Hemina Skin Rebuilding and Reconditioning Therapy: Treating Ichthyosis & Xerosis

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Technical Document
March 2005

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1. Introduction

1.1 Moisturizers

The purpose of moisturizers is to maintain hydration and smoothness of the skin. Moisturizers exist in forms of varying physical properties such as lotions, ointments, gels, and even sprays. The importance of moisturizers for 'treatment' of skin conditions is often overlooked by healthcare professionals and patients.[48] Skin care professionals have realized that putting water back into the skin is no longer the only method for hydrating the skin. With an understanding of skin structure and function, skin care has been restructured to restore and improve the natural mechanism of hydration in the skin. Many moisturizers contain active ingredients that are designed to correct abnormal conditions of the skin and these actives can be considered as treatments.

1.1.1 Ingredient Background

Moisturizer ingredients are composed of two types of ingredients: active and complementary. Actives provide the primary function of the product while complementary ingredients stabilize the formulation and add additional properties that make the product consumer-friendly. Actives are subdivided into four categories: occlusives, emollients, humectants and exfoliants. Complementary ingredients are also subdivided into four categories: emulsifying agents, preservatives, thickeners and pH adjusters. Each type of ingredient acts differently in the lotion and in the skin.

- Occlusives are ingredients that form a layer on the surface of the skin. This action retards water.[62]
- Emollients are ingredients that smooth the skin by filling the intercellular spaces with droplets of oil. These ingredients also decrease the water loss in the stratum corneum by partial occlusion.[62]
- Humectants are hygroscopic ingredients that draw water from the dermis into the epidermis[50] and at the same time they attract water moisture from the air to themselves by hydrogen bonding.[58] Since humectants are much more effective in drawing water from the dermis into the epidermis than from the atmosphere, it is recommended to use it along with an occlusive ingredient to prevent an increase in water loss from the skin.[50]

- Exfoliants are ingredients added to a product in order to increase sloughing of dead cells on the surface of the skin.[11] Some of these ingredients include the α-hydroxy acids like salicylic acid and the beta hydroxy acids like maleic acid. It is believed that by removing some of these drier outer cells, some improvement in the surface wrinkles and dryness may result.
- Emulsifying agents are used in production to help the emulsion between the two immiscible liquids, in this case, oil and water phases. These agents are large molecules containing both hydrophilic and lipophilic divisions in the molecule that allow the molecule to bind to water as well as to oils by London forces.[50]
- Preservatives are necessary in cosmetic products in order to prevent the product from microbiologic contamination.[19]
- Thickeners are used in the formulations when a specific viscosity is needed in the formulation.
- pH adjusters are sometimes used in order to reach the desired pH by the formulator which tends to match the skin's natural pH.
- Antioxidants are sometimes added to the formulation in order to inhibit oxidation by reacting with free radicals blocking the chain reaction.[49] These prevent oxidative damage in the skin.[11]

1.1.2 Delivery Systems

Various delivery systems are being used today to enhance the diffusion of active ingredients through the skin. Some of the delivery vehicles considered for the production of the product included liposomes, nanospheres or microspheres, encapsulations, multiple emulsions, and microemulsions.

1.1.3 FDA Regulations

Skin moisturizers are considered cosmetic products by the Federal Food and Drug Administration. A cosmetic is defined as "an article intended to be rubbed, poured, sprinkled, sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance."[46] The FDA does not regulate cosmetics as it does for other products such as drugs. A drug is

defined as "an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man."[46]

Cosmetic product and ingredients are not subject to FDA pre-market approval authority, with the exception of color additives. FDA cannot require companies to do safety testing of their cosmetic products before marketing. Therefore, FDA is only able to regulate cosmetics after products are released to the marketplace and is able to pursue enforcement action against violative products, firms or individuals that violate the law.[26]

Today, many moisturizing products are including ingredients that could be classified as drugs at certain concentrations. In order to prevent regulation by the FDA, cosmetic producers must keep these ingredients below the regulated concentration. For example, in the α-hydroxy acid preparations proposed in this project, a value less than 10% by weight was used in order to keep the lotion as a cosmetic product instead of converting it into an over-the-counter drug (OTC).

