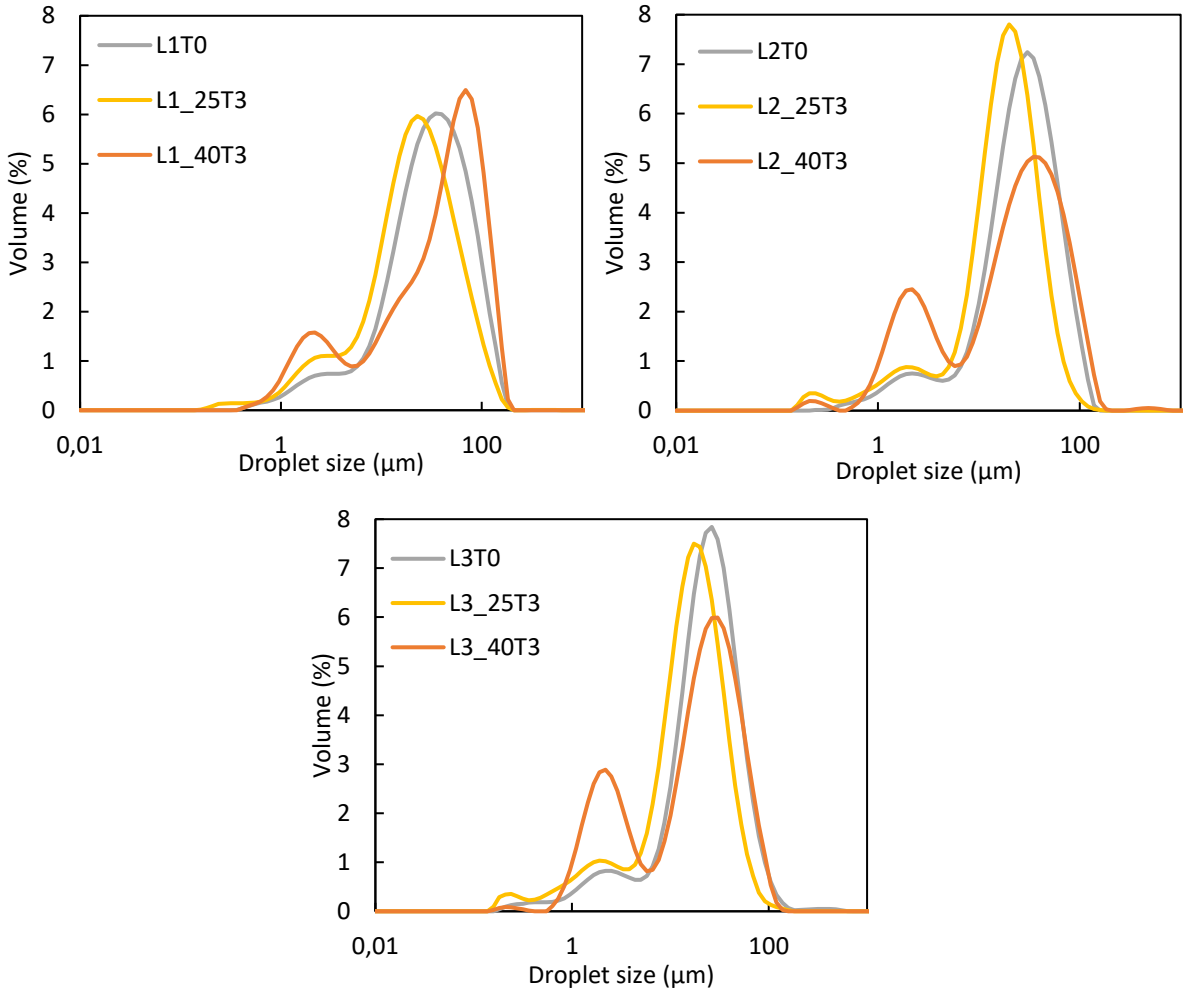
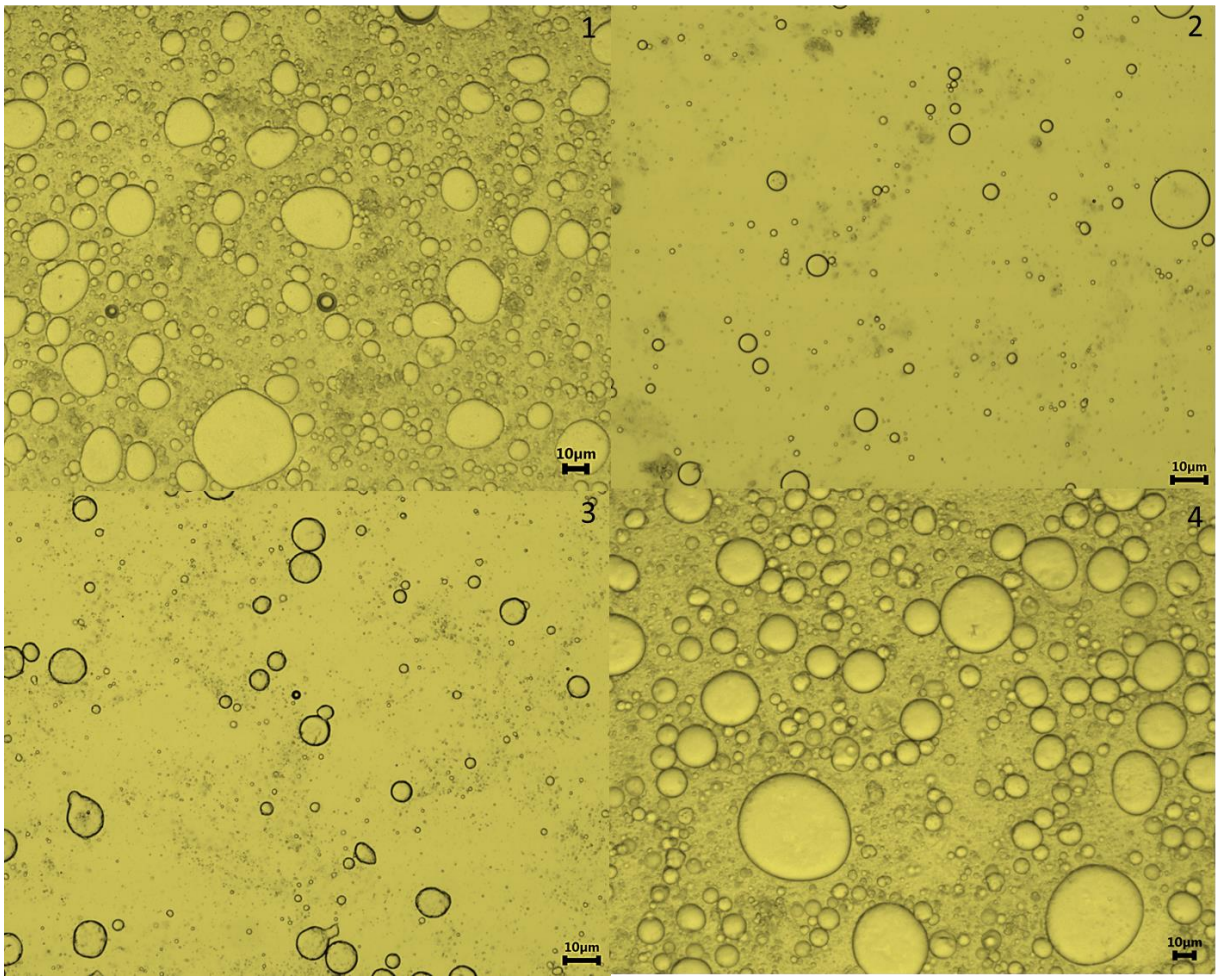


Figure 11 Droplet size distribution of batch L1, L2 and L3, at two different time points (T0-One week after production; T3-Five months after production), at two different temperatures (25ºC and 40ºC).

4.3.3 Microscopic analysis



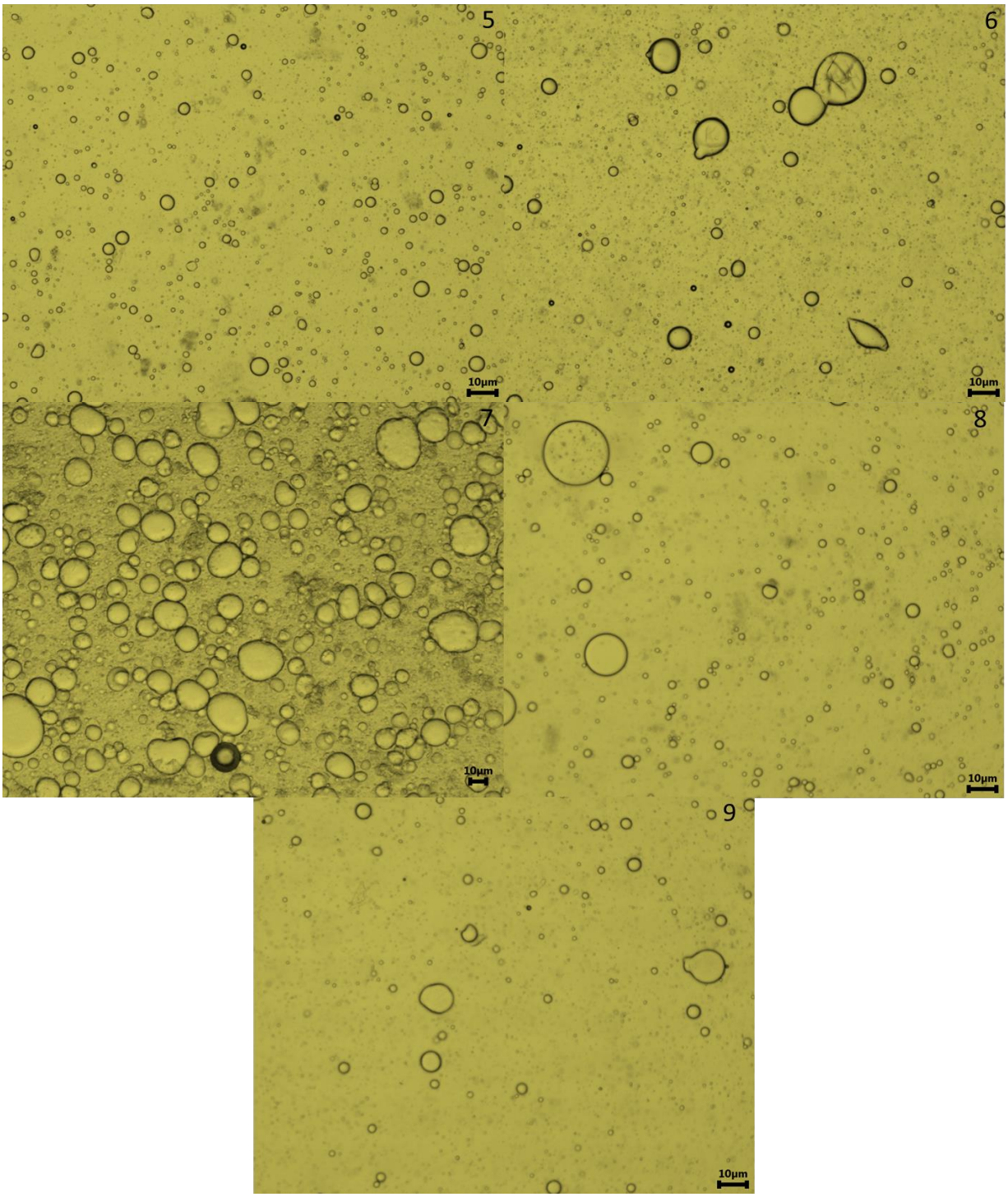


Figure 12 Representation of microscopic analysis of batch 1, 2 and 3 in study (1-L1T0; 2-L1 at 25ªC at T3; 3- L1 at 40ªC at T3; 4-L2T0; 5-L2 at 25ªC at T3; 6- L2 at 40ªC at T3; 7-L3T0; 8-L3 at 25ªC at T3; 9- L3 at 40ªC at T3)

