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**MISS AZUMAH PHILOMINA EDINAM**

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# CREAM AND MILK PARAPHARMACEUTICAL FORMULATIONS

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| | | | |
|---|---|---|---|
| Mr. ZIANI-CHERIF Houcine | Professor | University of Tlemcen | Chairperson |
| Mme. GUENDOUZ Souhila | Doctor | University of Tlemcen | Examiner |
| Mr. Ziani-Cherif Chewki | Professor | University of Tlemcen | Supervisor |

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## DEDICATIONS

Glory be to the Lord for how far He has brought me. Glory to God for this work!

To my dearest parents, Mr. Solomon Kofi Azumah and Mrs. Charlotte Azumah. Thank you for your sacrifice, prayers and your support that brought me where I am today and will take me to where I will be tomorrow. Words cannot express my profound gratitude.

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## ABSTRACT

The increased risk associated with the metabolism of most oral antifungal drugs has given to the question of finding safe, efficient, and cost-effective ways to treat nail fungal infections. In Ghana, the lack of effective antifungal drugs has given rise to the use of costly imported drugs. Separately, regular bathing of the infant dries out the skin which could compromise the skin barrier function and also lead to skin irritation. This has given rise to concerns about finding safe and cost-effective methods of cleansing the baby while retaining its nutrients and body moisture. The objective of this study is the formulation of parapharmaceutical products for treating nail fungus infections and also cleansing and retaining the baby's skin respectively. In this study, various parapharmaceutical formulations were developed and their physicochemical and rheological properties were evaluated. Results proved the formulation of various topical formulations which were stable under storage conditions. Moreover, a limitation of this study is the lack of a good homogenizer to create smaller particle sizes resulting in the failure of baby cleansing milk formulation.



**Keywords**: Cream, Cleansing milk, Topical Formulation, Parapharmaceutical



## RESUME:

Le risque accru associé au métabolisme de la plupart des médicaments antifongiques oraux a posé la question de trouver des moyens sûrs, efficaces et rentables de traiter les infections fongiques des ongles. Au Ghana, le manque de médicaments antifongiques efficaces a donné lieu à l'utilisation de médicaments importés coûteux. Séparément, le bain régulier du nourrisson assèche la peau, ce qui peut compromettre la fonction de barrière cutanée et également entraîner une irritation cutanée. Cela a suscité des inquiétudes quant à la recherche de méthodes sûres et rentables pour nettoyer le bébé tout en conservant ses nutriments et son humidité corporelle. L'objectif de cette étude est la formulation de produits parapharmaceutiques permettant respectivement de traiter les mycoses des ongles mais aussi de nettoyer et de maintenir la peau du bébé. Dans cette étude, différentes formulations parapharmaceutiques ont été développées et leurs propriétés physicochimiques et rhéologiques ont été évaluées. Les résultats ont prouvé la formulation de diverses formulations topiques qui étaient stables dans des conditions de stockage. De plus, une limite à cette étude est l'absence d'un bon homogénéisateur pour créer une taille de particules plus petite, ce qui entraîne l'échec de la formulation du lait de toilette pour bébé.



**Mots clés** : Crème, Lait démaquillant, Formulation topique, Parapharmaceutique

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## LIST OF ABBREVIATIONS

BC: Before Christ

Bronidox:5-bromo-5-nitro-1,3-dioxane

DCM: Dichloromethane.

FDA: Food and Drugs Authority

LCSO: Laboratory of Catalysis and Organic Synthesis.

US: United States

pH: the potential of hydrogen

q.s: quantity sufficient

W: Watts

# GLOSSARY

**Active Ingredient**: The active ingredient performs the main function of what the end product is supposed to do.

**Adjuvant**: a drug or other substance, or a combination of substances, used to increase the efficacy or potency of certain drugs.

**Aerosols**: Suspension of fine solid/liquid particles with the gas used to apply the drug to the respiratory tract having atomizer with in-device.

**Anti-freeze agents**: They are ingredients that help keep the end product from freezing.

**Antimicrobial Agents**: Antimicrobial agents could be used to enhance the shelf life of the final product. They inhibit or avert the end product's degradation.

**Cream**: Creams are semi-solid emulsions that contain oil and water mixtures, and consistency varies between liquids and solids.

**Diluents**: Diluents are inert ingredients that are used to adjust quantities and balance in a formulation. They occupy space without modifying other characteristics.

**Emulsions**: A non-uniform mixture of two liquids that don't dissolve in each other, held together by emulsifiers.

**Functional Agents**: Functional agent is an ingredient required to help the end product penetrate the target's surface or delay drying time.

**Gel**: Gel is a two-phase elastic colloidal material, consisting of a dispersed liquid incorporated in the solid phase.

**Inactive ingredients**: Any substance of a drug product other than its active constituent.

**Inhalations**: Internal liquid preparations containing medications dissolved in a suitable solvent or if insoluble suspended in the propellant.

**Oil-in-water emulsions:** An emulsion in which oil is the dispersed phase and water is the continuous phase

**Ointment:** Semi-solid substance which contains 20% water phase and about 80% oil phase.

**Oleaginous base:** These are greasy bases, mostly fats and oils.

**Paste** Semi-solid substances which are either stiff or thick and contain largely fine solids mainly used for skin application.

**Pharmacological activity**: pharmacological activity describes the beneficial or adverse effects of a drug on living matter.

**Rheological agents**: Rheological agents are used to thicken or thin formulations. These agents create viscosity to improve stability and functionality.

**Solutions**: A uniform mixture of a solid, liquid or gas dissolved in another liquid.

**Sprays**: Gaseous preparations of drugs containing alcohol applied to the inner lining of the nose or throat with an atomizer or nebulizer.

**Suspensions**: A non-uniform mixture of insoluble solid particles held within a liquid.

**Surfactants and Dispersants**: Surfactants and dispersants are ingredients necessary to improve the stability of products and achieve acceptable mixing with water.

**Topical preparations**: Any medication applied to a body surface, including the skin or the oral cavity.

**Water-in-oil emulsion:** an emulsion in which water is the dispersed phase and oil is the continuous phase.

# GENERAL INTRODUCTION

## GENERAL INTRODUCTION

The pharmaceutical industry is an innovative economic sector that assembles companies or individuals in the research, manufacturing and distribution of medicines for human and veterinary use. They are primarily driven by the innovation and production of products such as oral drugs, parenteral formulations, topical medicines, and oncological formulations amongst others. The parapharmaceutical industry is primarily concerned with developing products intended to help with specific health issues ranging from skin blemishes to sunburns.

Many companies tend to increase sales of existing products by revisiting and improving upon earlier formulations.[1] The cost of researching and developing a new chemical or biological entity was estimated at £1,926 million in 2014 ($2558 million in 2013)[2]. As a result of the high cost involved in product development, most pharmaceutical companies keep their formulations secret, making it nearly impossible to obtain bibliographic materials on formulations.

Since the independence of Ghana in the year 1957, local pharmaceutical companies have focused on the formulation and production of medication to address public health and economic challenges in the country[3]. Faced with fierce competition from Asia, Europe, and the United States, these industries are forced to supply only a portion of medicines locally, with only a few able to import to neighboring countries[4]. In this work, I hope to contribute to the local production of drugs in order to reduce the country's dependence on foreign imports and thus contribute to Ghana's economic sector.

In general, formulations include a variety of ingredients such as active ingredients, rheological agents, functional agents, antimicrobial agents, antifreeze agents, surfactants and diluents. Although there are no chemical reactions in the preparation of formulations, there are many chemical aspects to formulation. These include mixing thermodynamics, phase equilibrium, solutions, colloids, emulsions, and suspensions.

In this work, using Ghana as a case study, my work focuses on the formulation and preparation of para-pharmaceutical milk and creams, primarily baby cleansing milk and anti-fungus nail creams.

## STATEMENT OF THE PROBLEM

In Ghana, a tropical country in the western part of Africa, major agricultural and other farming activities are carried out at the village level with poor or no health facilities. As a result, the majority of these populations are exposed to infectious agents responsible for many microbial infections, including

[1] Strausburgh M., Optimized formulation can boost your commercial Success, CAS, American Chemical Society, 2019.

[2] DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of health economics*, *47*, 20-33. https://doi.org/10.1016/j.jhealeco.2016.01.012.

[3] Pourraz, J. (2022). Making medicines in post-colonial Ghana: State policies, technology transfer and pharmaceuticals market. *Social Science & Medicine*, *311*, 115360. DOI:10.1016/j.socscimed.2022.115360

[4] Chaudhuri, S. (2016). Can foreign firms promote local production of pharmaceuticals in Africa? In *Making Medicines in Africa* (pp. 103-121). Palgrave Macmillan, London. DOI: 10.1007/978-1-137-54647-0 ,ISBN: 978-1-137-57133-5

fungal infections[5]. Compounding the lack of good facilities, the most effective antifungal drugs are not available in the country, and those available are not always accessible and also expensive for those who need them[5]. The question of finding safe, efficient, and cost-friendly ways to treat nail fungal infections has been raised due to the increased risk associated with the metabolism of most oral antifungal drugs. A proposed anti-fungal formulation is presented to address issues associated with the oral treatment of nail fungal infections.

Daily bathing is a good practice in general, but it is not ideal for the baby because it can dry out and irritate its skin, especially when aggressive anionics with high-degreasing properties are involved.[6] Babies exhibit messy behaviors that make them more exposed to factors that could compromise the skin barrier function and also lead to skin irritation[7]. This study seeks to address problems related to proper cleansing and retention of the baby's body moisture and nutrients without comprising the skin barrier.