The only requirement for the α-hydroxy acid preparations is a proper package labeling.[39] Proper labeling implies that the product ingredients must be listed sequentially in the order of highest concentration without reporting the actual concentrations. FDA does not have the authority to require manufacturers to register their cosmetic establishments, file data on ingredients, or report cosmetic-related injuries after the product has been marketed. However, companies are encouraged to register their establishments and file Cosmetic Product Ingredient Statements with FDA's Voluntary Cosmetic Registration Program (VCRP).[26]

1.2 Background of the Skin

The skin is considered the biggest organ in the human body. It exists as a semipermeable barrier layer that covers the entire body. In the average adult, the skin covers approximately 1.75 m^2 and weighs between 3.5 – 4.5 kg, comprising about 7% of total body weight.[60] The skin has many functions including but not limited to production of keratin, sebum, sweat, and melanin, heat exchange, protection, wound repair, perception of sensations and temperature regulation.[67] It is composed of two main structural layers with interdependent functions. Components in the skin regulate these functions and must be

considered when analyzing abnormal conditions of the skin. The main functions that Hemina, Inc is pursuing are skin hydration and the prevention of desiccation.

1.2.1 Skin Structure

The skin is divided into two main structural layers: the dermis and the epidermis. The epidermis is the outer layer and the dermis is just underneath. The dermis is a connective tissue layer and functions as a source of nutrition for the epidermis as well as having a controlling influence on the growth and maintenance of the epidermis.[67] It is richly supplied with nerve endings, blood vessels, hair follicles, and lymphatic vessels.[60] It is considered a connective tissue because it "joins" tissue which connects collagen to bones, muscles and cartilage.[60]

The epidermis is divided into four layers: the basal layer (stratum basale), the spinous layer (stratum spinosum), the granular layer (stratum granulosum), and the outermost stratum corneum.[40] Figure 1 shows these layers. The basal layer is the deepest layer and is adjacent to the dermis. The basal layer and dermis are separated by a thin membrane. Undifferentiated epidermal cells are lined up along the membrane.[67] These cells are constantly regenerated by mitosis in the basal layer. Upon commencement of differentiation, the cells detach from the border and migrate upwards.[40] During differentiation the epidermal cells undergo a series of biochemical changes as they migrate to the outer layer of the epidermis.[40] The spinous layer is above the basal layer. In this layer, the cells that have divided in the basal layer are now being joined together by "intercellular bridges" known as desmosomes.[67] Also, in this layer a hydrolipid film is secreted that locks in moisture and keeps the skin at optimal pH which is slightly acidic to retard possible bacteria growth.[60] The cells then move up to the granular layer. In the granular layer the cells accumulate basophilic keratohyalin granules which contain important lipids that will later on form a waterproof lipid barrier to prevent desiccation.[74] The accumulation of keratin in the cells causes lipid membranes to rupture and lysosomal enzymes are released that cause cell death. The dead and dying cells form the outer layer of the skin.[74]

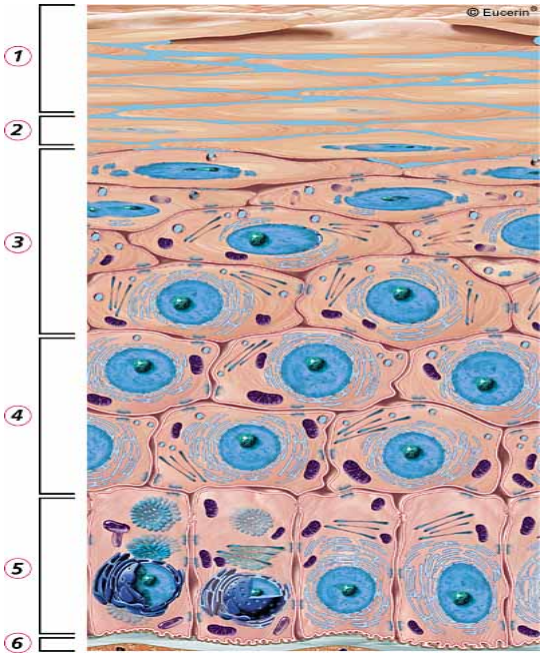

Figure 1: Epidermis Layers[21]