Microscopic analysis (Figure 12) revealed the occurrence of droplet coalescence, which aligns with the findings in the literature. Coalescence is a phenomenon where two or more parts of a phase merge to form a single entity. In the case of emulsions, this happens when droplets merge, resulting in larger droplets. At elevated temperatures like 40°C, this process can be accelerated due to increased particle collisions and separation. However, it is possible to slow down the coalescence kinetics by increasing viscosity, maintaining a uniform droplet size, and improving solubility. These measures help reduce the likelihood of coalescence and ensure emulsion stability (106).

4.3.4 Viscosity flow behavior

The figure 13 present the results of particle size distribution at time T0 and T3 at two different temperatures (25°C and 40°C).

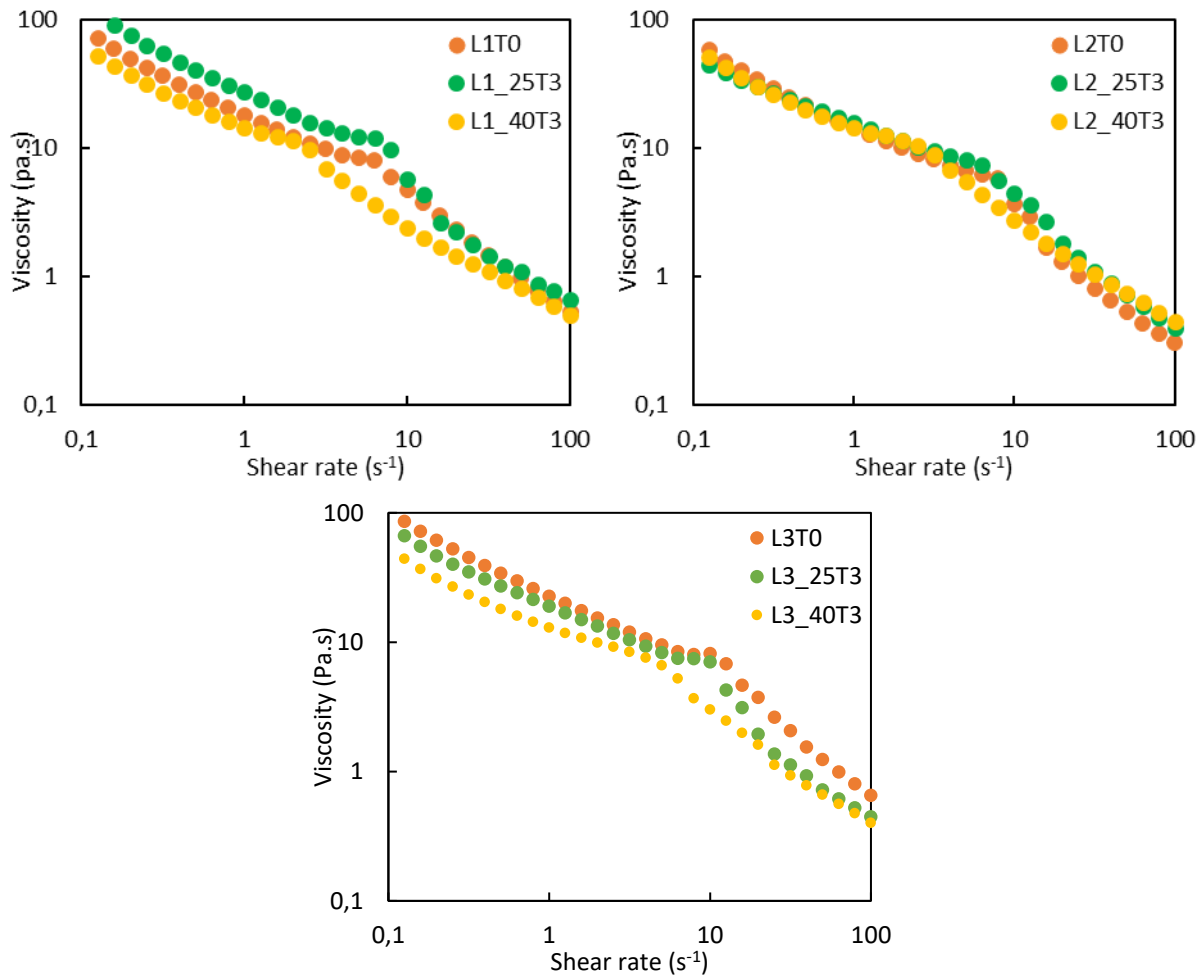


Figure 13 Viscosity flow behavior (viscosity against shear rate) of batch L1, L2 and L3, at two different time points (T0-One week after production; T3-Five months after production), at two different temperatures (25°C and 40°C)

There were no significant changes in the viscosity of the batches. The only notable aspect is a slight decrease in viscosity at 40°C. According to the literature, a decrease in viscosity is expected at high temperatures. This decrease was also visually apparent when removing the product from the packaging at 40°C (107).

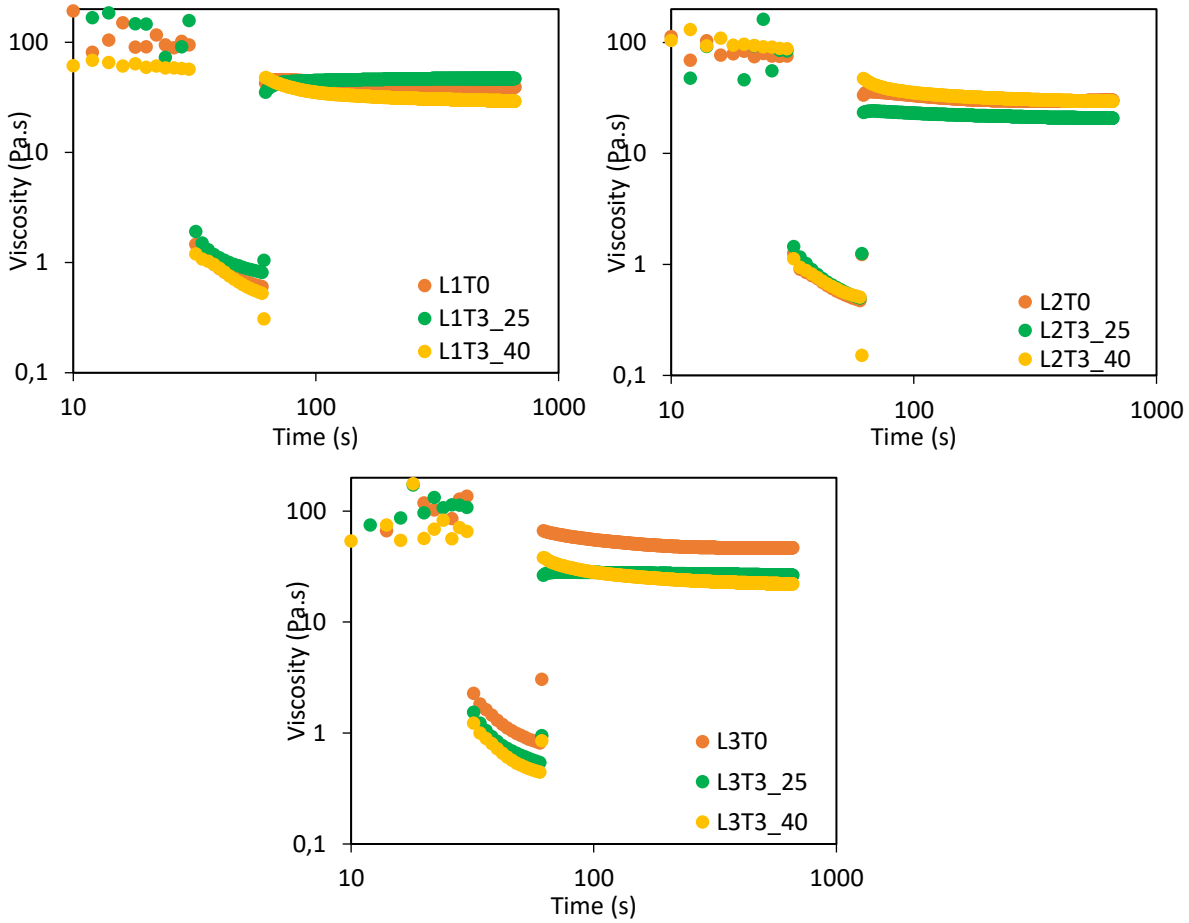


Figure 14 Viscosity flow behavior (Three step of shear rate) of batch L1, L2 and L3, at two different time points (T0-One week after production; T3-Five months after production), at two different temperatures (25°C and 40°C)

From figure 14, the TI value was calculated (Table 5). A TI value of 1 indicates flow behavior that is not affected by time, a TI value greater than 1 indicates time-dependent shear-thinning behavior, and a TI value less than 1 indicates time-dependent shear-thickening behavior. It is important to note that the term "thixotropic index" may be misleading, as it actually measures structural decomposition rather than regeneration.

A TI value of 1 indicates flow behavior that is not affected by time, a TI value greater than 1 indicates time-dependent shear-thinning behavior, and a TI value less than 1 indicates time-dependent shear-thickening behavior. It is important to note that the term "thixotropic index"

may be misleading, as it actually measures structural decomposition rather than regeneration (94).