## AIM AND OBJECTIVES.

This work aims to formulate and prepare effective and efficient cleansing milk suitable for babies of all skin types, as well as to prepare and formulate an effective anti-fungal cream to treat and improve infected nails with no or fewer side effects to the body. Finally, it is to produce potent and less expensive products while increasing the revenue of the economy.

## METHODOLOGY.

In this work, in order to prepare the various formulations, it is necessary to consult various topical formulation reviews in order to know the ingredients that will be used for the proposed formulations.

For this work, the first chapter is divided into two sections. The first section discusses generalities about various para-pharmaceutical formulation processes and the physio-chemical properties of primary and secondary ingredients in these formulations. The second section deals with a bibliographic study of topical pastes, topical ointments, anti-fungal creams and also baby cleansing milk. For each of the sections, I will proceed to adequate formulations, based on the then available ingredients. Each formulation that I would prepare will be submitted to various analytical and stability tests. The second chapter is also divided into two sections: the first section outlines the materials, apparatus, and methods used in the formulation of various topical formulations. The second section addresses the presentation and interpretation of the experimental analysis of the formulated products.

Finally, a general conclusion summarizes all results obtained.

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[5] Ocansey, B. K., Pesewu, G. A., Codjoe, F. S., Osei-Djarbeng, S., Feglo, P. K., & Denning, D. W. (2019). Estimated burden of serious fungal infections in Ghana. *Journal of Fungi*, *5*(2), 38.

[6] Sushmitha, C. (2019). Baby Care–Baby Care Products and Harmful Ingredients Used in Baby Products. *American Journal of PharmTech Research*, 9(6), 57-76.

[7] Stamatas, G. N., Walters, R. M., & Martin, K. M. (2011). Formulating for unique needs of baby skin. *Personal Care*, 31-36.

# CHAPTER 1

# GENERALITIES OF FORMULATIONS

## 1.1. Introduction

A formulation is a mixture (with desired characteristics and properties) of specific amounts of ingredients that do not react with each other to suit a particular application or use. The meaning of the word 'formulations' in various fields such as law, mathematics, food, cosmetics, pharmaceuticals, etc... varies from each other depending on the field. Examples of formulations in the consuming industries include pharmaceutical products, cosmetics, and paints amongst others. Formulations in pharmaceutical and para-pharmaceutical fields have provided the advantage of achieving effects that cannot be obtained when its components are used singly. Generally, formulations can be classified based on various factors such as their state of matter, but also their functions. Table 1.1 illustrates the classification of formulation based on the state of matter.

| Class Of Formulation | Type Of Examples |
|---|---|
| **Solid** | Tablets, capsules<br>Topical preparations are semisolid (creams, ointments, gels, suppositories, pastes) |
| **Liquid** | Solutions, suspensions, emulsions |
| **Gaseous** | Aerosols, Inhalations, Sprays |

***Table1.1 :Classification of Formulation according to their states of matter***.

The objective of this chapter is to introduce general concepts relevant to our thesis, starting with formulations and the various ingredients used in para pharmaceutical products. This section will therefore lay down the foundation for an extensive comprehension of the subsequent chapter of this thesis.

## 1.2. History of Formulation [8]

Formulation or mixing various substances to achieve a specific goal dates back to prehistory. The oldest paintings date between 10,000 and 40,000 BC. Prehistoric humans used pigments for obtaining color and binders, which allowed pigments to bind to a surface. The natural pigments had to be ground between stones, and then water, grease, saliva, or clay was added to make the paste. The pigments found through an analysis were, in fact, carbon black and oxide minerals. Pigments with subtle differences could be obtained by mixing and heating pigments, such as hematite, an iron oxide found in the famous caves of Lascaux (13,000 BC).

[8] Anne-Marie Pensé-Lhéritier, Formulations, 2011, p 03, ISBN 978-1-84821- 259-6.

## 1.3. Ingredients Used In Formulations.

An ingredient can be defined as a component that is part of a formulation. In the preparation of formulations, ingredients are measured by weight for solids and volume for liquids. These ingredients are primarily divided into two: the active (primary) and inactive (secondary) ingredients. The secondary ingredients usually represent more than 50% of the total formulation.

In topical formulations, primary ingredients include the hydrophilic phase (mostly water) along with other hydrophilic ingredients, lipophilic phase, emulsifier, and preservatives. Examples of lipophilic ingredients include: mineral oils, stearic acids, stearyl alcohol, etc. Secondary ingredients include pigments, perfumes among others. Table 1.2 illustrates some common ingredients used and their functions in various parapharmaceutical products.

| Function | Examples of ingredients |
|---|---|
| Hydrophilic phase solvent | Primary ingredient used is water |
| Emulsifier | Primary ingredient used is stearic acid<br>Cetyl alcohol |
| Solvent for lipophilic phase | Paraffin, Mineral oil |
| Emollient | Decyl oleate, stearic acid, Octyl dodecanol |
| Humectant | Glycerin |
| Preservatives | Parabens, Benzyl alcohol, sodium benzoate, bronidox |
| Lubricant | Magnesium stearate, lanolin |

***Table 1.2 Some Ingredients used in Parapharmaceutical Formulations.***

### 1.3.1 Properties Of Some Ingredients.

The stability and rheological characterization of emulsions can be affected by the physical and chemical properties of the ingredients used. It is therefore important to consider the properties of these ingredients used in topical formulations. Table 1.3 illustrates the properties of some ingredients used in formulations.

| Ingredient | Physical/Chemical Property. |
|---|---|
| Tego Care CARE 215(Glyceryl Stearate) | Non -ionic emulsifier<br>It is a mixture of glycerol mono distearat with ethoxylated cetyl/stearyl alcohol.<br>Concentration used in emulsions is 2.0%-3.0%.<br>Mostly found in pellets form.<br>Stable at 40°C<br>Not subject to changes in preparation.<br>pH range 5-8. |
| Bronidox | It can be combined with other preservatives due to its good compatibility. |

| | |
|---|---|
| | ✚ Correct use depends including the physical and chemical nature of product, its ability to support microbial growth and likelihood of recontamination during use. |
| Phenonip | ✚ Effective against bacteria, yeasts and mould and retains activity in the presence of moist.<br>✚ It is oil soluble. |
| Glycerin | ✚ Normally used in concentration 5% or less for moisturizers<br>✚ Amounts of 10% or greater can be used in clinical circumstances for healing.<br>✚ It has a pale yellow color and is liquid in nature. |
| Emulgin B1 | ✚ A non-ionic self-emulsifying cream base for various oil in water emulsions.<br>✚ It is a white cream base in color. |

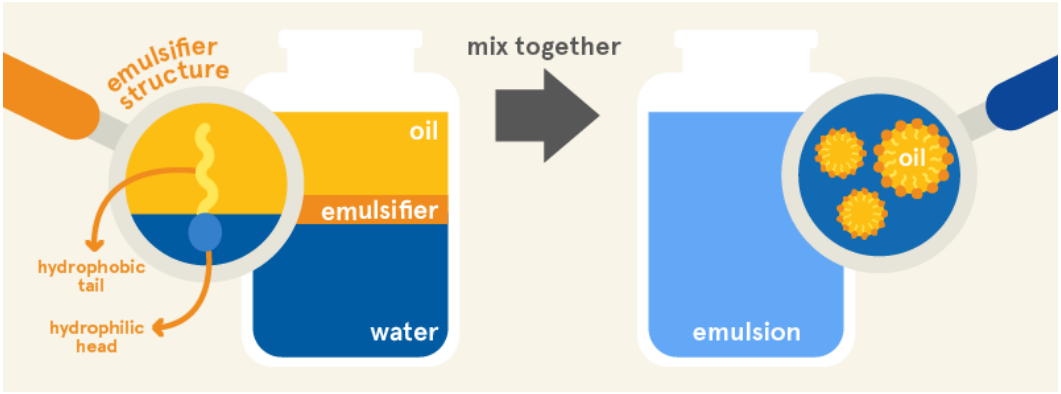
**Table 1.3 Properties of Some Ingredients.**

### 1.3.2 Emulsifiers [9]

Emulsifiers are substances that aid in mixing of two substances that normally separate when combined (for example, oil and water).[10] Emulsifiers are typically amphiphilic, with polar (hydrophilic) and non-polar (lipophilic) parts that impart varying degrees of solubility in water or oil. When emulsifier molecules are added to an unmixable liquid, they position themselves along the interfacial layer (which is where the oil separates from the water). The emulsifier is positioned in this case so that its hydrophilic end faces the water phase and its hydrophobic end faces the oil phase, allowing the water and oil to become finely dispersed in each other.

Finally, the emulsifier forms a stable, homogeneous, and smooth emulsion. Oil-in-water emulsions are formed by emulsifiers that are more soluble in water, whereas water-in-oil emulsions are formed by emulsifiers that are more soluble in oil.[10]

**Figure 1.1: How Emulsifiers Work**[9]




[9] https://www.eufic.org/en/whats-in-food/article/what-are-emulsifiers-and-what-are-common-examples-used-in-food. Retrieved May 26, 2023.