The stratum corneum (SC) is the outermost layer of the epidermis. It is the principle barrier to penetration of exogenous substances, both unintentionally encountered and deliberately applied.[51] The SC has two major components arranged in a "brick and mortar" arrangement. The "bricks" are the final result of differentiation known as corneocytes. These are the keratin-filled, anucleated, hydrophilic, nonviable cells that have been pushed up from the basal layer. These cells are flattened and connected by the "intercellular bridges" known as desmosomes.[52] The cells are surrounded by a cornified envelope, around 10 nm thick[51], formed from highly cross-linked isopeptide bonded proteins.[41] The envelope consists of two components: a layer of defined structural proteins and a layer of ceramide lipids. The protein envelope and ceramide lipids are covalently attached together. The ceramide lipids on the outside of the cornified envelope contribute to the hydrophobic surface of the corneocytes which is important for preventing desiccation.[41]

1.2.2 Crucial Components of the Skin

Inside the cells is a group of low molecular weight, water soluble compounds known as the Natural Moisturizing Factor (NMF). This group of compounds makes up 30% of the cellular components of corneocytes. NMF consist primarily of amino acids and their derivatives, including pyrrolidone carboxylic acid (PCA), urocanic acid, lactic acid, urea,

citrate, and sugars.[63] These molecules are hygroscopic. They are derived from the granules that are present in the granular cell layer. These granules are filled clumps of filaggrin that have formed a complex with the cell's keratin . Just after the filaggrin joins with the keratin, disulphide bonds form between the keratin to strengthen the cell envelope. Once the network is sufficiently stable, the keratin/filaggrin complex is broken down.[63] As the cells move farther out in the SC, the water content in the SC decreases. At a certain point, the water content is low enough that proteolytic enzymes are activated to degrade filaggrin into the individual amino acids that make up the NMF.

The other component of the "brick and mortar" arrangement is the lipid matrix that fills the spaces between the corneocytes. The matrix is composed of hydrophobic, highly structured lipid lamellae that provide an effective barrier to water loss.[40] These intercellular lipids include 40-50% ceramides, 25% cholesterol, 10-15% free fatty acids, and less than 5% of several other lipids. It is crucial that the three major lipids in the lipid barrier exist in the correct ratio. Ceramides are the most important of the intercellular lipids. They are very complex lipids that take a much longer time to regenerate when compared to cholesterol and free fatty acids.[40] The intercellular lipids are derived from lamellar granules, small organelles found in the granular layer. These structures are released into the extracellular spaces of degrading epidermal cells during differentiation (physiology). The lipid granules are thought to fuse with the plasma membrane of the granular cell and discharge their lipids along with enzymes that govern processes such as lipid metabolic changes, desmosome breakdown, and ceramide production.[51] The lipids form stacked bilayers that surround the corneocytes incorporating water between the bilayers (Figure 2).[52] The newly formed matrix provides an impermeable barrier for the passage of water out of the SC and the prevention of the NMF from leaking out of the surface layers of the skin.[52]

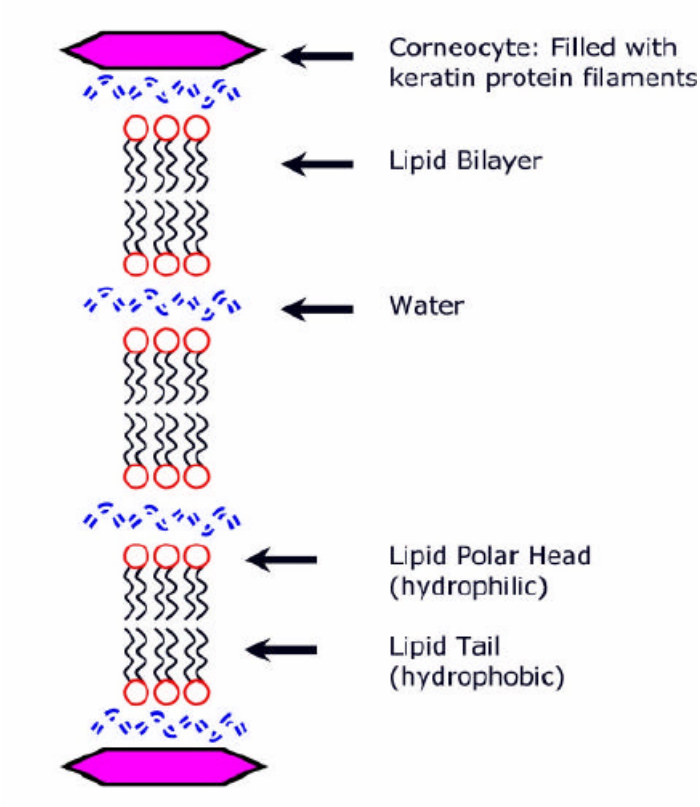

Figure 2: Lipid Bilayer Structure[60]