Table 5 Representation of TI value for the different batches and each temperature

Batch	L1			L2			L3		
Condition	T0	25ºC	40ºC	T0	25ºC	40ºC	T0	25ºC	40ºC
TI (Pa.s)	2.67	2.62	3.09	2.30	2.13	2.82	1.63	3.25	3.07

In fact, there have been some changes in the sample recovery capacity, which can also be observed through the value of TI. It is possible to observe that different temperature conditions affect the TI values. For example, for batch L1 and L2, the TI value is higher at the 40ºC condition compared to the other conditions. This may indicate a higher rate of structural decomposition at this temperature. Decrease in viscosity is expected at high temperatures according to the literature (107).

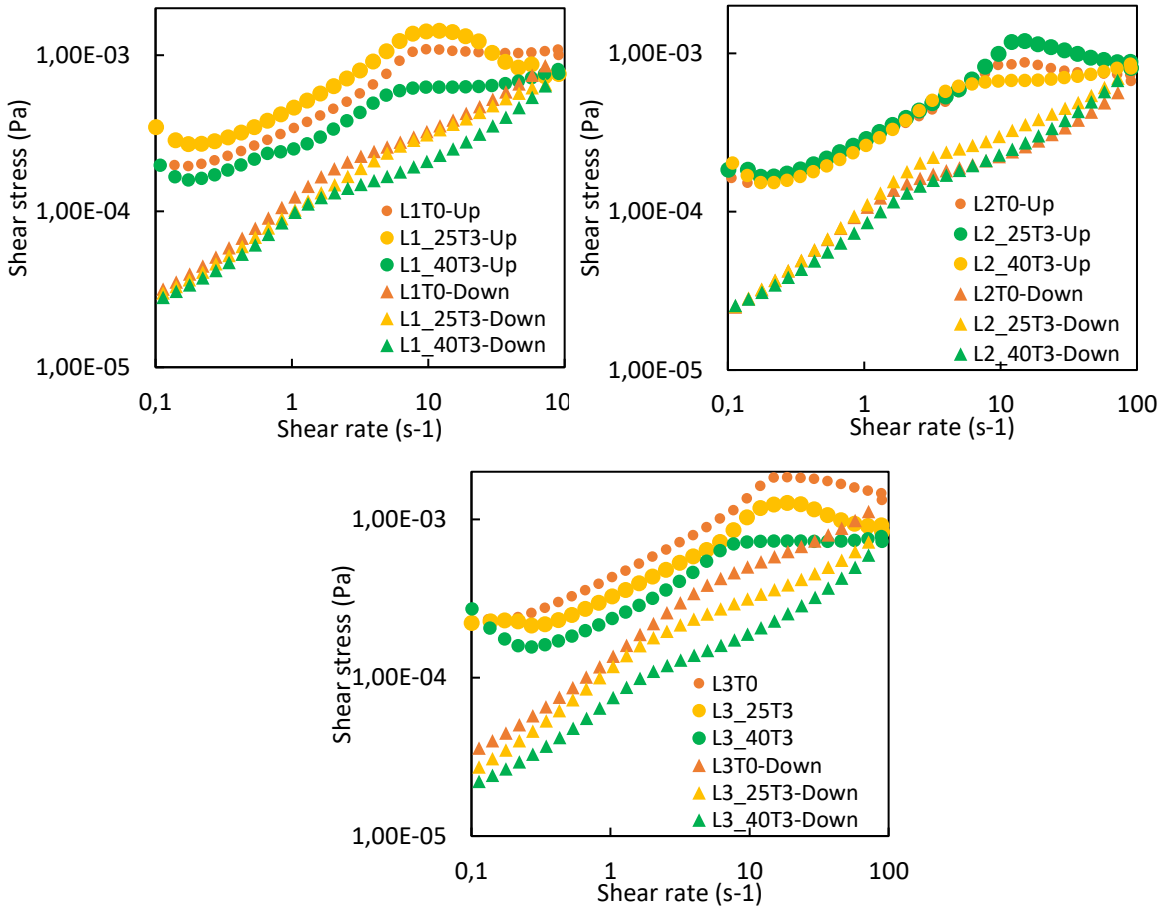


Figure 15 Viscosity flow behavior (Ramp up and ramp down) of batch L1, L2 and L3, at two different time points (T0-One week after production; T3-Five months after production), at two different temperatures (25ºC and 40ºC)

Based on the findings presented in figure 15, it can be concluded that the Ramp up and Ramp down test did not reveal any substantial variations. This observation leads us to infer that there was no discernible alteration in the product's capacity to endure damage (96).

4.3.5 Oscillatory behavior

The values G' and G'' are notations used in rheology to represent the storage modulus and loss modulus, respectively. These moduli describe the elastic and viscous behavior of materials under deformation.

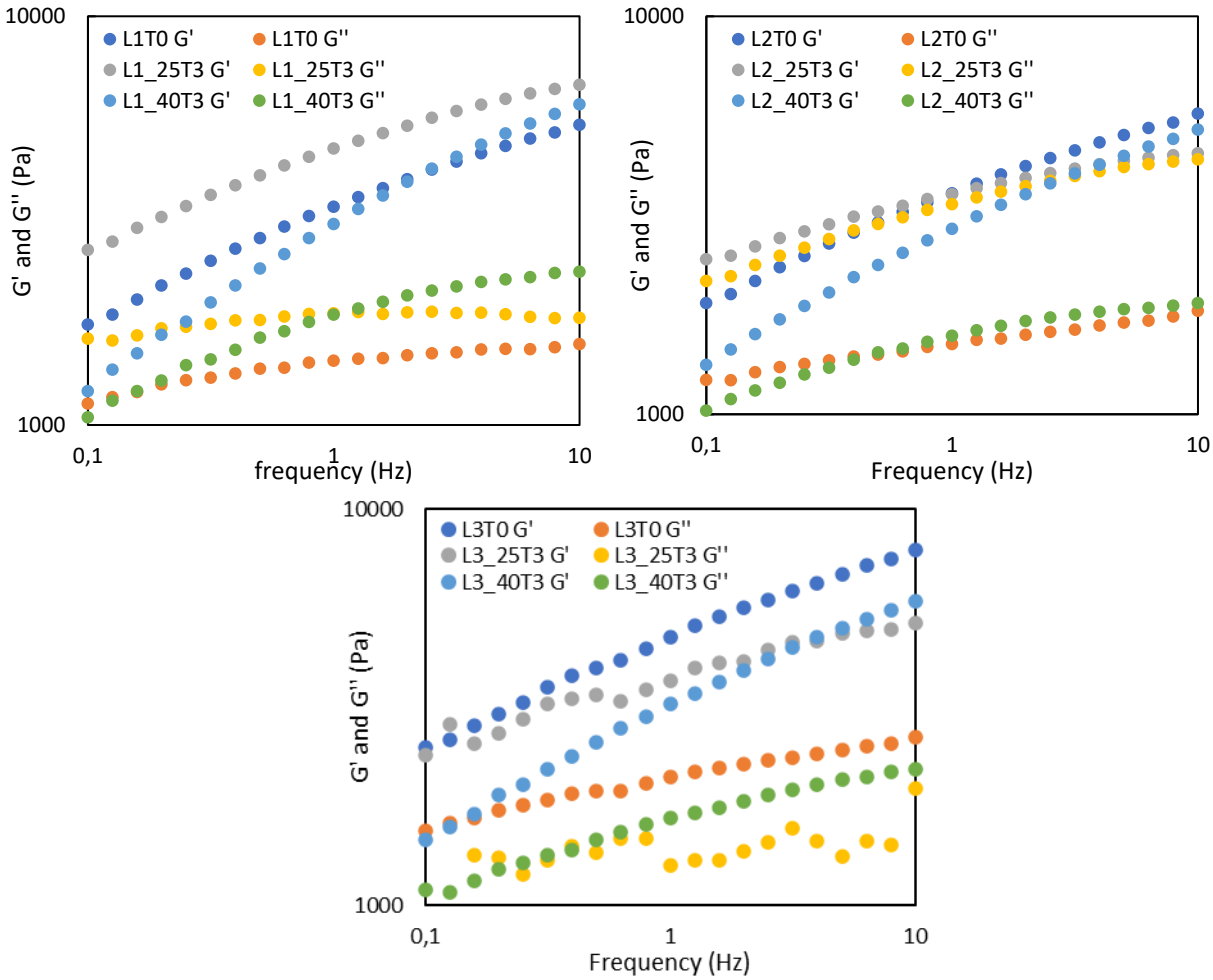


Figure 16 Oscillatory behavior of batch L1, L2 and L3, at two different time points (T0-One week after production; T3-Five months after production), at two different temperatures (25°C and 40°C)

While there have been some significant changes in terms of oscillatory behavior, the overall formulations have remained unchanged.

5 QUESTIONNAIRE

5.1 Objectives

Oncological treatments can cause skin changes and undesired effects such as itching. These effects can greatly impact patients' daily lives. Adapted care can help prevent or minimize these effects, improving the quality of life. This research aims to identify cutaneous side effects during and after cancer treatments. It will provide a detailed analysis of these side effects. The research will also evaluate the physical-chemical characteristics required for a cosmetic product to be used on the skin of cancer patients, according to the patients' preferences. The findings will enhance the understanding of skin-related side effects and identify effective cosmetic products to alleviate them, benefiting the health and well-being of cancer patients.

The questionnaire is divided into four parts, each with different objectives:

- The first part aims to gather data about the type of treatment the patient is undergoing or has undergone.
- The second part aims to identify the most common and concerning cutaneous side effects experienced by patients.
- The third part aims to identify the cosmetic market needs and trends specific to this population.
- The fourth part aims to collect patients' opinions regarding their preferences for cosmetic products during or after undergoing oncological treatments.

5.2 Materials and methods

5.2.1 Study type

The presented study will use a cross-sectional and descriptive design, collecting information at a single point in time using a self-administered questionnaire between June and July 2023. Partner associations will approach patients and provide the questionnaire.

5.2.2 Essay sample

5.2.2.1 Inclusion and exclusion criteria

In order to ensure that the study was conducted in a rigorous and thorough manner, specific criteria were developed to determine which participants would be included and which would be excluded. These criteria were carefully considered and designed to ensure that the study would yield accurate and meaningful results.

Inclusion Criteria:

- Individuals who are 18 years or older and receiving any type of treatment (e.g., radiation therapy, chemotherapy, etc.).
- Individuals who authorize their participation after reading and understanding all provided information.

Exclusion Criteria:

- Patients with cognitive deficits.
- Patients who do not have the capacity to autonomously authorize.
- Pregnant women.