[10] Barnes, T. M., Mijaljica, D., Townley, J. P., Spada, F., & Harrison, I. P. (2021). Vehicles for drug delivery and cosmetic moisturizers: review and comparison. Pharmaceutics. 2021; 13: 2012

### 1.3.3 Preservatives.

Preservatives are primarily used to prevent the growth of microorganisms such as fungi and bacteria in formulations. Preservatives can be either lipophilic or hydrophilic; however, their concentration should also be taken into consideration since other excipients within the vehicle may have some antimicrobial properties.[10] Generally, preservatives used in formulations should be active against a wide range of microorganisms, and their election should be based on several factors such as compatibility with the formulation, toxicity, irritancy potential, and the application site.[10]

Major ingredients used in the formulation of topical products by the BFGoodrich companies include carbomer, paraben as well as acrylates cross polymer (a copolymer of acrylic acid, methacrylic acid, or one of its simple esters, crosslinked with glycol dimethacrylate).[11]McIntyre Group Ltd.'s cream formularies primarily contain cetostearyl alcohol, mineral oil, glyceryl stearate, and emulsifying wax. [12]Generic formulations of such creams with ingredients such as glyceryl stearate, cetostearyl alcohols, and water amongst others can significantly be less or more potent than the original trade name preparations. Because no single approach is appropriate for all drugs and uses, a suited approach based on the physiochemical properties of the drug is required.[13] Despite containing the same active ingredients, one manufacturer's cream may be more acidic than another, causing skin irritation or changing the rate of absorption.

### 1.3.4 Homogenizer

A homogenizer is a laboratory or an industrial instrument used to homogenize (a process of making a product completely uniform in terms of particle size) different materials or liquids. In the formulation of topical vehicles, it is critical that both the hydrophilic and lipophilic phases are mixed uniformly. This helps to ensure that the formulated product does not degrade quickly thus improving the stability and the shelf life of the product.

[11] http://www.bfgoodrich.com/ last consulted October 2000.
[12] http:www.mcintyregroup ltd/last consulted March 2001.
[13] Danby, S. G., Draelos, Z. D., Gold, L. F. S., Cha, A., Vlahos, B., Aikman, L., ... & Cork, M. J. (2022). Vehicles for atopic dermatitis therapies: more than just a placebo. *Journal of Dermatological Treatment*, *33*(2), 685-698

*Figure 1.2 High speed Homogenizer System*[14]

### 1.3.5 Effect of Temperature on Emulsion Stability.

Studies have shown that the rheological properties of emulsions (topical vehicles) are significantly affected by the formation of temperatures.[15] An increase in temperature usually causes a decrease in emulsion viscosity; consequently, at high oil concentrations, coalescence and phase separation occur at low temperatures.[16] Droplet bursting due to shear forces may occur at high temperatures, resulting in an increase in viscosity.[16]

### 1.3.6 Rheological Characterization of Topical Formulations.

Rheology is the study of the flow of materials and deformation behavior, which can be measured by applying an external force to a sample (shear-induced deformation).[17] Rheological behavior, which is related to formulation viscosity, elasticity, and plasticity, can have an impact on product manufacturing, appearance, packaging, long-term stability, dispensing, and *in vivo* performance.[17] Rheological properties influence stability and physical appearance. A comprehensive rheological characterization provides insight on why products settle or separate over time.[17] Studies have shown that patient acceptability, which is heavily influenced by rheological properties, should be the primary concern when developing a product.[17] This is relevant to an innovator product, but it is also essential when dealing with a generic product.

[14] https://www.coleparmer.co.uk/p/ika-high-speed-homogenizer-system/2206
[15] Nebogina, N. A., Prozorova, I. V., & Yudina, N. V. (2020, December). The influence of the temperature of the formation of water-oil emulsions on their dispersion. In *AIP Conference Proceedings* (Vol. 2310, No. 1, p. 020221). AIP Publishing LLC.
[16] Partal, P., Guerrero, A., Berjano, M., & Gallegos, C. (1997). Influence of concentration and temperature on the flow behavior of oil-in-water emulsions stabilized by sucrose palmitate. *Journal of the American Oil Chemists' Society*, *74*(10), 1203-1212.
[17] Simões, A., Miranda, M., Cardoso, C., Veiga, F., & Vitorino, C. (2020). Rheology by design: A regulatory tutorial for analytical method validation. *Pharmaceutics*, *12*(9), 820.

*Figure1.3. The discovery Hybrid Rheometer (HR-20)*

## 1.4 Topical Formulations

The topical route of administration has been used to produce either a local effect for treating skin problems or systemic drug effects. [18] Topical therapy is an appealing option as compared to the oral route of drug administration due to its non-invasiveness, drug targeting to the site of action, elimination of systemic side effects and drug interactions, increased patient compliance, and possibly lower treatment costs[19]. Topical formulations can be designed for potent drugs to facilitate optimal drug concentrations at the site of action, to allow drug absorption with the appropriate physicochemical properties into the skin, and as penetration enhancers to facilitate topical drug absorption.[18]

### 1.4.1 Topical Vehicles

A topical vehicle is a "carrier system" for an active pharmaceutical (or cosmetic) substance; however, it may also be used as an emollient to treat dry skin.[13] A topical formulation's therapeutic efficacy is determined by the active ingredient's vehicle and physicochemical characteristics.[20] Common vehicles used in topical preparations include creams, ointments, pastes, gels, lotions, etc. Studies have shown that the choice of a drug vehicle is important in topical formulations as the effectiveness of the active ingredient could change.[21] Minor differences in the formulation can make differences in the effectiveness of a topical medication.[20] The potency of an active ingredient is frequently altered by the topical vehicle. Table 1.3 illustrates the advantages and disadvantages of selected topical vehicle.

[18] Helal, D. A., El-Rhman, D. A., Abdel-Halim, S. A., & El-Nabarawi, M. A. (2012). Formulation and evaluation of fluconazole topical gel. *Int J Pharm Sci*, *4*(5), 176-183.
[19] Murdan, S. (2002). Drug delivery to the nail following topical application. *International journal of pharmaceutics*, *236*(1-2), 1-26.
[20] Celebi, N., Ermiş, S., & Özkan, S. (2015). Development of topical hydrogels of terbinafine hydrochloride and evaluation of their antifungal activity. *Drug development and industrial pharmacy*, *41*(4), 631-639.
[21] Mayba, J. N., & Gooderham, M. J. (2018). A guide to topical vehicle formulations. *Journal of Cutaneous Medicine and Surgery*, *22*(2), 207-212.

| VEHICLE | ADVANTAGES | DISADVANTAGES |
|---|---|---|
| **Creams** | ✚ Easy to spread and less greasy than ointments.[21]<br>✚ Creams are easily absorbed into the skin.<br>✚ Moisturizing and emollient properties.[21] | ✚ Less hydrating as compared to ointments. |
| **Ointment** | ✚ They are extremely lubricating and can be used on dry skin lesions.[13]<br>✚ They allow better penetration of medication through the skin and higher potency.[13]<br>✚ They are thicker hence more hydrating. | ✚ Have a greasy and sticky feel.<br>✚ Less spreadable than creams. |
| **Pastes** | ✚ They are less greasy. | ✚ They are generally stiff and thick.<br>✚ Less macerating in nature. |

***Table 1.4: Advantages and Disadvantages of selected Topical Vehicles.***

### 1.4.2 Anti-Fungal Cream

Despite the numerous antimicrobial agents available today, topical skin infections are common and frequently present therapeutic challenges to practitioners[22]. These anti-microbial medications (agents) kill the protective parts of the cell (cell membrane and cell wall) or stop them from growing and multiplying. Fungal nail infections are caused by different fungi that live in the environment. These infections (which affect the toenail more often than fingernails) may cause nails to become discolored, thick, fragile, or cracked as illustrated in figure 1.4. The nail may also become separated from the nail bed. Over the years, oral drug therapies for nail fungus infections have become problematic due to systemic toxicity, drug depletion due to metabolism, an extensive treatment regimen, adverse side effects, and high patient expenses.[23] Consequently, attention has been devoted to safe, effective and alternative anti-fungal nail medication.[22] A US FDA-approved topical treatment for fungal toenail infections (Penlac with ciclopirox) has a very low clinical cure rate of 10%-13% [23]. This has given rise to the need for an effective topical drug that has the ability to penetrate nail plates, with strong anti-fungal properties.[23] Furthermore, it should be cost-effective and has no adverse toxicity or side effects during the treatment regime.[23]

[22] Chen, M. X., Alexander, K. S., & Baki, G. (2016). Formulation and evaluation of antibacterial creams and gels containing metal ions for topical application. *Journal of Pharmaceutics, 2016*.

[23]Polson, G., Skoulis, N., Ciccognani, D., Roberts, K., DiNicola, K., Lou, K., & Gruber, J. (2010, April). A Safe and Effective New Topical Treatment for Nail Fungus (Onychomycosis). JOURNAL OF INVESTIGATIVE DERMATOLOGY, Vol. 130,S106 S106-S106).