1.2.3 Desquamation

Desquamation is a very important process that occurs in the SC. Cohesion in the Sc is controlled primarily by the desmosomes that connect the corneocytes. These desmosomes are extensively cross-linked with the cornified envelope late in differentiation which locks the structure in place.[40] Van der Waal forces also help to hold the lipid lamellae and the corneocytes together. The lipid lamellae interact with the outer lipid membrane of the cornified envelope.[40] Desquamation is the enzymatic process of dissolving the desmosomes that connect the corneocytes in the SC. The enzymes responsible for desquamation are present only in a well-hydrated SC; in the absence of water, cells do not desquamate steadily.[52] In normal skin, cells are shed all the time in an invisible manner. When desquamation is impeded, the dead cells build up which causes thick, rough, scaly skin. The effectiveness of the desquamation process is intimately dependent upon the composition and organization of the intercellular lipids and effective tissue hydration.[40]

1.2.4 Skin Hydration

One attractive feature of the skin is that it keeps a constant level of hydration. Healthy skin contains more than 10% water.[51] The two components that maintain hydration are NMF and the lipid barrier. They function by limiting water loss from the tissue.[51] NMF retains water by absorbing it and the lipid barrier provides a complex matrix designed to keep the water from diffusing out of the skin. Water originates from within and so the SC receives the majority of its water from the dermis. Water is considered the "plasticizer" of the skin because it gives the skin its smooth and pliable qualities.[52] When damage is done to upset the balanced state of hydration, dry skin occurs. This damage can exist in many forms: i.e. removal of NMF components or interruption of the lipid bilayers.[52] Without NMF, water does not absorb in the corneocytes. With interruption of lipid bilayers, a collapse of the lipid barrier occurs and water diffuses more freely out into the environment. When skin hydration falls below the normal 10%, the skin develops a fine scale and feels rough and dry.[74] Typical dry skin is known as xerosis and is defined as a decrease in the amount of water in the SC.[11] Common causes for xerosis work by dehydrating the SC and include overexposure to water, harsh soaps or irritants, and the environment. Cold, dry weather tends to cause xerosis because there is a lower amount of humidity in the air. More severe forms of dry skin exist and several are genetically linked.

1.3 The Disorder

Ichthyosis is a family of xerotic disorders characterized by severely scaly skin. These disorders are inherited genetically or in some cases acquired. A genetic defect causes abnormal skin function which leads to a buildup of the SC, producing very dry scales on the surface of the skin. Ichthyosis vulgaris is the most familiar form of the disorder. Patients affected by ichthyosis vulgaris lack water-binding components in the top layer of the skin, yielding low levels of hydration which produces scaling. Treatment for these disorders is focused at managing the symptoms as there is currently no cure for ichthyosis.

1.3.1 Ichthyosis Disorders

In this group of disorders, the SC is the main focal point of the abnormality.[15] Ichthyoses are generally caused by abnormal production and/or desquamation of epidermal

cells. A layer of corneocytes builds up that is much thicker than normal. This buildup eventually causes the skin to shed in clumps and cracking of the skin can occur. The cause of these disorders is usually genetic defects, but there are some acquired forms of ichthyosis. Hereditary forms of ichthyosis can be present at birth or can develop later in life.[15] X-linked ichthyosis is an example of a hereditary form that only affects males. Acquired forms can exist as symptoms of other diseases or reaction to medicine. Infections such as leprosy, HIV and human T-lymphotrophic virus 1 and 2 have been associated with acquired ichthyosis along with Hodgkin's lymphoma and metabolic diseases.[15] As with xerosis, conditions of the disorder are exacerbated in cold, dry climates.