5.3 Ethical Considerations

To ensure the confidentiality and anonymity of patient data, the research team has taken necessary precautions to avoid identification of patients in any publication resulting from this study. All results will be presented in an aggregate form and authorized by study participants. The study participants were required to give their informed consent, which included details regarding the study's purpose, methodology, and data collection procedures. Patient anonymity will be maintained as the consent forms will not be linked to the questionnaires. The informed consent process will be conducted with utmost care and attention to ensure that participants are fully informed and understand the implications of their participation.

5.3.1 Data Collection Procedure

To collect data from cancer patients, an online questionnaire (Annex B) was created using Google Forms. It was distributed through partner associations such as Associação Careca Power and AOA-Associação Oncológica do Algarve, as well as social networks and oncology patient support groups. Participants were given an information leaflet (Annex B; B1) to provide them with necessary details and empower them to make an informed decision about participating in the study. The use of an online questionnaire and multiple dissemination channels

allowed for a broader sample collection, leading to more comprehensive and accurate data. The information leaflet ensured participants had the necessary knowledge to decide whether to participate.

The introduction of the questionnaire provided important information about the study, including the author's details, purpose, objectives, and assurance of voluntary participation, data confidentiality, and anonymity.

The study aimed to assess the impact of oncological treatment by evaluating skin damage, and understand preferences for cosmetic products. The findings would contribute to the development of products that meet the needs of these patients.

The questionnaire had a total of 28 questions, including multiple-choice and open-ended questions. It was open from June 1st to July 15th. After collecting data, we analyzed it using Microsoft Office Excel and SPSS (Software Package for Social Science), descriptive analysis. This analysis revealed how oncological treatment affects the patient's skin and preferences for cosmetic products, which is valuable for developing products that cater to their needs.

5.4 Presentation and analysis of results

5.4.1 Sociodemographic characterization of the sample

The questionnaire application resulted in a total of 58 complete and valid responses.

Based on the data in table 6 and table 7, it is clear that the vast majority of respondents were female (94.8%), with males only making up 5.2% of the sample. Notably, most participants were middle-aged, with 48.3% falling between the ages of 41-50 and 39.7% between 51-60. This suggests that the study has a broad representation of this age group.

Table 6 Sociodemographic characterization, specifically the gender of the sample (N=58)

Gender	N	%
Female	55	94.8
Male	3	5.2
Total	58	100

Table 7 Sociodemographic characterization, specifically the age groups of the sample (N=58)

Age	N	%
31-40	2	3.4
41-50	28	48.3
51-60	23	39.7
61-70	5	8.6
Total	58	100

It is important to explore the reasons behind the gender imbalance in the study, such as potential biases in recruitment or survey design. Understanding these factors could lead to more inclusive research practices in the future.

This gender difference may be related to one of the two partner associations selected to distribute the questionnaire, which supports people with breast cancer. Breast cancer is more prevalent in women, with an estimated 297,790 new cases expected in women in the United States in 2023, compared to only around 55,720 new cases in men. Another important factor to consider is that breast cancer is the most common cancer in Portugal. As shown in figure 17, 74% of patients that enrolled in this project have had or currently have breast cancer. This may contribute to the higher number of female respondents in the questionnaire. An alternative reason to consider is that cosmetics are still more commonly associated with females. However, as more men become concerned about their appearance, this gender difference is becoming less pronounced and is likely to eventually decrease (108,109).

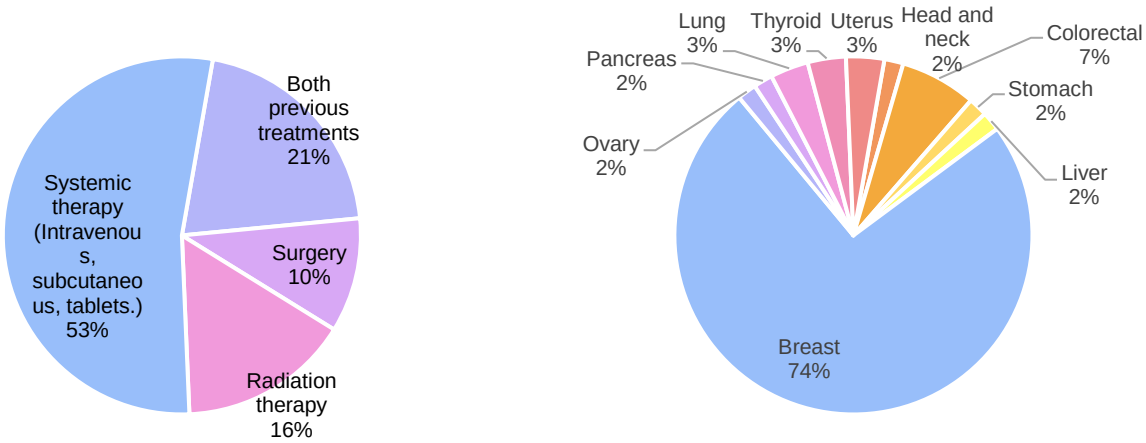


Figure 17 Type of cancer (Left) and treatment instituted (Right) (N=58)

5.4.2 Type of cancer and treatment instituted

When conducting an analysis of the figure 17, as mentioned earlier, it becomes apparent that breast cancer is the predominant type of cancer in the sample analyzed, accounting for 74% of cases.

This aligns with the statistical data from Portugal, where breast cancer is indeed the most prevalent form of cancer. As for the second most common type of cancer in Portugal, it is prostate cancer. However, it is important to note that the number of male participants in the study was relatively low, which may explain why prostate cancer is not present in the graph. On the other hand, colorectal cancer is the third most frequent cancer in Portugal. In this questionnaire, it is identified as the second most frequent cancer, accounting for 7% of cases (109).

5.4.3 Relationship between the type of treatment and the damages experienced as a result of it

The purpose of the following table 8 is to establish a connection between the specific type of treatment that has been prescribed and the various symptoms that the participants have reported experiencing as a result of undergoing said treatment.

Table 8 Relationship between the type of treatment and the damages experienced as a result of it, results are presented in absolute values.

		Radiation therapy	Systemic therapy	Both previous treatments	Surgery	Total	Total (%)
I have dry skin.	No	2	5	6	2	15	25.9
	Yes	7	25	6	4	42	72.4
	I don't know /I don't want to answer	0	1	0	0	1	1.7
I feel pruritus (itching).	No	5	13	7	3	28	48.3
	Yes	4	18	4	3	29	50.0
	I don't know /I don't want to answer	0	0	1	0	1	1.7
The skin appears sunburned (visual aspect).	No	3	18	10	3	34	58.6
	Yes	6	13	2	3	24	41.4
	I don't know /I don't want to answer	0	0	0	0	0	0.0
	No	5	24	9	5	43	74.1
	Yes	3	6	2	1	12	20.7

I feel a burning sensation.	I don't know /I don't want to answer	1	1	1	0	3	5.2
There was a skin rash (rash or redness).	No	4	15	6	4	29	50.0
	Yes	5	16	5	2	28	48.3
	I don't know /I don't want to answer	0	0	1	0	1	1.7
There was development of acne (pimples)	No	9	23	12	5	49	84.5
	Yes	0	8	0	1	9	15.5
	I don't know /I don't want to answer	0	0	0	0	0	0.0
Wounds have appeared.	No	7	24	11	4	46	79.3
	Yes	2	7	1	2	12	20.7
	I don't know /I don't want to answer	0	0	0	0	0	0.0
I have flaky. scaly. or crusted skin.	No	5	22	12	4	43	74.1
	Yes	4	9	0	2	15	25.9
	I don't know /I don't want to answer	0	0	0	0	0	0.0
There have been changes in skin tone.	No	2	10	4	2	18	31.0
	Yes	7	21	8	4	40	69.0
	I don't know /I don't want to answer	0	0	0	0	0	0.0

As observed, the issue of "dry skin" was frequently reported by participants, with 72.4% expressing this concern. This condition was experienced by a significant majority. Dry or moist desquamation was commonly reported as a side effect, aligning with the study results (110,111).

In response to the question about feeling pruritus, participants had mixed responses. About 50.0% confirmed experiencing this symptom, while 48.3% denied it. In the literature, Itching is a common side effect of cancer treatment and is associated with dry skin. Pruritus, or itching, is a distressing symptom experienced by cancer patients. This sensation can greatly impact their quality of life. Addressing and managing pruritus effectively is important for comprehensive care and support, as it affects both physical and emotional well-being (110,112).

Regarding the question about the visual aspect of the skin, specifically "The skin appears sunburned", 58.6% of participants denied experiencing this condition, while 41.4% confirmed it. In terms of the sensation aspect of the skin, when asked about feeling a burning sensation, a significant percentage of 74.1% denied it. In some cases, radiation therapy may cause the treated area to appear burnt or swollen. Chemotherapy can also make the skin more vulnerable

to sunburn, known as photosensitivity. Another side effect of cancer treatments is a burning sensation on the skin (112,113).

Skin rashes are common in people receiving various treatments like chemotherapy, stem cell transplants, immunotherapy, and targeted therapy. Immunotherapy and chemotherapy can both cause severe rashes, sometimes widespread. This rash is a common side effect of systemic therapy and affects a significant percentage of patients undergoing targeted chemotherapy, ranging from 43% to 85%. Based on the data, the responses varied. Around 50.0% of respondents reported no skin rash, while 48.3% confirmed having one (110,113).

In the question about the appearance of acne, the majority (84.5%) denied experiencing it, indicating a low prevalence among the participants. Only a small minority reported having this skin condition. According to the literature, certain medications have the potential to cause a skin reaction that resembles acne. This condition is less common but can still be observed in the collected data (114).

In the question "There was the appearance of wounds", 79.3% of participants preferred the option "No". This suggests that nearly 80% of participants did not observe any wounds or injuries. However, It is worth noting that certain medical treatments like Radiotherapy or Chemotherapy can potentially cause chronic wounds, as reported in literature (115).

In response to the question "I have flaky, scaly, or crusted skin", 74.1% of participants answered no. Desquamation, which refers to the shedding or peeling of skin, can occur as a side effect of cancer treatments, particularly certain medications. It is the second most common side effect of these treatments (113,116).

Regarding the question "There were changes in skin tone", 69.0% of the participants confirmed these changes. They are usually associated with chemotherapy treatment. It is important to mention that targeted therapy and radiotherapy can also cause skin discoloration, which can vary in intensity (113,117,118).

5.4.4 Study regarding existing personal care products, specifically cosmetic products

In the next section, we will focus on participants' satisfaction with their personal care products, specifically cosmetics. We will explore their opinions and feedback on the effectiveness, quality, and overall experience of using these products. This is important as it provides insights into participants' preferences and satisfaction levels with their daily cosmetic routines.