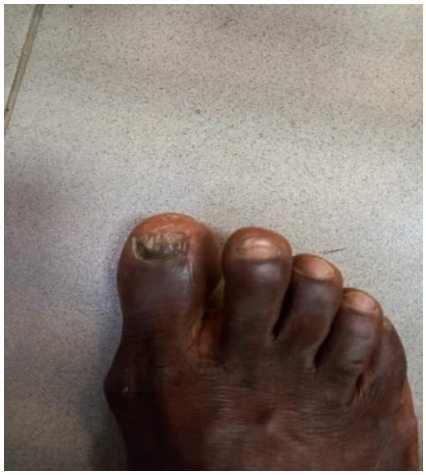


***Figure 1.4: Fungal Nail Infection (personal, unpublished results)***

Topical agents are generally regarded as ineffective, owing to poor penetration into the nail, however, newer topical agents, such as ciclopirox and amorolfine have been developed to provide efficient nail unit delivery.[24] According to a Cochrane review,[25] the treatment failure rate of ciclopirox 8% (a synthetic hydroxy pyridine antifungal formulated as a nail lacquer) was 60% to 64% after 48 weeks of use. Combination therapy of terbinafine (oral anti-nail fungal drug) and ciclopirox (nail lacquer) is a safe and more effective treatment than terbinafine alone, especially in younger patients and in shorter duration of fungal nail infections.[24] In one study, a combination of ciclopirox and oral terbinafine had a complete cure rate of 68%, while terbinafine alone had a 50% complete cure rate after 9 months of treatment. In recent years, a number of metal ions have been studied as potential antimicrobial agents, including silver, copper, zinc, iron, magnesium, and titanium.[22] Zinc when used alone or as an adjuvant has been found to be advantageous in a number of dermatological infections and inflammatory diseases.[22] Copper has been used for decades as a fungicide due to its antimicrobial properties.[22]

Studies showed that copper sulfate and zinc sulfate have synergistic activity in creams and gels. However, incorporating metal ions (zinc ions and copper ions) often creates a formulation challenge due to the high reactivity of these ions.

### 1.4.3 Topical Ointments

In the pharmaceutical industry, ointments are made by melting the oil and aqueous phases in two separate jacketed vessels with agitators for proper mixing.[26] The two phases are transferred to the main ointment vessel through valves and pipes.[26] Topically, ointments are used for a wide range of purposes,

[24] Avner, S., Nir, N., & Henri, T. (2005). Combination of oral terbinafine and topical ciclopirox compared to oral terbinafine for the treatment of onychomycosis. *Journal of dermatological treatment*, *16*(5-6), 327-330

[25] Crawford, F., Hart, R., Bell-Syer, S., Torgerson, D., Young, P., & Russell, I. (2003). Topical treatments for fungal infections of the skin and nails of the foot (Cochrane Review). *The Cochrane Library*, https://doi.org/10.1002%2F14651858.CD001434.pub2

[26] Bhagurkar, A. M., Angamuthu, M., Patil, H., Tiwari, R. V., Maurya, A., Hashemnejad, S. M., ... & Repka, M. A. (2016). Development of an ointment formulation using hot-melt extrusion technology. *Aaps Pharmscitech*, *17*, 158-166.

such as protection, antiseptic, emollient, antipruritic (anti-itch) and astringent.[27] The composition of the ointment base defines not only the extent of absorption but also the transfer of drug formulations from the base to body tissues. Recent work has suggested that the preparation of 1% bifonazole plus 40% urea in an ointment base is effective in the treatment of onychomycosis.[28]

### 1.4.4 Topical Pastes

Topical pastes are homogeneous semisolid dosage forms that contain a high concentration of insoluble powder substance (at least 20%) dispersed in the appropriate base. Generally, pastes are typically less greasy, more absorbent, and stiffer than ointments.[29] Fingernail infection can result in physical disability as well as cosmetic distress, however less common than toenail infection (which is normally manifested by tissue degeneration of one or both great nails as well as the involvement of a variable number of other nails).[28] Studies have shown that patients with these nail infections are usually treated long-term with griseofulvin which works well in the fingernail but gives disappointing results in the case of toenail infections, even when in adequate dosages (10-15 mg/kg)daily.[28] Generally, different bases are used in making topical pastes. However, lanolin and vaseline are vastly used in the formulation of topical pastes.

#### 1.4.4.1 Lanoline

Lanoline is an emollient that is classified into two types: hydrous and non-hydrous. Anhydrous lanoline has a boiling point of 38°C-42°C and a mild odor.[30] Naturally, lanolin is a yellow fat obtained from the wool of the sheep. It is an ingredient that helps reduce the loss of water from the skin. It is mostly used as an emollient in most pharmaceutical and cosmetic formulations.

Lanoline alcohol is the most common type of lanoline found in skin care products. Generally, lanoline is used in many ways such as chapped lip treatments, healing cracked and dry skin, etc. Lanoline has traditionally been used to treat sore nipples caused by breastfeeding. Due to its super emollient properties, this molecule has traditionally been used as a healing balm, as well as a diaper rash moisturizer.[31]

#### 1.4.4.2 Vaseline

Vaseline (an oleaginous base) is composed of pure petroleum jelly, minerals, and microcrystalline wax, which makes it smoother. Generally, vaseline also be used as a lubricant and aids in the healing of minor cuts and burns [32]. When used on the skin, vaseline becomes sticky and attracts dust particles,

[27] Maru, A. D., & Lahoti, S. R. (2019). Formulation and evaluation of ointment containing sunflower wax. *Asian Journal of Pharmaceutical and Clinical Research*, 115-120.
[28] Hay, R. J., Roberts, D. T., Doherty, V. R., Richardson, M. D., & Midgley, G. (1988). The topical treatment of onychomycosis using a new combined urea/imidazole preparation. *Clinical and experimental dermatology*, *13*(3), 164-167
[29]https://courseware.cutm.ac.in/wp-content/uploads/2020/06/semisoliddosageformfordiploma-180924113501-1.pdf
[30] Chauhan, L., & Gupta, S. (2020). Creams: a review on classification, preparation methods, evaluation, and its applications. *Journal of drug delivery and therapeutics*, *10*(5-s), 281-289.
[31] Dr.Lim D.,Why Don't Dermatologists Like Lanolin., https://theformulated.com/blogs/news/lanolin.
[32] http://www.differencebetween.net/business/product-services/differences-between-vaseline-and-petroleum-jelly/

which causes acne later on.[32] It is, however, useful for moisturizing dry, chapped, or sore skin. It is also used to make lip balms. It is also considered not eco-friendly.[32]

#### 1.4.4.3 Advantage of Vaseline Over Lanoline

Despite the numerous advantages of lanolin, most cosmetic and para-pharmaceutical products are made with vaseline. This is because lanolin is frequently identified as an allergen in routine skin patch testing.[31] Studies have shown that routine patch testing revealed lanolin allergies in 3-6% of patients in a dermatology clinic.[31]

### 1.4.5 Baby Cleansing Milk

The skin's primary function is to protect against water loss, toxic and harmful substance absorption, microorganism invasion, and physical trauma.[33]Infant skin is structurally and functionally distinct from adult skin.[33] The baby's skin is characterized by being sensitive, thin, and fragile.[34] Generally, cleansing milk is made from an emulsion of fats and water and helps to cleanse the skin without stripping away its natural oils. Baby cleansing milk is used for the cleansing of the baby, especially the diaper area when water and wash clothes are not well tolerated by the baby.[6] The acidic pH of the skin surface in adults and adolescents protects against microorganisms whereas, in babies, the skin surface tends to be neutral hence reducing protection against excessive microbial growth significantly.[34] In light of the characteristics of newborn babies', infants', and children's skin, topical preparations for their hygiene and protection require special consideration in their formulation.[34] The physical and chemical properties of the topical agent as well as the properties of the skin barrier influence absorption of these topical agents.[34] The greater the ratio of body surface area to body weight, the greater the risk of skin toxicity.[34] The significance of infant cleansing in maintaining good hygiene and skin health is widely acknowledged, but questions about the use of adequate and safe newborn cleansing procedures (products) remain.[33] Studies have showed that a mild cleanser is preferable to the use of water for bathing.[35] Existing studies although conducted on only adults, have showed that one has to avoid adding olive oils and mustard oils to bath due to risks of contact dermatitis.[34]. Health professionals agree that babies should not be bathed more than twice a week until they crawl.[34]

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[33] Blume-Peytavi, U., Hauser, M., Stamatas, G. N., Pathirana, D., & Garcia Bartels, N. (2012). Skin care practices for newborns and infants: a review of the clinical evidence for best practices. *Pediatric dermatology*, *29*(1), 1-14.

[34] Fernandes, J. D., Machado, M. C. R., & Oliveira, Z. N. P. D. (2011). Children and newborn skin care and prevention. *Anais brasileiros de dermatologia*, *86*, 102-110.

[35] Dizon, M. V., Galzote, C., Estanislao, R., Mathew, N., & Sarkar, R. (2010). Tolerance of baby cleansers in infants: a randomized controlled trial. *Indian Pediatrics*, *47*(11), 959-963.

### 1.4.6 CONCLUSION

In summary, the first chapter was devoted to describing the initial phase of this work and presenting general concepts on topical formulations which will serve as a good foundation for understanding the subsequent chapters. Firstly, general concepts of various formulations and also ingredients used were described.

# CHAPTER 2

# EXPERIMENTAL WORK

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## 2.1 INTRODUCTION

This chapter gives emphasis to the experimental methods implemented to carry out our research, which consists of the formulation of various topical products necessary for our active ingredient. It comprises of two sections: the first describes the various products and apparatus used during manipulation, as well as the various devices, and the second describes the various methods used during the manipulations.