1.3.2 Ichthyosis Vulgaris

Ichthyosis vulgaris is the most common of the ichthyoses. The incidence of this form of ichthyosis is 1 in 250.[15] The cause of ichthyosis vulgaris is thought to be a post-transcriptional defect in profilaggrin expression.[64] Pro-filaggrin is a histidine-rich basic protein, which is proteolytically processed into filaggrin[69], which is further degraded into NMF during differentiation. This lack in profilaggrin expression causes a lack of NMF in the corneocytes which severely reduces hydration of the SC. Also, with decrease water content in the SC, proteases are inhibited for many enzymatic processes. The main process that is hindered in ichthyosis disorders is desquamation. The decreased water content causes abnormal desquamation, and consequently scaly, dry skin.

The skin appears to be scaly due to the reflection of the light from the curled edges of the dried squamous cells on the surface of the skin.[15] Areas of the body that are more hydrated such as the face and folds of the body do not exhibit scaly features. In ichthyosis vulgaris, the most involved regions of the body are those of the lower extremities, such as the lower legs.[15] Some itching accompanies the disorder.

1.3.3 Current Treatment

Treatment for all forms of ichthyosis is considered as symptomatic treatment because the symptoms are treated, rather than the disorder. There is currently no cure for ichthyosis. So in order to treat the symptoms, it is important to rehydrate the skin and retain the new moisture. Moisturizers work in many ways to treat dry skin. Trapping water is one

method of moisturizing. There are recommendations for patients to take a bath and then apply a thick moisturizer to hydrate the SC and then seal it off.[64] Thick, greasy agents that work as occlusives are recommended when working to stop water from escaping from the SC. Keratolytic agents are used to promote desquamation and increase water binding. These agents include α-hydroxy acids, such as lactic acid and glycolic acid, salicylic acid, urea, and propylene glycol.[15] The most important idea behind the moisturization of ichthyotic skin is to restore the hydration and chemical balance of the SC. Lipids are also being used to repair the lipid barrier. Externally applied lipids diffuse down in between the corneocytes. With the restoration of the lipid barrier comes an increased level of hydration which will reinstate the normal process of desquamation. All of this will lead to a smoother, softer feel to the skin.

2. The Product

The product is a moisturizing package designed as a process of treatment for patients suffering from the hereditary skin disorder, ichthyosis vulgaris. The package consists of three individual products: a pre-shower lotion, a shower gel, and an after shower lotion. Each individual product performs separate tasks that will collectively restore the diseased skin to a more balanced state. The design is focused on active ingredient function and consumer aesthetics. The combination of the three products is intended to improve skin conditions above and beyond other products on the ichthyosis market.

2.1 Objective

In order to effectively restore the skin, we have proposed a system of moisturizers incorporating knowledge of the components of the skin and their function with understanding of how water travels through the skin. There are three individual products included in the package.

1. Pre-Shower Lotion – a lotion that promotes desquamation
2. Shower Gel – a gel that cleanses as well as adds water absorbing components called natural moisturizing factors (NMF) that exist abundantly in normal skin. Ichthyotic skin lacks NMF which causes a reduced level of hydration.

3. After-Shower Lotion – a lotion that is meant to replace the barrier lipids, thereby restoring the matrix so that the skin can retain the water that it absorbs into the skin. There are also actives that are intended to hydrate and smooth the skin.

With this package, a process is developed that will better restore the skin to a balanced state. The dead skin that has built up will first be loosened and removed with the Pre-Shower Lotion. Some form of scrubbing tool (i.e. loofah, pumice stone) will be recommended to facilitate desquamation. Then actives in the Shower Gel replace the NMF enhancing the ability of the skin to absorb water. The After-Shower Lotion contains actives that replace barrier lipids, restoring the matrix that prevents water loss. Also the After-Shower leaves the skin smooth and soft, which is aesthetically pleasing to the consumer.

2.2 Package Ingredients

In order to develop the system, ingredients were chosen as actives because of their known function in the skin. Each product has a specific objective and depending on that objective, actives were chosen for each product. Complimentary ingredients are added to give the additional properties.