By gathering this information, we can understand our target audience's needs and expectations better, and make informed decisions to improve our products and meet their demands.

In table 9, the participants' responses regarding their self-esteem and satisfaction with the products they use are represented.

Table 9 Answers regarding the existence of personal care products (N=58)

		N	%
The personal care products I use improve my self-esteem.	No	11	19.0
	Yes	45	77.6
	I don't know /I don't want to answer	2	3.4
The personal care products I use improve how I am perceived by others.	No	18	31.0
	Yes	28	48.3
	I don't know /I don't want to answer	12	20.7
The personal care products I use improve my quality of life.	No	8	13.8
	Yes	45	77.6
	I don't know /I don't want to answer	5	8.6
The personal care products I use meet my needs. .	No	8	13.8
	Yes	49	84.5
	I don't know /I don't want to answer	1	1.7

In the first question, 77.6% agreed that the products improve self-esteem, while 19% disagreed.

The following question explores whether participants believe that the products they use affect how others perceive them. Dissatisfaction increased to 31% indicating that the perception of these products' impact on others' perceptions may differ from their impact on self-esteem.

Regarding quality of life, 77.6% agreed the products improve it, while 13.8% disagreed.

Finally, 84.5% agreed the products meet their needs, indicating a strong majority find them effective.

Table 10 Answers regarding the interest and opinion of the participants about cosmetics (N=58)

		N	%
I am looking for information about cosmetics/cosmetic products before purchasing.	No	8	13.8
	Yes	50	86.2
I feel that I can easily access information about cosmetic products.	No	16	27.6
	Yes	40	69.0
	I don't know /I don't want to answer	2	3.4
Do you select your hydration products based on their composition?	No	15	25.9
	Yes	43	74.1

In table 10, 86.2% of participants actively seek information about the products they use, indicating a strong desire for consumer knowledge. Additionally, 69.0% find it easy to access information about cosmetic products, showing a positive perception of availability. However, 27.6% disagree, suggesting room for improvement in accessibility and clarity.

However, 74.1% of participants consider product composition when making purchasing decisions, reflecting a growing awareness of the impact of ingredients on personal health and well-being.

5.4.5 Study regarding the routine and preferences in cosmetic products

In this section, various points will be analysed regarding the participants' preferences for cosmetic products. This includes the ingredients they seek to include and eliminate in their routine, as well as some steps of their cleansing and moisturizing routine.

Participants were asked about the source of advice for the cosmetic product they currently use. It is interesting to note the variety of sources from which participants seek guidance.

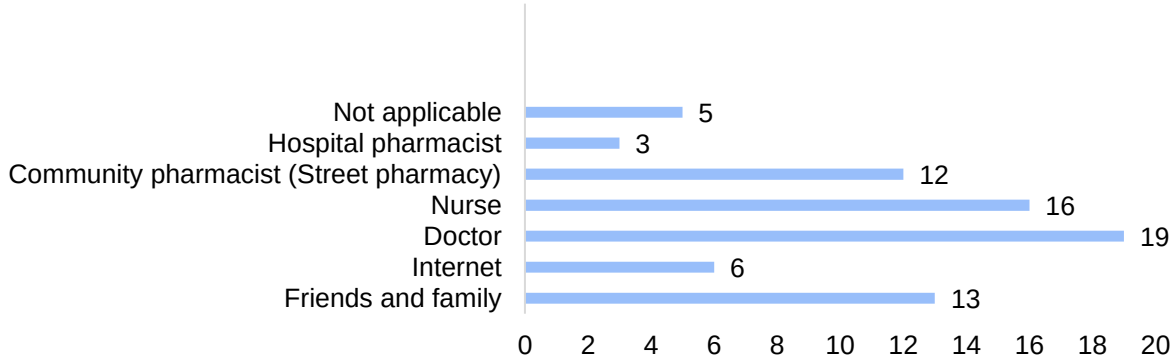


Figure 18 Source of advice for cosmetic products (N=74)

Observation: Since it was allowed to select more than one response option, the number of answers does not correspond to the number of respondents.

The majority of participants report using a product recommended by a healthcare professional (Figure 18), such as a doctor (25.7%) or a nurse (21.6%). Additionally, 17.6% rely on recommendations from friends and family members. Furthermore, a significant number of participants (16.2%) seek advice at local pharmacies.

During the evaluation process, it became evident that certain characteristics stood out and were particularly appealing to the participants.

As it is possible to observe in figure 19, participants prefer an odorless product (46), that is oil-based (38), and with sun protection (36).

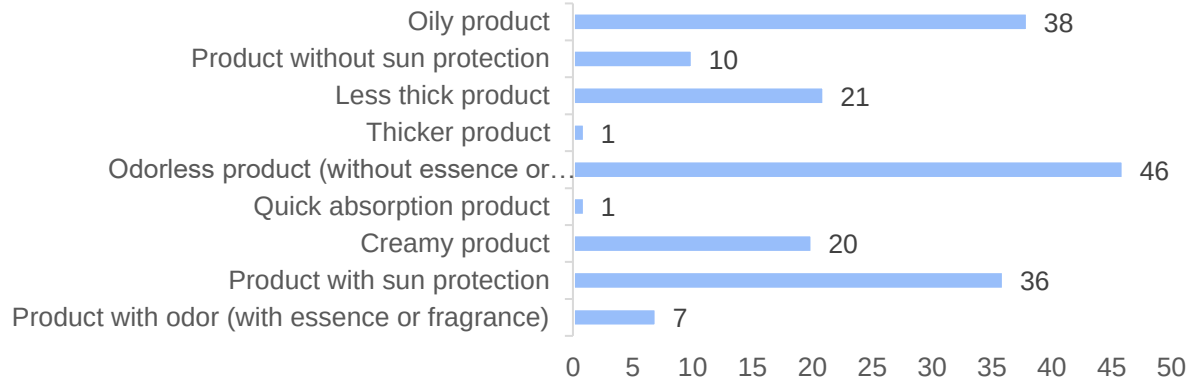


Figure 19 Representation of the preferences and expectations of the participants, (N=180)

Observation: Since it was allowed to select more than one response option, the number of answers does not correspond to the number of respondents.

This coincides with the recommended advice for patients undergoing cancer treatment. To ensure the health and well-being of your skin, it is highly recommended to incorporate a few simple practices into the daily routine. Firstly, it is advisable to opt for mild soaps that are specifically formulated to be gentle on the skin. This will help to minimize the risk of any potential irritation or discomfort. In addition to using mild soaps, it is crucial to keep the skin adequately hydrated. This can be achieved by regularly applying moisturizing lotions or creams. These products not only help to lock in moisture, but they also act as a barrier preventing dryness and itching. Furthermore, it is essential to prioritize sun protection. Applying sunscreen with a broad-spectrum SPF is highly recommended, as it shields the skin from harmful UV rays. Lastly, it is important to be mindful of the ingredients in the skincare products selected. Avoiding products that contain alcohol or fragrances is advisable, as these can potentially exacerbate skin irritation (113).

This section assesses the participants' preferences and routines, including the ingredients they seek to include or eliminate from the products (Figure 20).

Upon observation, 39.7% of individuals prefer micellar water for face cleansing, while 31.0% prefer soap.

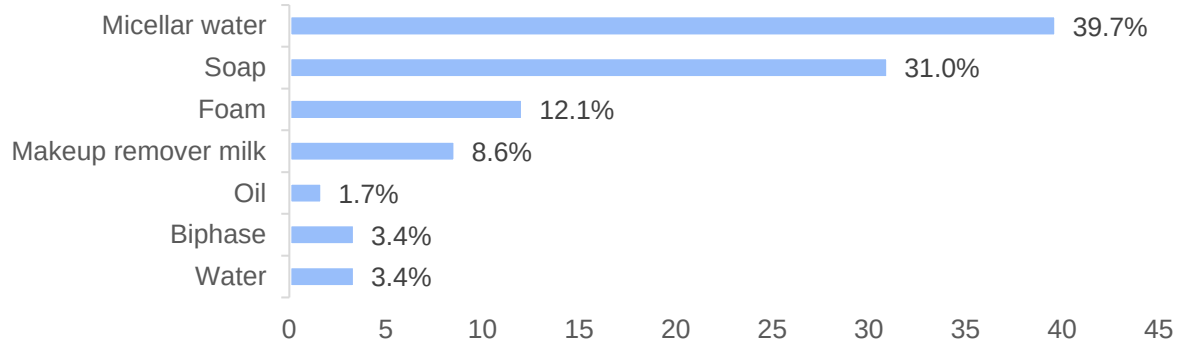


Figure 20 Representation of the selected method to clean the participants face (N=58)

This step of the skincare routine is aligned with the recommended method as it takes into consideration the slightly acidic pH of the skin's surface (pH 4.5-5.7). It is advised to use mild cleansers with a similar pH to that of the skin. Natural soap is not recommended for skin cleansing as it has an alkaline pH (7-12) that can potentially harm the skin barrier. Instead, micellar water is an excellent option for effectively and gently cleansing the skin, especially for those with dry and sensitive skin types. Micellar water, a popular skincare product, combines water with a very gentle surfactant in its unique formulation (119,120).

The objective of this section is to illustrate the routines for body skincare (Figure 21), with a focus on the types of products used by the participants.

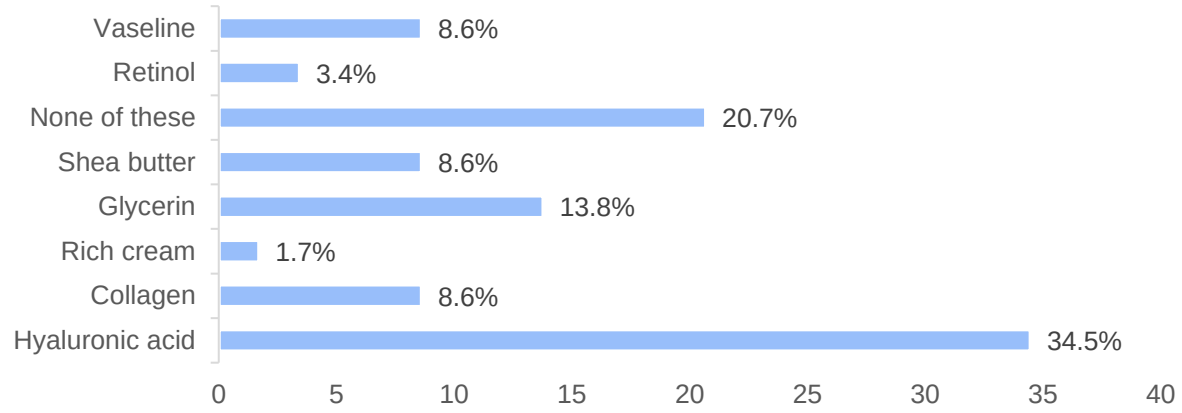


Figure 23 Representation of the Ingredients that the participants look to Include Into their routine (N=58)

Moreover, the preferred method for cleansing the body is soap (31.0%), which, being a gentle soap with a pH identical to that of the skin, is highly recommended by dermatologists and skincare experts worldwide. Using soap not only helps to remove dirt and impurities from the skin, but it also helps to maintain the natural balance and moisture levels of the skin (119,120).