## 2.2 MATERIALS

### 2.2.1 Chemicals

Bronidox L. by Cognis, Phenonip by Clariant, Glycerin, Tego Care 215(glyceryl stearate), Tego SML-20(Polysorbate 20) by Evonik, Tego alkanol 1618(keto stearyl alcohol) by GSH, Stearic acid, Citric acid, Essences, Lanolin, Cremaphor A6, Emulgin B1, Liquid Solubilizer were procured from the Girene company. Salicylic Acid was obtained from the chemistry laboratory of the University of Tlemcen. Terbinafine capsules were purchased from the pharmacy shop. Essential oils (cinnamon oil, eucalyptus oil) were purchased from the local spices shop. Vaseline (100 ml) was purchased from the cosmetic shop. Methyl salicylate (oil of wintergreen) was synthesized in the Laboratory of Catalysis and Organic Synthesis (LCSCO). Methanol, Concentrated Sulfuric Acid, Potassium Bicarbonate, Dichloromethane, Menthol were all obtained from the Laboratory of Catalysis and Organic Synthesis. pH paper was gifted by a doctorate student of the Laboratory of Catalysis and Organic Synthesis. All glassware and distilled water were provided by LCSCO.

### 2.2.2 Apparatus

Sample storage containers (50 ml) were purchased from the pharmacy, Food thermometer was purchased from the local market; Piece of glass was provided by Prof.Ziani-Cherif Chewki, Several 150 ml disposable syringes were obtained from the Laboratory of Catalysis and Organic Synthesis. Moulinex 350 W turbomix hand blender was purchased from the local market. Rotatory evaporator, Lyophilizer (Alpha 1-2LD plus) used were provided by the LCSCO.

The discovery Hybrid Rheometer (HR-20) used for rheological analysis was made available by the Laboratory of Polymers of the University of Tlemcen.

## 2.3 METHODS

### 2.3.1 Synthesis Of Methyl Salicylate (Oil of Wintergreen).

In a 250 ml round bottom flask, 34.32g (43.39 ml, 1.07 mol) of methanol is added to 15 g (0.1086 mol) of salicylic acid. A few drops of concentrated sulfuric acid are added to the mixture. A reflux condenser was set to the flask and allowed to boil gently under agitation at about 100C° for about 20 hrs. The mixture was placed in a refrigerator for about 1 hour and excess methanol was distilled off using a rotary evaporator. The mixture was transferred to a separating funnel. A saturated solution of potassium bicarbonate and also about 25ml of dichloromethane (DCM) was added to the mixture. It was then shaken and the organic phase separated. The organic phase was dried with magnesium sulfate and the solvent (DCM) was evaporated with a rotary evaporator. The percentage yield was 81.72%.

### 2.3.2 Formulation Of Topical Cream

The lipophilic phase was prepared by melting all waxes and mixing the lipophilic ingredients at about 80°C-85°C. The hydrophilic phase was prepared by heating distilled water to about 80°C-85°C. Terbinafine chlorhydrate capsules were grounded and set aside. When both lipophilic and hydrophilic phases were about the same temperature, the lipophilic phase was slowly added to the hydrophilic phase with vigorous agitation and kept stirred until the temperature dropped to about 25°C. The mixture was preserved with preservatives and also perfume was added for scent. The emulsion was cooled at room temperature to form a semi-solid cream base. The exact concentration of each ingredient is shown in Table 2.1.

**Table 2.1:Composition of Topical Cream.**

| Ingredients | C1 | C2 | C3 | C4 |
|---|---|---|---|---|
| Tego Alkanol 1618 | 6 | 2 | 5 | 6 |
| Tego Care 215 | 3 | 3 | 3 | 3 |
| Tego SML 20 | 4 | 4 | 4 | 4 |
| Vaseline Oil | 17 | 25 | 20 | 17 |
| Distilled water | 55 | 55 | 55 | 55 |
| Glycerin | 4 | 4 | 4 | 4 |
| Stearic acid | 3 | 1 | 2 | 2 |
| Terbinafine chlorhydrate | - | - | - | 2 |
| Preservatives | q.s | q.s | q.s | q.s |
| Perfume | q.s | q.s | q.s | q.s |

**q.s** means quantity sufficient.

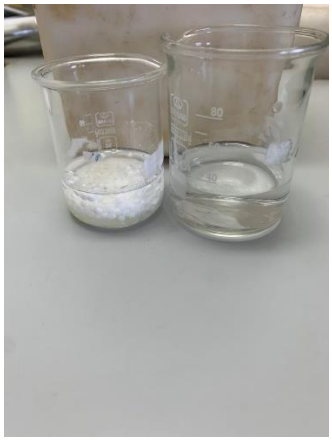


***Figure 2.1:*** *Lipophilic Ingredients and Hydrophilic Ingredients before melting. (Personal, unpublished results*)

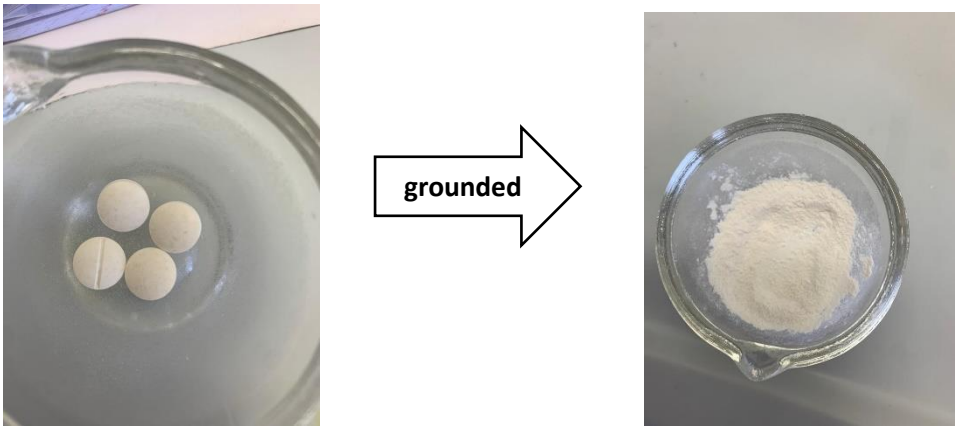



***Figure 2.2****: Terbinafine Chlorhydrate(personal, unpublished results)*

***Figure 2.3.:*** *Semi-solid topical cream (personal, unpublished results)*

***Figure 2.4**:Anti-Fungal cream(2% terbinafine chlorhydrate, personal unpublished results).*

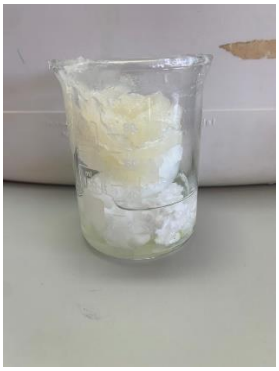
### 2.3.3 Formulation of Topical Pastes.

The lipophilic phase was prepared by melting all waxes and mixing all ingredients together at about 80°C-85°C. Salicylic acid was grounded into a smooth powder and added to the emulsion under vigorous agitation. The mixture is mixed uniformly together and kept stirred together until the temperature dropped to about 25°C. The mixture was preserved with preservatives and also parfum was added for scent. The emulsion was cooled to room temperature to form a semi-solid paste. The exact concentration of each ingredient is shown in Table 2.2.

**Table 2.2: Composition of Topical Paste.(volume 50 ml)**

| INGREDIENTS | P1 | P2 | P3 | P4 | P5 |
|---|---|---|---|---|---|
| Lanolin | 15 | 45 | 50 | - | 55 |
| Vaseline | - | - | - | 45 | - |
| Glycerin | 5 | 5 | 10 | 6 | 10 |
| Cremophor A6 | 5 | 6.5 | - | 6 | - |
| Vaseline Oil | 50 | 20 | 10 | 20 | 10 |
| Salicylic Acid | 5 | 6 | 6 | 10 | 6 |
| Tego SML-20 | 7 | 7 | - | - | - |
| Tego Care 215 | 6.5 | 5.5 | 5 | 5 | 5 |
| Tego Alkanol 16 | - | - | 3 | - | - |
| Solubilizer | - | - | 4 | 4.5 | 3 |
| Emulgin B1 | - | - | 5.5 | - | 5 |
| Preservatives | q.s | q.s | q.s | q.s | q.s |
| Perfume | q.s | q.s | q.s | q.s | q.s |

**q.s** means sufficient quantity.



**A**(paste with lanolin base) **B**(paste with vaseline base)

***Figure 2.5:*** *Lipophilic ingredients and waxes before melting. (Personal, unpublished results).*

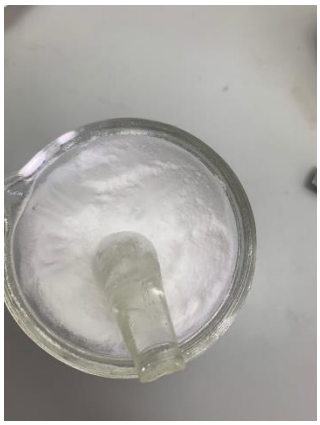
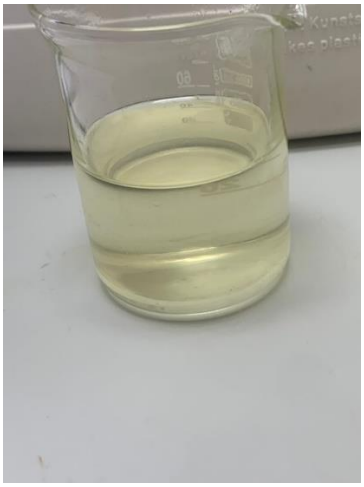