2.2.1 Pre-Shower Lotion

Ammonium lactate is the active ingredient of the pre-shower lotion. It has been shown that ammonium lactate is effective for treatment of ichthyotic disorders by helping to shed the built up layers of corneocytes. FDA approved this chemical under the name Lac-Hydrin (ammonium lactate) 12% lotion for treatment of ichthyosis vulgaris and dry, scaly skin (xerosis) and for the temporary relief of itching associated with these conditions (FDA, 1988). Ammonium lactate has been used for the treatment of dry skin of the heels (Jackson, 1994).[75] Other chemicals were chosen to give additional properties for consumer aesthetics. Retinyl palmitate was chosen to act as an effective anti-oxidant and skin-cell regulator.[56] Jojoba oil mimics the lipid content of the skin and was chosen to act as an emollient oil. Polyethylene glycol is a common ingredient in moisturizing lotions. It promotes emulsions between the oil and water phases and coats liposomes, making them more stable so they can diffuse deeper into the skin.[56] Cetyl alcohol is another common ingredient that is used as an

emollient, emulsifier, thickener, and carrying agent for other ingredients. Octyldodecanol was chosen as a thickener because of lubricating and emollient properties. Phenoxyethanol is a common cosmetic preservative that is considered one of the less irritating ones to use in formulations.[56] Finally, maleic acid is used as a pH adjustor for the lotion.

Table 1: Pre-Shower Lotion Ingredients

Ingredient	Function
Water	Solvent
Ammonium Lactate	Desquamation
Retinyl Palmitate	Antioxidant
Jojoba Oil	Emollient
PEG-4	Emulsifier/Liposome Formation
Cetyl Alcohol	Emulsifier
Octyldodecanol	Thickener
Phenoxyethanol	Preservative
Maleic Acid	pH Adjuster

*Active Ingredient

2.2.2 Shower Gel

The active ingredients in the Shower Gel are all compounds of the NMF that is found abundantly in the SC in unaffected, normal skin. NMF compounds act as naturally-occurring humectants in the skin.[49] These chemicals are too large to diffuse through the cornified envelope of the corneocytes, so it is important for these to be delivered deeper into the stratum corneum. The cornified envelope is formed during the differentiation process, so undifferentiated cells in lower layers of the skin could possible receive these compounds. These ingredients include lactic acid, urea, sodium PCA, urocanic acid, and citric acid. Lactic acid will also increase ceramide production which will help to start the improvement of the lipid barrier.[46] Other complimentary ingredients include cetyl alcohol, phenoxyethanol and maleic acid. Glycerol oleate was also added to the formulation for emollience and thickness.

Table 2: Shower Gel Ingredients

Ingredient	Function
Water	Solvent
Polysorbate-20	Surfactant
Cocoamidopropyl Betaine	Surfactant
Lactic Acid*	NMF
Urea*	NMF
Sodium PCA*	NMF
Urocanic Acid*	NMF
Citric Acid*	NMF
Glycerol Oleate	Emollient/Thickener
Cetyl Alcohol	Emulsifier
Phenolxyethanol	Preservative
Maleic Acid	pH Adjustor

*Active Ingredient

2.2.3 After-Shower Lotion

The active ingredients included in the after-shower lotion are humectants and barrier lipids. The humectants are expected to bring water into the skin and also absorb moisture from the dermis, while the barrier lipids are used to rebuild the lipid matrix that prevents water loss out into the environment. Ceramide, γ-linoleic acid, and cholesterol are the three SC barrier lipids. The composition of these components in the lipid matrix is crucial to its efficiency. The ratio of ceramide to cholesterol to free fatty acids is 3:1:1 which is desired in the lotion. Dimethicone and lanolin are the two humectant actives. Dimethicone is a form of silicone which is used in lotions to reduce the greasy, sticky feel that is undesirable to the customer.[46] Lanolin also acts as an emollient because it accounts for the enhancement of the adhesion of the formula to the skin. Complimentary ingredients such as PEG, cetyl alcohol, phenoxyethanol, and maleic acid were chosen for the same purpose as the other products. A second emollient, palm oil, was chosen because it also exhibits antioxidant properties. Isostearic acid was selected as a binding agent and thickener.[56]

Table 3: After-Shower lotion

Ingredient	Function
Water	Solvent
Dimethicone*	Humectant
Lanolin*	Humectant/Emollient
PEG-4	Emollient/Liposome Formation
Cetyl Alcohol	Emulsifier
Ceramide*	SC Lipid/Humectant
Isostearic Acid	Thickener
Palm Oil	Emollient/Emollient
γ-Linoleic Acid*	SC Lipid
Cholesterol*	SC Lipid
Phenoxyethanol	Preservative
Maleic Acid	pH Adjustor