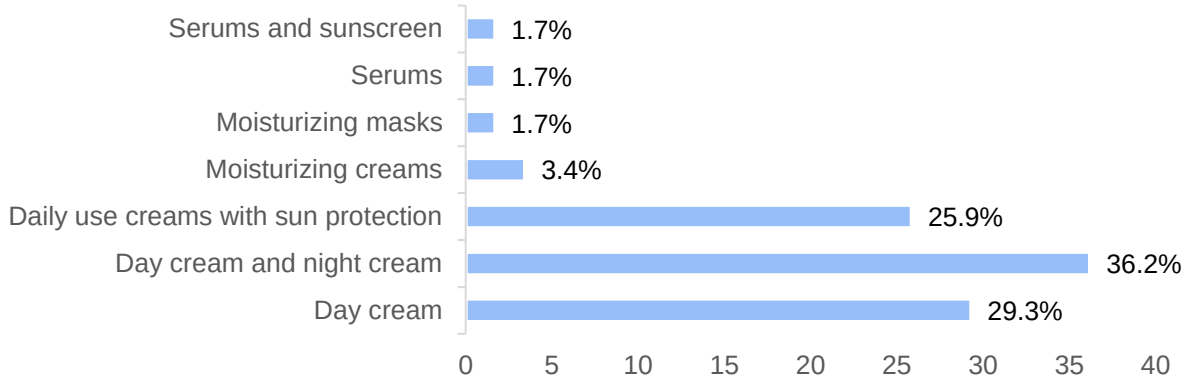


Figure 22 Representation of the selected method to hydrate the skin (N=58)

According to figure 22, most participants (36.2%) prefer using both day cream and night cream for their daily hydration routine. However, a significant number of participants (29.3%) opt for using only day cream for a simpler approach. The data also shows that participants (25.9%) prioritize products with effective sun protection.

A detailed analysis will be conducted to identify the ingredients participants want to use and avoid in their skincare routine.

According to the survey, HA received the highest vote frequency at 34.5%. "None of these" also received a considerable response, accounting for 20.7% of the votes. This suggests that some participants either do not actively seek out specific ingredients or prefer ingredients not on the provided list. The choice of HA aligns with professional advice, as it offers numerous benefits for wound regeneration and skin care. It moisturizes the skin, improves elasticity, reduces wrinkles, promotes skin cell migration, and aids the absorption of active substances into the epidermis. Some HA products also provide protection against harmful UV radiation and exhibit antioxidant effects, supporting overall skin health and vitality (121,122).

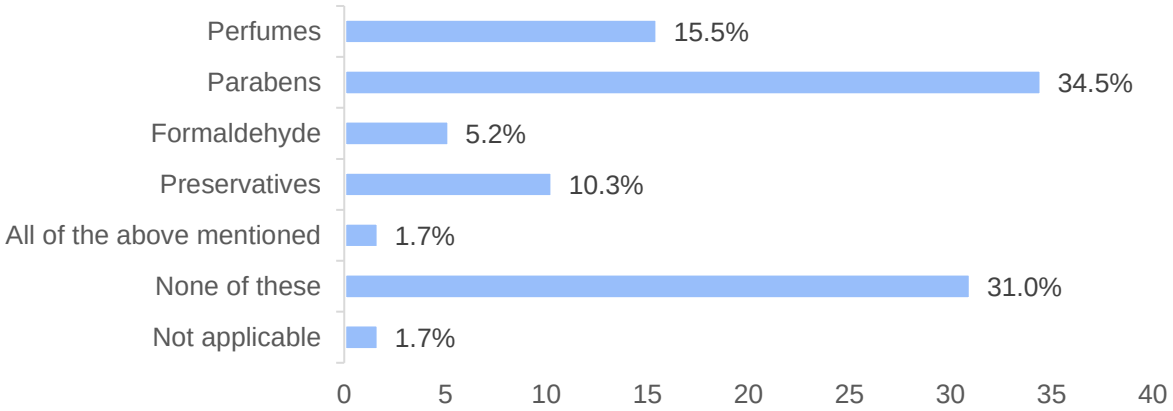


Figure 24 Representation of the Ingredients that the participants look to remove from their routine (N=58)

Based on the survey results (Figure 24), Parabens received the highest number of votes (34.5%) among participants. "None of these" also received a substantial response (31.0%), indicating that some participants either do not actively eliminate any specific ingredient or eliminate ingredients not listed. Parabens can extend the shelf life of products and prevent the growth of microorganisms. However, there are concerns about their use in creamy or liquid cosmetics due to potential adverse effects. Parabens, commonly used in cosmetics and personal care products, have raised concerns about hormone function, allergies, weight gain, and fertility. While the Food and Drug Administration (FDA) considers their use in food and beverages safe up to 0.1%, cosmetics typically contain parabens in concentrations ranging from 0.01% to 0.3% (66).

5.4.6 Conclusion

Common side effects from oncology treatments reported included dry skin, itching, burning sensation, and rashes. Acne and wounds were less frequently mentioned. Many

participants experienced changes in skin tone, emphasizing the need for tailored skincare solutions.

The self-esteem and satisfaction survey revealed that participants believe skincare products positively impact their self-esteem and quality of life. However, fewer participants think these products affect how others perceive them, showing the complex relationship between personal care and the patient's perception.

Participants actively seek information about cosmetic products and rely on healthcare professionals, friends and family, and local pharmacies for advice. They prefer odorless, oil-based products with sun protection. Skincare recommendations include mild soaps, moisturizing lotions, sunscreen, and micellar water for facial cleansing. Day and night creams with effective sun protection are also important, with HA being a popular ingredient and concerns raised about parabens.

In conclusion, this study highlights the importance of addressing the unique skincare needs of cancer patients. Tailored products can meet their needs and expectations. Understanding the impact of personal care products on self-esteem and external perceptions can enhance overall well-being.

6

CONCLUSION AND FUTURE WORK

The creation of formulations that are suitable for cancer patients necessitates various modifications in the choice of ingredients and the improvement of manufacturing processes. The findings derived from this extensive study offer compelling evidence to validate the notion that it is feasible to formulate products that mitigate the likelihood of skin sensitivity and irritation. This accomplishment can be primarily attributed to the meticulous selection of components.

Looking forward, it is important to acknowledge that the final formulations created in this study demonstrate the efficacy of formulating with specific components. It is worth noting that formulation F1 was selected based on its distinct characteristics that closely align with the preferences of the intended recipients, as indicated by the survey. It is noteworthy that individuals undergoing cancer treatment prefer oil-based formulas that are fragrance-free and provide sun protection. While F1 meets most of these criteria, it lacks adequate sun protection. The outcomes derived from various tests validate the stability of the developed formulation. Moreover, the implications of this formulation are significant, as it has the potential to significantly enhance treatment compliance and mitigate associated adverse effects.

To further advance knowledge in this domain, it is recommended that future investigations delve deeper into exploring this formulation and assess its applicability in diverse settings and populations. Additionally, conducting *in vivo* experiments to evaluate the effectiveness of the formulation and considering the inclusion of sunscreen, which is essential for the sensitized skin of the target audience, would substantially contribute to the overall comprehension and efficacy of this formulation.

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A
An Appendix

A.1 Stability essay

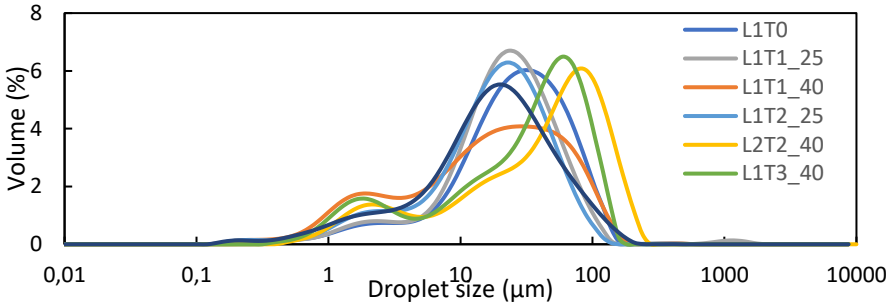

Figure 26 Comparison of droplet size distribution in batch 1 different conditions, 25°C, 40°C and Plastic Jar (B), with n=6

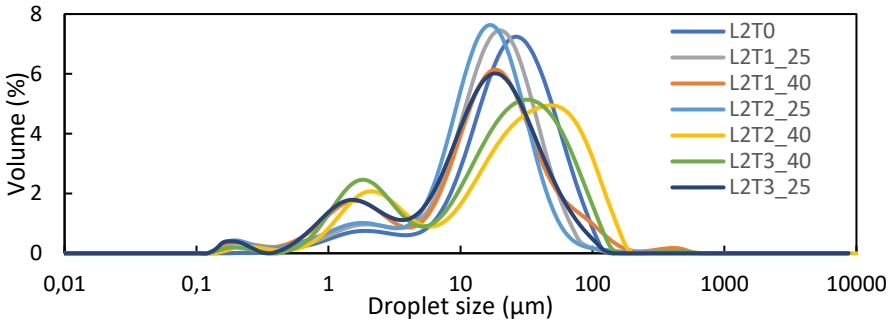

Figure 25 Comparison of droplet size distribution in batch 2 different conditions, 25°C, 40°C and Plastic Jar (B), with n=6

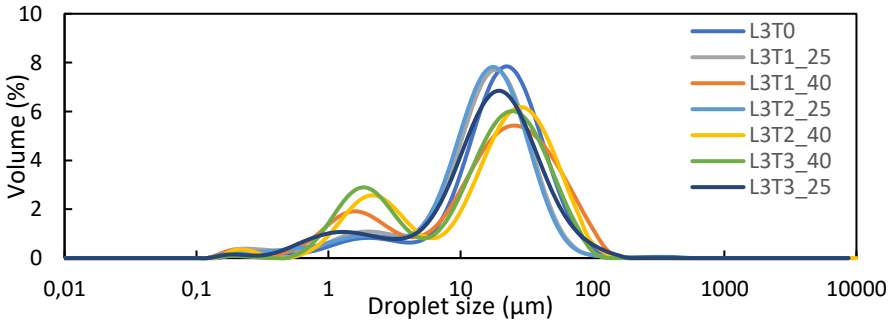

Figure 27 Comparison of droplet size distribution in batch 3 different conditions, 25°C, 40°C and Plastic Jar (B), with n=6