***Figure 2.6:*** *Grounded Salicylic Acid (Personal, unpublished results)*



**A**-Lanolin base **B**-Vaseline base

***Figure 2.7:*** *Lipophilic phase of Topical Paste after melting. (Personal, unpublished results)*

**A** (Lanoline base)

**B**(Vaseline base)

***Figure 2.8:*** *Semi-solid Topical paste (Personal, unpublished results)*

### 2.3.4 Formulation of Topical Ointment (Pain Relief Ointment)

Following the modified form of a pain relief spray, the lipophilic phase was prepared by melting all waxes and mixing the lipophilic ingredients together at about 80°C-85°C. The hydrophilic phase was prepared by heating distilled water to about 80°C-85°C. When both lipophilic and hydrophilic phases were about the same temperature, the lipophilic phase was slowly added to the hydrophilic phase with a hand blender and kept stirred until the temperature dropped to about 25°C. The essential oils were added as well as the oil of wintergreen. Grounded terbinafine capsules was used in place of oil of wintergreen for formulations with terbinafine. The emulsion was preserved with preservatives. The emulsion was then left to cool at room temperature. The exact concentration of each ingredient is shown in Table 2.3

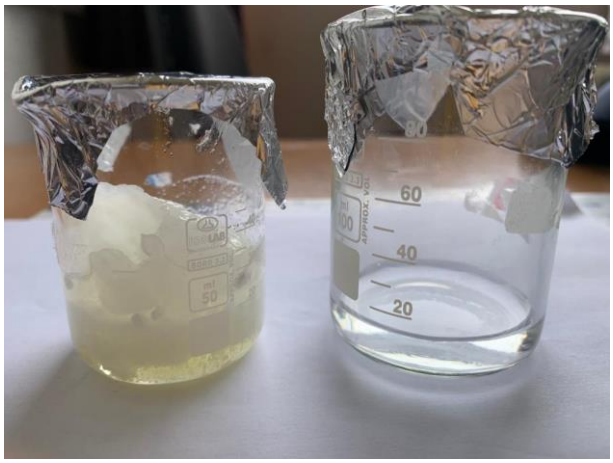



***Figure 2.9:*** *Lipophilic ingredients and 20% water before heating. (Personal, unpublished results)*

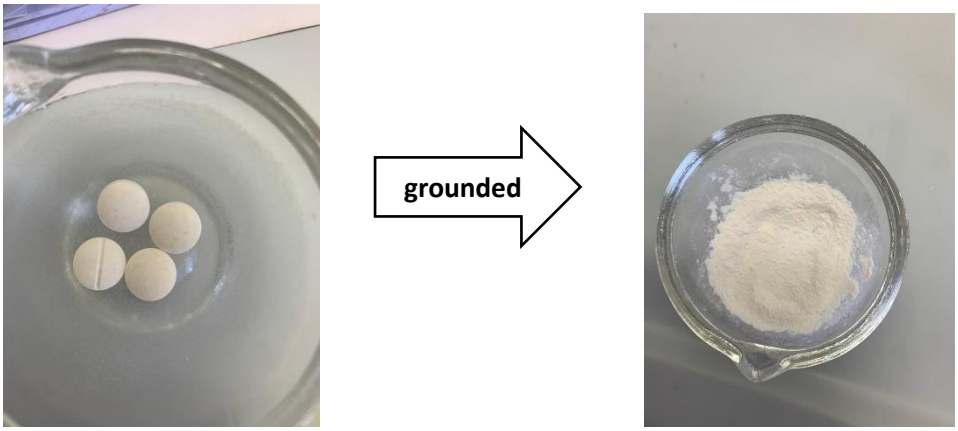



***Figure 2.10****: Terbinafine Chlorhydrate(personal, unpublished results)*

***Figure 2.11:*** *Topical Ointment (Personal, unpublished results)*

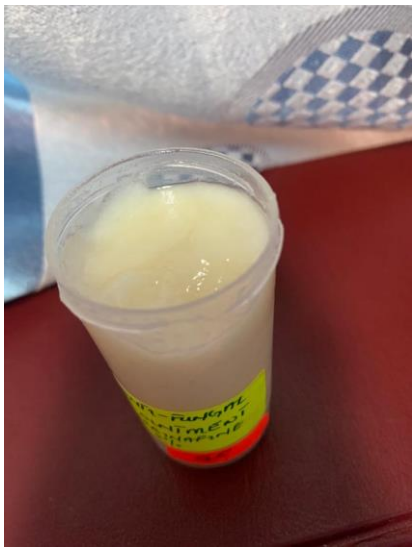


***Figure 2.12****:Anti-Fungal Ointment (2% terbinafine chlorhydrate, Personal, unpublished results).*

**Table 2.3 :Composition of Topical Ointment.(volume=50 ml)**

| INGREDIENTS | G1 | G2 | G3 | G4 | G5 |
|---|---|---|---|---|---|
| Oil of wintergreen | 15 | 15 | 15 | 17 | - |
| Vaseline oil | 17 | 12 | 10 | 10 | 10 |
| Glycerin | 3 | 5 | 3 | 3 | 3 |
| Menthol | 5 | 5 | 5 | 6 | - |
| Vaseline | - | - | 20 | 15,5 | 20 |
| Stearic acid | 3 | 3 | 3 | 3 | 3 |
| Emulgin B1 | 5 | - | - | - | - |
| Tego Alkanol 16 | 3 | - | - | - | - |
| Solubilizer | - | - | 6 | - | - |
| Eucalyptus oil | 2 | 1.5 | 1 | 1 | - |
| Tego SML-20 | 4 | - | - | 7 | 7 |
| Cinnamon oil | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Tego Alkanol 1618 | - | 6 | 5 | 6 | 6 |
| Tego Care 215 | 4 | 4 | 3 | 3 | 3 |
| Cremaphor A6 | 5 | 5 | - | 6 | 7 |
| Terbinafine Capsules | - | - | - | - | 2 |
| Distilled water | 40 | 41 | 20 | 20 | 20 |
| Perfumes | - | - | - | - | q.s |
| Preservatives | q.s | q.s | q.s | q.s | q.s |

**q.s** means quantity sufficient

### 2.3.5 Formulation Of Baby Cleansing Milk.

In a 150mL beaker, all lipophilic ingredients were measured and poured in. In another 150mL beaker, the hydrophobic phase was also prepared. Both beakers were heated to about 75°C-80°C.When both phases were about the same temperature, the lipophilic phase was poured onto the hydrophilic phase. In a water bath and with the help of a hand blender, the emulsion was then mixed to about 30°C. It was then left at room temperature overnight. The exact concentration of each ingredient is shown in Table 2.4.

**Table 2.4:Composition of Baby Cleansing Milk.(volume=150 ml)**

| INGREDIENTS | B1 | B2 | B3 | B4 | B5 | B6 | B7 | B8 | B9 |
|---|---|---|---|---|---|---|---|---|---|
| Tego Alkanol 1618 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 |
| Tego Care 215 | 2.5 | 1.5 | 1.5 | 2.5 | 2.5 | 2.5 | 2.5 | 3 | 2.5 |
| Vaseline Oil | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 18 | 15 |
| Glycerin | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 |
| Tego SML-20 | - | - | - | - | 2 | - | 3 | 5 | 3 |
| Solubilizer | - | - | - | - | - | 1.5 | - | - | - |
| Cetyl Alcohol | - | - | - | - | - | - | - | - | 1.5 |
| Water | 71 | 72 | 72 | 71 | 69 | 69.5 | 68 | 61.5 | 60 |
| Preservatives | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |
| Perfume | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |

**q.s** means sufficient quantity.

***Figure 2.13:*** *Mixing of lipophilic and hydrophilic phases with a hand blender. (Personal, unpublished results)*

***Figure 2.14:*** *Baby cleansing milk (personal, unpublished results)*

## 2.4 EXPERIMENTAL ANALYSIS.

### 2.4.1 Physical Evaluation of Topical Formulations.

Physical appearance, color, texture, and homogeneity were tested on all blank formulations (i.e., formulations without any active ingredients). Visual observation was used to assess these characteristics. The uniformity and texture were tested by pressing a small amount of the topical product between the thumb and index finger. These were evaluated using the consistency of the formulations .Immediate skin feeling was also assessed (including stiffness, greasiness, and time of skin absorption).

### 2.4.2 Emulsion Stability

All formulated emulsions were left to sit at room temperature for at least 24 hours to check for separation of the two phases.

### 2.4.3 Spreadability Test.

Two lines 15cm apart were drawn on a piece of glass. With the help of a syringe, 0.5mL of topical product was applied to spotted areas of the glass. Subsequently indenting the glass at approximately 45°, the spreadability of the products was timed.

***Before*** ***After***

***Figure 2.15:*** *Spreadability Test for Selected Topical Formulations.*

### 2.4.4 Determination Of pH

In a 20 mL beaker, about 2.5g of topical product was added to 10 mL of distilled water and stirred. The emulsion was then heated for about 2 minutes. With the aid of a pasteur pipette, 2-3 drops of the emulsion were placed on a litmus paper (pH paper).

### 2.4.5 Rheological characteristics.

Rheological analysis of selected formulations was carried out using the Discovery Hybrid Rheometer (HR-2).With the help of a spatula, the samples were carefully placed onto the surface of the lower plate, and the upper cone was lowered to a 1 mm gap distance. Viscosity curves were recorded by varying the shear rate at 20℃.

## 2.5 CONCLUSION

In this chapter, experiments on the formulation of various topical products were conducted and analyzed. The study produced a set of findings, which will be discussed further below.