*Active Ingredient

2.3 Determination of Composition

The weight percents in the formula were mainly based on maximums allowed by the Cosmetic Ingredient Review which are admitted and used by the Federal Drug Administration. According to Suzanne Mabrouk[50] states that commercial lotions usually contain 76-84% of water while the rest is made up of active and complementary ingredients. When deducing the percentages for the products, research of formulations of shower gels and lotions already on the market was done. For the lotions, it was observed that the actives, such as emollients and humectants, are second to water regarding to weight percent. For the shower gel, the major component is water while the surfactant ingredients are second in the rank of weight percentages.

2.3.1 Pre-Shower Lotion

Water is the main ingredient with a percentage of 60% which is lower than the actual percentage stated by Mabrouk.[50] The value was chosen since most of the other ingredients are water soluble and liquids as well, which would allow for more actives and complementary weight percentages to increase in the formulation, increasing effectiveness of the lotion. The active ingredient in the lotion is ammonium lactate which is needed at its allowable

maximum concentration in the lotion for effectiveness purposes. According to the Cosmetic Ingredient Review, the recommended and safe usage percentage present in the formulation needs to be 10%, which was the value chosen. The next ingredient in the list with the highest weight percentage in the formulation is the jojoba oil and polyethylene glycol (PEG) with 8%. Jojoba oil is an emollient that mimics the lipid lamellae of the skin with a maximum of 25% allowed into the formulation. An 8% weight was chosen since a higher percentage than the active ingredient (10%) would interfere with the action of the active ingredient, in addition to its competing as the active ingredient instead of as a complementary ingredient. Furthermore, since it is an oil, a higher percent weight in the formulation would contribute to the oily feeling which might bother the customer during application of the lotion. For PEG, an 8% weight was chosen since its action it to serve as the organic continuous phase for the production of liposomes in the formulation. It was decided that since the oil phase constitutes 12% of the formulation, 8% weight of the PEG would be enough to account for the emulsification between the oil and water phases.

The next ingredient is octyldodecanol which constitutes 5.9% weight of the formulation but is safe to use as high as 85% in formulations. The 5.9% value was chosen since it is a thickener that would affect the viscosity of the formulation which due to its lower percentage of water in the formulation might have a higher viscosity than what is usual for a lotion.

The following ingredient in the list is the Retinyl Palmitate which accounts for 5% weight of the formulation. This ingredient is the combination of retinol (pure vitamin A) and palmitic acid. Its recommended usage is 5% weight in the formulation which was the value chosen since the activity of vitamin A and palmitic acid are beneficial ingredients to be applied to the skin. Vitamin A is important since it can have the same action on skin as tretinoin which affects cell production in the skin.[56] Palmitic acid is important since it is a natural component present in the lipid lamellae.[46] The subsequent ingredient in the formulation is cetyl alcohol which accounts for 2.9% weight in the formulation while its safe to use as high as 50%. The value of 2.9% was chosen since its function as an emollient, emulsifier, and thickener are already being represented by other chemicals. It was added to the lotion because of its multiple actions into the formulation, as well as being an endorsement of other ingredients having the same properties. The following ingredient is

phenoxyethanol which accounts for 0.196% weight of the formulation while it is safe to use at 5%. Since this ingredient is a preservative, a high percentage of it is not needed. Additionally, irritation increases in the skin if high levels of the ingredient are used. The last ingredient in the formulation is maleic acid which accounts for 0.004% which is the maximum percentage. Although the necessary value for the pH adjuster varies from each batch, the maximum was chosen since all of it might be needed in addition to the fact that maleic acid is a component of the lipid lamellae. The following table summarizes the formulation for the Pre-Shower Lotion.