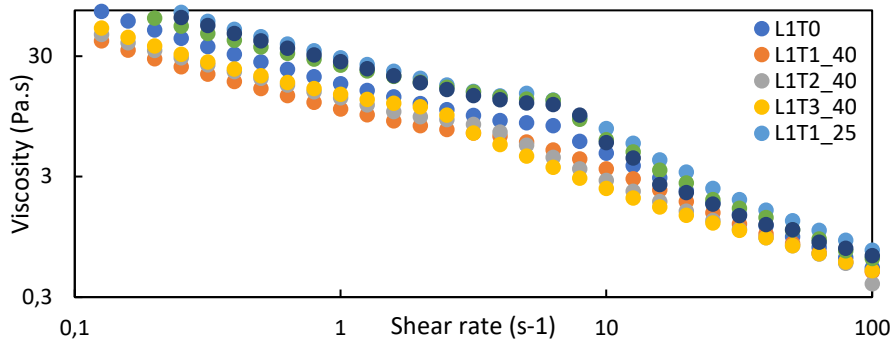

Figure 28 Comparison of Viscosity behavior in batch 1 different conditions, 25°C, 40°C

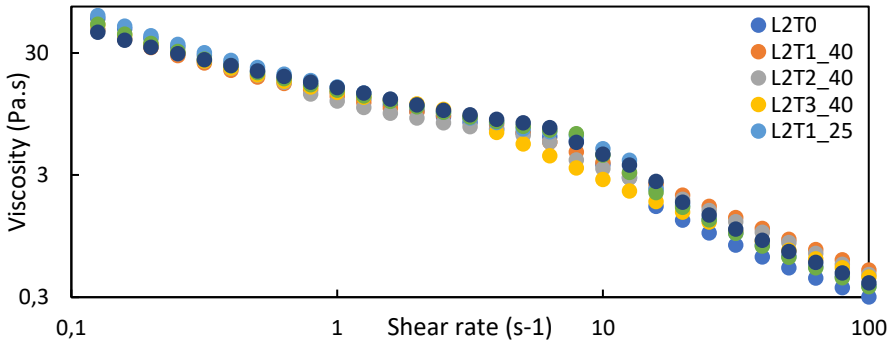

Figure 29 Comparison of Viscosity behavior in batch 2 different conditions, 25°C, 40°C

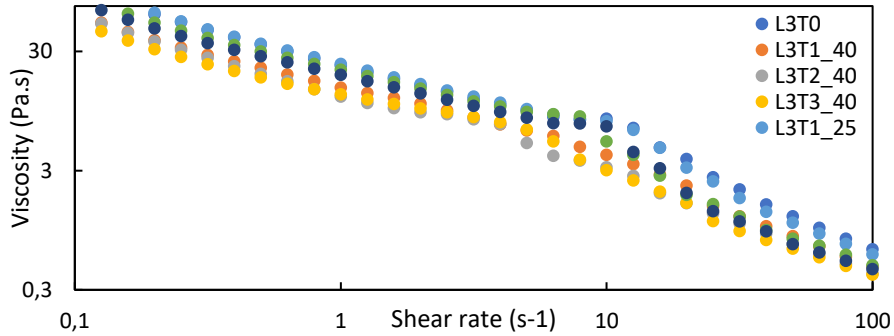

Figure 30 Comparison of Viscosity behavior in batch 3 different conditions, 25°C, 40°C

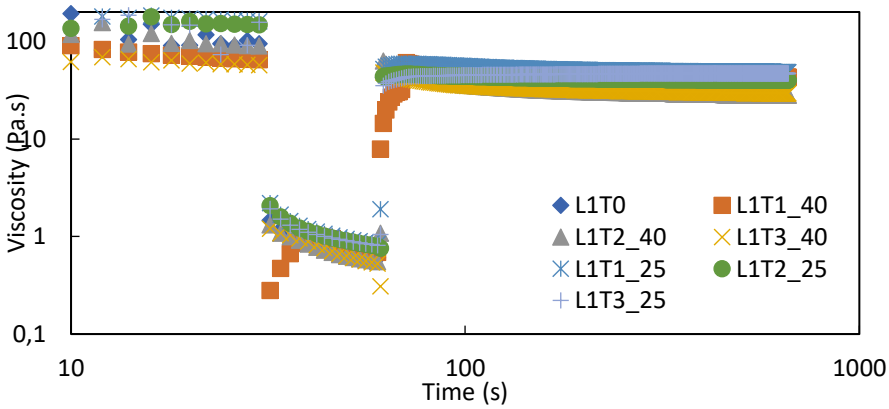

Figure 31 Comparison of Viscosity behavior (Three-step shear rate) in batch 1 different conditions, 25°C, 40°C

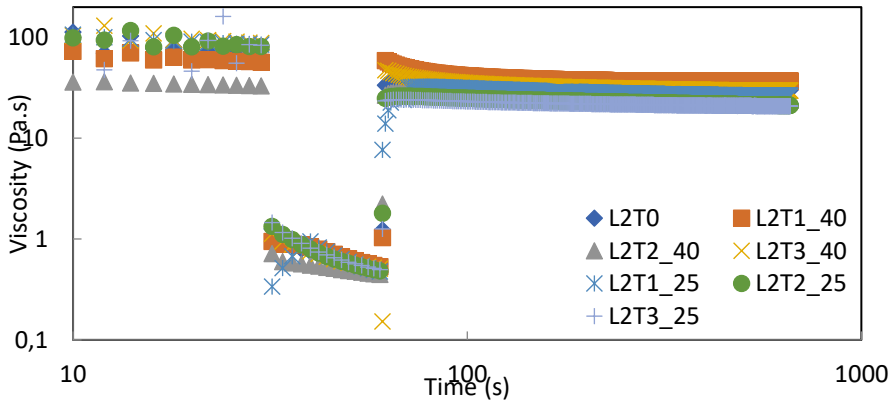

Figure 32 Comparison of Viscosity behavior (Three-step shear rate) in batch 2 different conditions, 25°C, 40°C

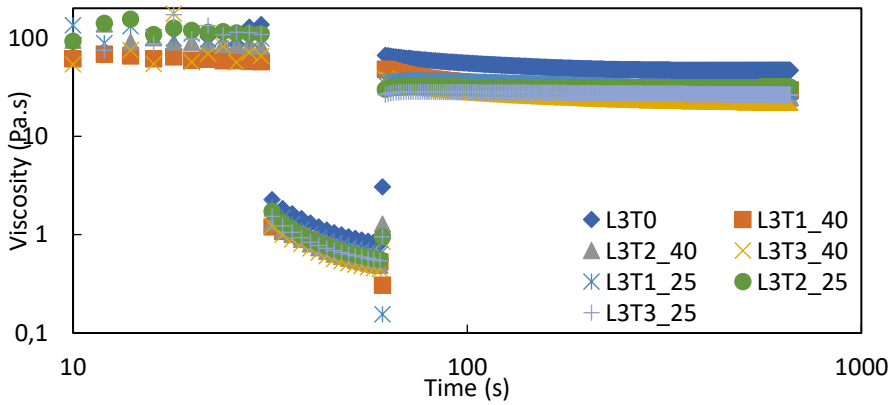

Figure 33 Comparison of Viscosity behavior (Three-step shear rate) in batch 3 different conditions, 25°C, 40°C

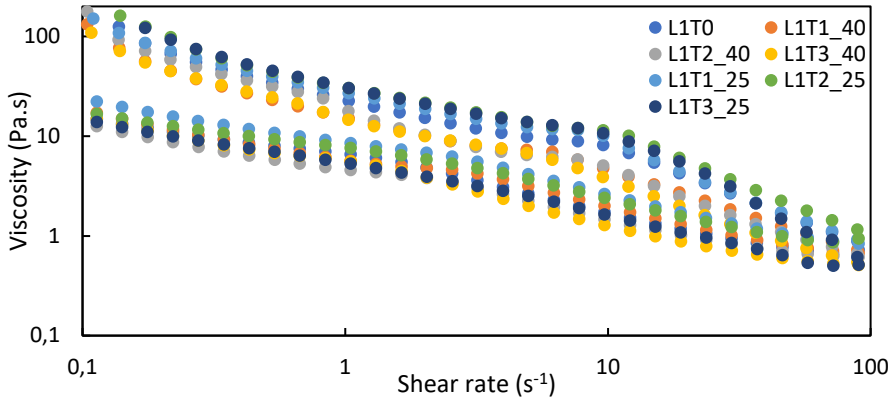

Figure 34 Comparison of Viscosity behavior (Ramp up-Ramp down) in batch 1 different conditions, 25°C, 40°C

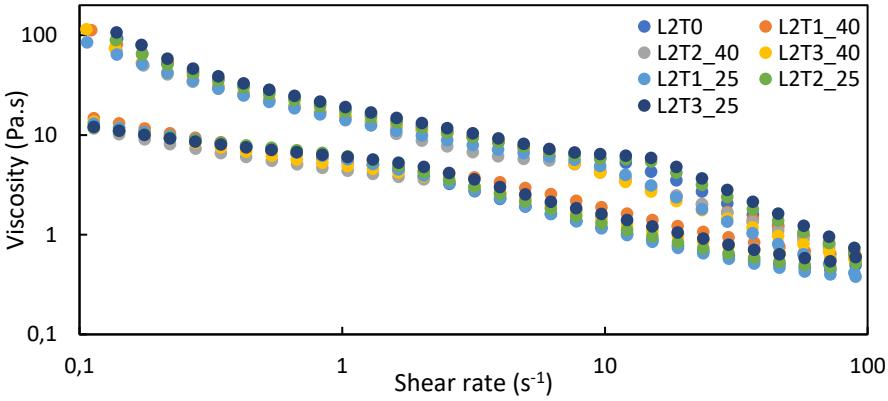

Figure 35 Comparison of Viscosity behavior (Ramp up-Ramp down) in batch 2 different conditions, 25°C, 40°C