# CHAPTER 3

# RESULTS AND DISCUSSION

## 3.1 INTRODUCTION

Different ingredients with different emulsifiers were used in the formulation of products in different concentrations to obtain various topical products. Degradation (stability) and texture were factors considered in determining the success of any formulated product. Furthermore, the thin and milky texture were also factors considered in determining the success of a good baby cleansing milk .This chapter is divided into three sections: The first part deals with the results of ingredient concentration in various topical formulations. The second part is devoted to discussing results obtained from the experimental analysis of formulated products. The third part discusses the physical characteristics, including rheological data.

## 3.2 Part I: RESULTS of ingredient concentrations

### Table 3.1 Composition of Topical Cream

The proportion of each ingredient (%); formulations are labeled from C1-C4.

| Ingredients | C1 | C2 | C3 | C4 |
|---|---|---|---|---|
| Tego Alkanol 1618 | 6 | 2 | 5 | 6 |
| Tego Care 215 | 3 | 3 | 3 | 3 |
| Tego SML 20 | 4 | 4 | 4 | 4 |
| Vaseline Oil | 17 | 25 | 20 | 17 |
| Distilled water | 55 | 55 | 55 | 55 |
| Glycerin | 4 | 4 | 4 | 4 |
| Stearic acid | 3 | 1 | 2 | 2 |
| Terbinafine chlorhydrate | - | - | - | 2 |
| Preservatives | q.s | q.s | q.s | q.s |
| Perfume | q.s | q.s | q.s | q.s |

**q.s** means sufficient quantity.

**Table 3.2: Composition of Topical Paste.**

The proportion of each ingredient (%); formulations are labeled from P1-P5.

| INGREDIENTS | P1 | P2 | P3 | P4 | P5 |
|---|---|---|---|---|---|
| Lanolin | 15 | 45 | 50 | - | 55 |
| Vaseline | - | - | - | 45 | - |
| Glycerin | 5 | 5 | 10 | 6 | 10 |
| Cremophor A6 | 5 | 6.5 | - | 6 | - |
| Vaseline Oil | 50 | 20 | 10 | 20 | 10 |
| Salicylic Acid | 5 | 6 | 6 | 10 | 6 |
| Tego SML-20 | 7 | 7 | - | - | - |
| Tego Care 215 | 6.5 | 5.5 | 5 | 5 | 5 |
| Tego Alkanol 16 | - | - | 3 | - | - |
| Solubilizer | - | - | 4 | 4.5 | 3 |
| Emulgin B1 | - | - | 5.5 | - | 5 |
| Preservatives | q.s | q.s | q.s | q.s | q.s |
| Perfume | q.s | q.s | q.s | q.s | q.s |

**q.s** means quantity sufficient

**Table 3.3: Composition of Topical Ointment.**

The proportion of each ingredient (%); formulations are labeled from G1-G5.

| INGREDIENTS | G1 | G2 | G3 | G4 | G5 |
|---|---|---|---|---|---|
| Oil of wintergreen | 15 | 15 | 15 | 17 | - |
| Vaseline oil | 17 | 12 | 10 | 10 | 10 |
| Glycerin | 3 | 5 | 3 | 3 | 3 |
| Menthol | 5 | 5 | 5 | 6 | - |
| Vaseline | - | - | 20 | 15,5 | 20 |
| Stearic acid | 3 | 3 | 3 | 3 | 3 |
| Emulgin B1 | 5 | - | - | - | - |
| Tego Alkanol 16 | 3 | - | - | - | - |
| Solubilizer | - | - | 6 | - | - |
| Eucalyptus oil | 2 | 1.5 | 1 | 1 | - |
| Tego SML-20 | 4 | - | - | 7 | 7 |
| Cinnamon oil | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Tego Alkanol 1618 | - | 6 | 5 | 6 | 6 |
| Tego Care 215 | 4 | 4 | 3 | 3 | 3 |
| Cremaphor A6 | 5 | 5 | - | 6 | 7 |
| Terbinafine Capsules | - | - | - | - | 2 |
| Distilled water | 40 | 41 | 20 | 20 | 20 |
| Perfumes | - | - | - | - | q.s |
| Preservatives | q.s | q.s | q.s | q.s | q.s |

**q.s** means sufficient quantity

**Table 3.4: Composition of Baby Cleansing Milk.**

The proportion of each ingredient (%); formulations are labeled from B1-B9.

| INGREDIENTS | B1 | B2 | B3 | B4 | B5 | B6 | B7 | B8 | B9 |
|---|---|---|---|---|---|---|---|---|---|
| Tego Alkanol 1618 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 |
| Tego Care 215 | 2.5 | 1.5 | 1.5 | 2.5 | 2.5 | 2.5 | 2.5 | 3 | 2.5 |
| Vaseline Oil | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 18 | 15 |
| Glycerin | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 3 |
| Tego SML-20 | - | - | - | - | 2 | - | 3 | 5 | 3 |
| Solubilizer | - | - | - | - | - | 1.5 | - | - | - |
| Cetyl Alcohol | - | - | - | - | - | - | - | - | 1.5 |
| Water | 71 | 72 | 72 | 71 | 69 | 69.5 | 68 | 61.5 | 60 |
| Preservatives | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |
| Perfume | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |

**q.s** means sufficient quantity

## 3.3. Part II: Experimental analysis

### 3.3.1 Physical Evaluation of Formulated Products.

Table 3.5 displays the organoleptic properties of the selected topical formulations, including physical appearance, color, texture, phase separation, consistency, and instantaneous skin feel.

### 3.3.2 Emulsion Stability.

Emulsion stability is the resistance of an emulsion to change in physiochemical properties over time. All formulated products maintained color and homogeneity for about 8 weeks in cabinets of the laboratory at room temperature(18°C -25°C). Comparably, the texture, homogeneity and physical appearance of topical creams, pastes and ointments remained the same during this period. However with the increase in climate temperature after 8 weeks, topical ointments, topical paste and topical cream began to show signs of degradation and phase separation in the containers.


***Figure 3.1:*** *Degradability of some Topical Formulation after increase in climate temperature.(Personal, unpublished results)*

**Table 3.5 Organoleptic Properties of selected Topical Formulation**

| Formulation | Phase separation | color | Texture | Homogeneity | Physical appearance | Immediate skin feels |
|---|---|---|---|---|---|---|
| **C1** | No | White | Smooth | Homogeneous | Opaque | less greasy and more moisturizing. |
| **C3** | No | White | smooth | homogenous | opaque | Greasy and less moisturizing. |
| **P2** | No | Yellowish brown | Smooth | Homogeneous | opaque | ++ |
| **P3** | No | Yellowish brown | Smooth | Homogeneous | opaque | ++++ |
| **P4** | No | Creamy | Smooth | Homogeneous | translucent | + |
| **P5** | No | Yellowish brown | Smooth | Homogeneous | opaque | +++ |
| **G2** | Yes | Creamy | Smooth | Homogeneous | opaque | Greasy and less moisturizing. |
| **G3** | No | Creamy | Smooth | Homogeneous | Opaque | Greasy and less moisturizing |
| **G4** | No | creamy | smooth | Homogeneous | opaque | Less greasy and less moisturizing. |

**+ - Least greasy** **+++ -greasy**

**++ - less greasy** **++++ -most greasy**

### 3.3.3 Spreadability Test.

Spreadability implies a cream's (or topical product's) ability to disperse on the skin. It is crucial in the administration of a medication to the skin as well as the efficacy of topical therapy. Table 3.6 illustrates the spreading values observed for a 5 cm gap space for formulations. The values indicate how easily the formulations spread out on the place of the application surface when a small amount of compression is applied.

**Table 3.6: Spreadability values for selected topical creams, pastes and ointments.**

| Formulation | C1 | C3 | P2 | P3 | P4 | P5 | G3 | G5 |
|---|---|---|---|---|---|---|---|---|
| **Time (secs)** | 00:47 | 2:33 | 04:43 | 29:50 | 03:23 | 40:15 | 03:30 | 01:55 |

### 3.3.4 Determination Of pH

The pH values of selected topical products are presented in table 3.7.The normal pH of the skin ranges from 4-5.The pH of topical pastes was more acidic as compared to the pH of topical creams and topical ointments respectively. However, upon addition of small quantity of a base (potassium bicarbonate,) the pH of topical creams, pastes and ointments was comparable to the skin pH of 5.

**Table 3.7: pH values of selected topical formulations.**

| Formulation | C1 | C3 | P2 | P3 | P4 | P5 | G3 | G4 |
|---|---|---|---|---|---|---|---|---|
| **pH** | 3 | 3 | 2 | 2 | 2 | 2 | 4 | 4 |

### 3.3.5 Rheological characteristics.

The selected formulations exhibited both non-Newtonian as well as pseudoplastic flow (shear-thinning behavior). This is illustrated by a constant decrease in viscosity as the shear rate increases. P4 and G5 exhibited similarly higher initial viscosity as compared to C1 and P3 which exhibited lower initial viscosity.

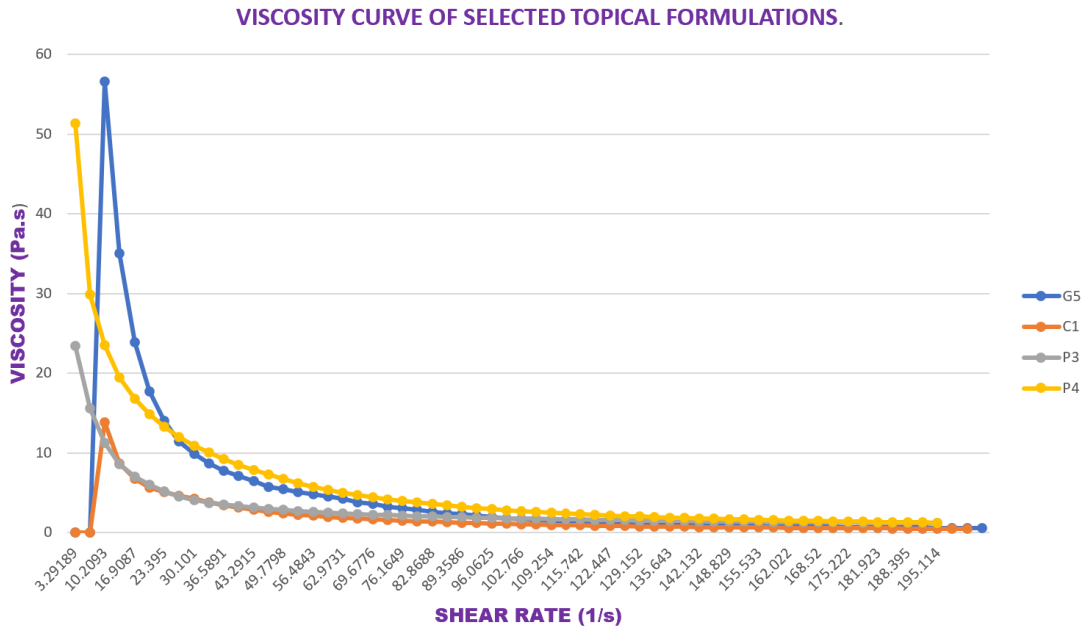



*Figure 3.2:Viscosity curve of selected Topical Formulations.*

## 3.4 Part III: Discussion of Physical Results Including Rheology

This work deals with the formulation of various topical creams, pastes and ointments, and baby cleansing milk. Topical formulations are developed by combining various ingredients in various concentrations. Bibliographic research indicates that various parapharmaceutical companies use common ingredients such as glycerin, water, vaseline oil, perfumes, and preservatives in the formulation of topical products. Nevertheless, the proportion of emulsifiers used in these topical formulations change. The success of a formulated topical product is determined by factors such as degradation (stability), texture, and spreadability.

Nine different baby cleansing milk (B1-B9) were created by combining varying ingredients in different concentrations with various emulsifier proportions. The physical stability of some baby cleansing milk was negatively affected by a change in the temperature of the cooling medium after mixing the two phases, resulting in coalescence and flocculation as illustrated in figure 3.3 . Formulations B1, B2, and B3 experienced such issues and were consequently discontinued of further analysis. B5, B7, B8, and B9 were made with the same ingredients but with varying emulsifier concentrations. Despite mixing uniformly, the formulation degraded in less than 24 hours due to a lack of a good homogenizer to create smaller particle size as shown in figure 3.4. Similarly, B4 and B6 were developed as well with the same ingredients but different concentrations of another emulsifier. These formulations (B4 and B6) however, degraded after a period of two hours.

Additionally, four topical creams (C1-C4) were developed. C2 was negatively affected by the concentrations of ingredients. After the physical evaluation of the formulated creams, C1 and C3 were selected for further analysis.C1 and C3 had comparable consistency and also had no color change. Both C1 and C3 were stable for 5 weeks, but C3 started degrading after the sixth week. This can be explained by the decrease in emulsifier proportion(in C3) and the increase in solvent for the lipophilic ingredients(C3). This caused the emulsion to be stable for a while but started degrading as compared to C1.The color of C4 changed after incorporating the active ingredient(terbinafine chlorhydrate) into it. However, the physical stability of C4 was not affected by active ingredient(terbinafine chlorhydrate).Topical cream, C1 and C4 were selected for further testing based on overall physical evaluation, appearance, and immediate skin feel.

Five topical pastes were developed with different ingredients and cream bases. P1 and P2 were created using different ingredients in different concentrations, as well as the same emulsifier in different concentrations. However, P2 produced a semi-solid product, whereas P1 produced a liquid emulsion. This can be explained by the decrease in lanolin for the paste P1 and the increase in concentration of the lipophilic solvent. Thus P1 was excluded from further investigation. Comparably P3, P4, and P5 were created using similar ingredients in varying concentrations and a different emulsifier, which is the liquid solubilizer. P5, on the other hand, was created with a different cream base (vaseline). For the first four weeks, all formulations P2-P4 were stable at the same storage conditions(that is laboratory cabinets and room temperature about (16°C-25°C); however, after week four, the physical stability of P3 was negatively affected by these conditions. This could be explained by the proportion of emulsifier and also the combination of two emulsifiers in smaller proportions. All of the formulated pastes had the same consistency and color. P2 and P4 were chosen for further investigation based on their immediate feel, spreadability and also stability.

Furthermore, five topical ointments (G1-G5) were developed. G1, G2 and G4 were created using similar ingredients in varying concentrations and emulsifier proportions. The physicochemical properties of G1 were negatively influenced by the concentration of the ingredients used and thus were not investigated further. The physical stability of G2 was also negatively affected by the emulsifier concentration, decrease in cream base(that is use of cremaphor A6 only)as well as the change in cooling medium, resulting in formulation agglomeration as shown in Figure 3.5.Thus G2 was not investigated further. However, the physical stability of G4 was not affected. This can be explained by the increase in emulsifier concentration and also the use of different cream base combinations(that is vaseline and Cremaphor A6). Formulation G3 was made with similar ingredients in varying concentrations and with different emulsifiers.G3 however started showing signs of degradation after 24 hours. This can be explained by the use of a different emulsifier,(solubilizer),decrease in the lipophilic solvent and also the use and increase of a single cream base(vaseline).Due to this ,G3 was excluded

from further investigation. Formulations G3 and G4 had similar consistency and no change in color were observed. All formulations G3 and G4 remained stable in storage for six weeks but began to degrade after the increase in climate temperature.G5 was made with similar ingredients as G3 but in varying concentrations and a different emulsifier. The physical stability of G5 was not affected. This can be explained by the use of a different emulsifier and also change of the active ingredient. The color of G5 was affected after incorporating the active ingredient(terbinafine chlorhydrate)into the formulation. On the basis of consistency, and spreadability, G4 and G5 were chosen for further research.

Studies have shown that formulation viscosity gives insight on the release of the active ingredient from the topical vehicle. The rheological characterization of selected formulations proved that G5 and P4 were highly viscous with C1 being the least viscous. Highly viscous formulations hinder the release of the active ingredient hence affecting drug metabolism and therapeutic efficacy.

The appearance, stability and homogeneity of the selected formulations were acceptable. Bibliographic research indicated the change in proportion of emulsifiers could affect emulsion stability which this study confirmed.

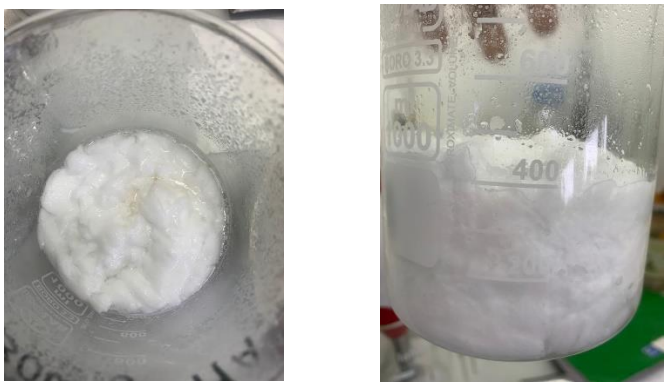


***Figure 3.3***:*Flocculation of Baby Cleansing Milk(Personal, unpublished results)*

***Figure 3.4***:*Degradation of baby cleansing milk.( Personal, unpublished results)*

***Figure 3.5***:*Formulation Agglomeration of Topical Ointment.( Personal, unpublished results)*

# GENERAL CONCLUSION

The main interest of this study was in the formulation of various cream and milk parapharmaceutical products. The goal was to develop an effective anti-fungal cream for the treatment of infected nails with minimal or no side effects on the body. Additionally, the goal is to produce parapharmaceutical product which will cleanse the baby's skin without compromising the skin barrier function. This enabled gain insight into the benefits and limitations of the topical route of drug administration. Different topical creams, pastes, and ointments were formulated in the proposed scheme to serve as topical vehicles for the active ingredient as well as baby cleansing milk. Subsequently, these formulations were evaluated. It has been suggested in this work that the formulation of various topical vehicles, such as creams, is possible using ingredients readily available on the pharmaceutical market.

In general, parapharmaceutical formulations have been shown to be time-consuming and sometimes complicated to apply, however they minimize the risk of adverse drug effects. Topical formulations primarily necessitate the use of a good homogenizer to create smaller particle size for longer product stability. It was discovered that the best results of a topical formulation are obtained using a good emulsifier or a combination of emulsifiers and a pH similar to the skin's pH. A well-formulated product is selected based on factors such as degradability, pH, rheological characteristics such as viscosity and spreadability.

In terms of future work, it is anticipated that subsequent studies will be capable :

- of developing locally parapharmaceutical products for various fungus infections as well as safe methods of drug administration with minimal or no side effects.
- of investigating the complete cure rate of formulated terbinafine topical creams and ointments.

-develop a good baby cleansing milk stable and safe for all babies especially babies born in tropical regions.