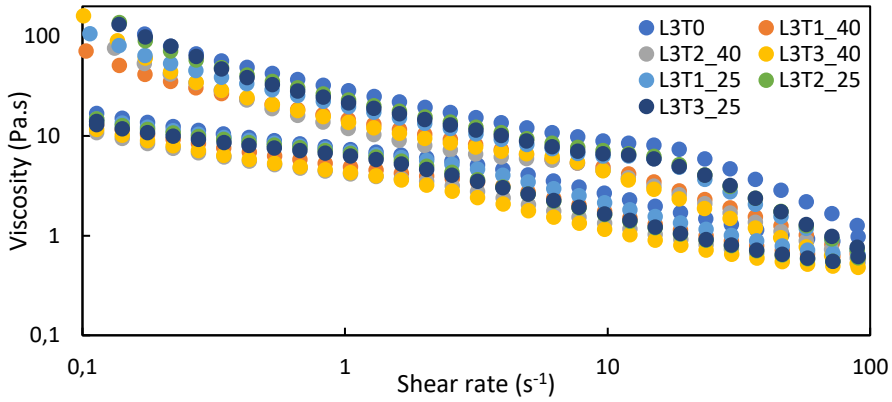

Figure 36 Comparison of Viscosity behavior (Ramp up-Ramp down) in batch 3 different conditions, 25°C, 40°C

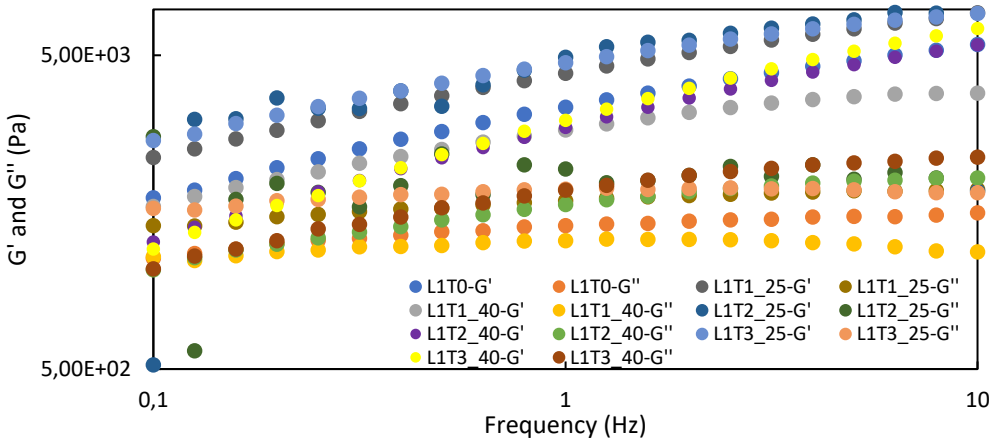

Figure 37 Comparison of Oscillatory behavior in batch 1 different conditions, 25°C, 40°C

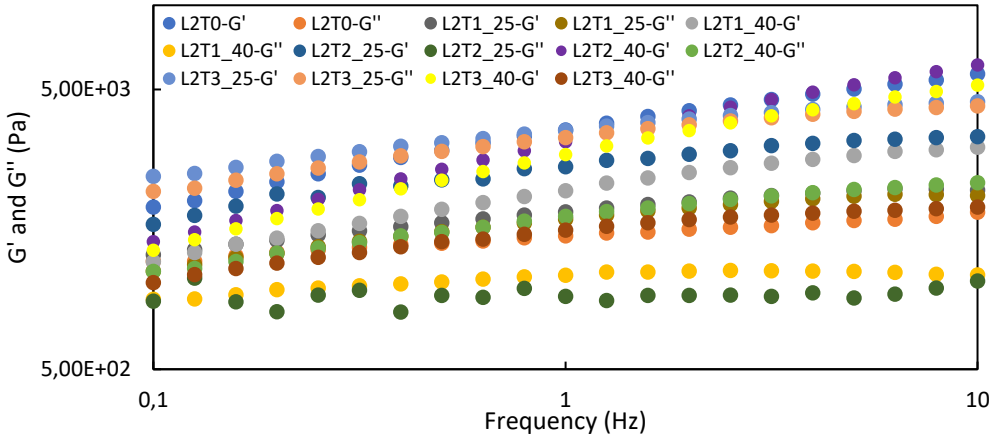

Figure 38 Comparison of Oscillatory behavior in batch 2 different conditions, 25°C, 40°C

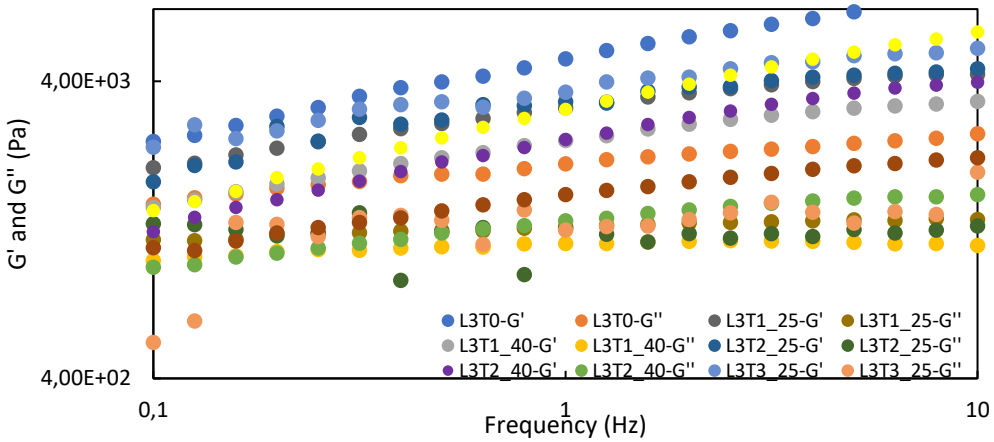

Figure 39 Comparison of Oscillatory behavior in batch 3 different conditions, 25°C, 40°C

B QUESTIONNAIRE

Formulário projeto de tese

Seguinte questionário foi realizado no decorrer da tese de mestrado, cujo tema centra o desenvolvimento de um produto cosmético auxiliar, a doentes de cancro. Pretende-se recolher a opinião dos doentes em relação a afirmações colocadas, bem como as preferências dos mesmos, por fim este questionário também visa entender as principais preocupações do público alvo.

1: Idade

2: Género

- Feminino
- Masculino
- Outro: _____

3: Diagnóstico apresentado pelo médico (cancro primário, quando o médico lhe deu o diagnostico pela primeira vez, onde estava o tumor?)

- Colorretal
- Mama
- Próstata
- Pulmão
- Estômago
- Bexiga
- Fígado
- Tiroide
- Outro: _____

4: Tratamento prescrito

- Terapia sistémica (Intravenoso, subcutânea, comprimidos.)
- Radioterapia
- Outra: _____

Questões relativas aos sintomas físicos após início de tratamento

As perguntas seguintes serão focadas nos sintomas e bem estar do doente, após o início do tratamento.

5: Sinto-me incomodado com os efeitos secundários cutâneos (pele) do tratamento.

- Sim
- Não
- Não sei/ Não quero responder

6: Tenho a pele seca.

- Sim
- Não
- Não sei / Não quero responder

7: Sinto prurido (Comichão)

- Sim
- Não
- Não sei/ Não quero responder

8: A pele parece queimada do sol (aspeto visual).

- Sim
- Não
- Não sei/ Não quero responder

9: Sinto sensação de queimadura.

- Sim
- Não
- Não sei/ Não quero responder

10: Houve erupção cutânea (rash ou vermelhidão).

- Sim
- Não
- Não sei/ Não quero responder

11: Houve desenvolvimento de acne (Borbulhas).

- Sim
- Não
- Não sei/ Não quero responder

12: Houve aparecimento de feridas.

- Sim
- Não
- Não sei/ Não quero responder

13: Tenho pele descamada, escamosa ou com crostas.

- Sim
- Não
- Não sei/ Não quero responder

14: Houve modificações na tonalidade da pele.

- Sim
- Não
- Não sei/ Não quero responder

Questões relativas aos produtos de cuidado pessoal existentes, especificamente produtos cosméticos:

15: Os produtos de cuidados pessoais que utilizo melhoram a minha qualidade de vida.

- Sim
- Não
- Não sei/ Não quero responder

16: Os produtos de cuidados pessoais que utilizo satisfazem as minhas necessidades.

- Sim
- Não
- Não sei/ Não quero responder

17: Os produtos de cuidados pessoais que utilizo melhoram a minha autoestima.

- Sim
- Não
- Não sei/ Não quero responder

18: Os produtos de cuidados pessoais que utilizo melhoram a forma como sou visto/a pelos outros.

- Sim
- Não

- Não sei/ Não quero responder

19: Os produtos cosméticos que utiliza regularmente foram aconselhados por:

- Enfermeiro
- Farmacêutico hospitalar
- Farmacêutico comunitário (Farmácia de rua)
- Médico
- Amigos e familiares
- Internet
- Outro

20: Procuro informação sobre cosmética/produtos cosméticos antes da aquisição.

- Sim
- Não

21: Sinto que consigo aceder facilmente a informação sobre produtos cosméticos.

- Sim
- Não
- Não sei/ Não quero responder

Questões relativas a preferências de produtos de cuidado, especificamente produtos cosméticos:

Esta ultima secção visa perceber as preferências dos doentes em relação aos produtos de cuidado pessoal, especificamente cremes.

22: Selecione as opções que preferir:

- Produto oleoso
- Produto cremoso
- Produto menos espesso
- Produto mais espesso
- Produto com proteção solar
- Produto sem proteção solar
- Produto inodoro (sem essência ou perfume)
- Produto com odor (com essência ou perfume)
- Produto de rápida absorção
- Outro

23: Rotinas na Limpeza de pele do Rosto: Que produtos usa:

- Água micelar
- Leite desmaquilhante

- Sabonete
- Óleo
- Bifásico
- Espuma
- Outro _____

24: Rotinas na Limpeza de pele do Corpo: Que produtos usa:

- Gel de banho
- Sabonete
- Óleo
- Espuma
- Outro_____

25: Rotinas na Hidratação da pele. Que produtos usa?

- Creme de dia
- Creme de noite
- Creme de dia e creme de noite
- Séruns
- Cremes de uso diários com proteção solar
- Máscaras hidratantes
- Óleos
- Outro_____

26: Seleciona os seus produtos de hidratação pela sua composição?

- Sim
- Não

27: Seleciona algum destes ingredientes como parte da formulação dos seus cuidados de hidratação?

- Ácido hialurónico
- Retinol
- Niacinamida
- Ácido glicólico
- Péptidos
- Colágeneo
- Manteiga de karité
- Glicerina
- Vaselina
- Nenhum destes
- Outro_____

28: Evita usar cosméticos que contenham:

- Parabenos
- Formaldeído
- Triclosan
- Perfumes
- Conservantes
- Nenhum destes
- Outro_____

Muito obrigada pela atenção e pelo tempo dispensado.

B.1 Informative Leaflet