Table 4: Composition of Pre-Shower Lotion

Material	Weight % in Pre-Shower Lotion
Deionized Water	60
Ammonium Lactate	10
Jojoba Oil	8
PEG	8
Octyldodecanol	5.9
Retinyl Palmitate (Vitamin A Palmitate)	5
Cetyl Alcohol	2.9
Phenoxyethanol	0.196
Maleic Acid	0.004

2.3.2 Shower Gel

Deionized water makes up 52% of the shower gel composition which is an average of the water percent present in other shower gels after researching their formulas. The next ingredient in the formulation is Polysorbate-20 which accounts for 20% weight while its safe-to-use amount is at 50%. A 20% weight of the surfactant was chosen since in a shower gel, the minimum range of surfactant present has to be of 25-35% according to the research done on products on the market. The following surfactant in the list constitutes the 5% of the formulation completing the 25% range of surfactant needed to be present in the formulation. 20% of the surfactant Polysorbate-20 was chosen since it is a nonionic surfactant being the least irritant surfactant in the skin while the lesser value of 5% for the cocoamidopropyl betaine was chosen due to its importance in the formulation of being able

to act with both nonionic and anionic ingredients which is because of its amphotericity and being able decrease the irritancy to the skin due to its low presence in the formulation.

The subsequent ingredient is lactic acid which constitutes for 4% weight in the formulation while it is safe to use up to 10%. 4% was chosen since it is the middle equilibrium between necessary action in the skin and level of irritability created by the ingredient when used at high levels. The next ingredient is urea which constitutes 4% of the formulation while its maximum percentage is 10%. 4% weight was chosen since it is the medium equilibrium between the necessary action in the skin and level of irritability created by the ingredient when used at high levels. The next ingredients are sodium PCA, urocanic acid, citric acid and oleic acid which each constitute 3% weight of the formulation. Their maximum allowable percentages have not been reported by the Cosmetic Ingredient Review, except for the oleic acid percentage which is at 50%. These ingredients are present in the NMF and lipid lamellae by different percentages. The value of 3% was chosen for the ingredients since it is an average of their presence in the human body.

The subsequent ingredient in the formulation is cetyl alcohol which accounts for 2.796% weight in the formulation while its maximum usage is up to 50%. The value of 2.796% was chosen since its function as an emollient, emulsifier, and thickener are already being represented by other chemicals. It was added to the lotion because of its multiple actions in the formulation, in addition to being an endorsement of other ingredients having the same properties.

The following ingredient is phenoxyethanol which accounts for 0.2% weight of the formulation while its safe-to-use percentage is at 5%. Since this ingredient is a preservative, a high percentage of it is not needed in addition to the increase of irritation in the skin if high levels of the ingredient are used. The last ingredient in the formulation is maleic acid which accounts for 0.004% in the formulation which is the maximum safe-to-use percentage. Although the necessary value for the pH adjuster varies from each batch, the maximum was chosen since all of it might be needed in addition to the fact that maleic acid is a component of the lipid lamellae. Table 5 summarizes these results for the Shower Gel.

Table 5: Composition of Shower Gel

Material	Weight % in Shower Gel
Deionized Water	52
Polysorbate-20	20
Cocoamidopropyl Betaine	5
Lactic Acid	4
Urea	4
Sodium PCA	3
Urocanic Acid	3
Citric Acid	3
Oleic Acid (Glycerol Oleate)	3
Cetyl Alcohol	2.796
Phenoxyethanol	0.2
Maleic Acid	0.004

2.3.3 After-Shower Lotion

For the after-shower lotion, water is the main ingredient with a percentage of 60% which is lower than the actual percentage stated by Mabrouk. The value was chosen since this lotion is meant to be a little bit greasier than the first one due to its high content of insoluble ingredients in the formulation and low percentage of water in the formulation. One of the active ingredients is dimethicone which constitutes 10% weight of the formulation while its safe-to-use percentage is at 24% in make-up preparation which was assumed to be similar to a lotion due to the time the product would be in contact with the skin. A 10% weight was chosen since it was assumed to be enough quantity in order to form the occlusive film over the surface in the skin.

The next ingredient is lanolin which accounts for 8% weight in the formula while the safe-to-use percentage is 37%. 8% was chosen since it acts as an emollient and it was assumed that this percentage would account for the necessary enhancement of the adhesion of the formula to the skin. The following ingredient is PEG which accounts for 7% weight of the formula. This percentage was chosen since its action is to serve as the organic continuous phase for the production of liposomes in the formulation. It was decided that

the oil phase constitutes 32% of the formulation, and that 7% weight of the PEG would be enough to account for the emulsification between the oil and water phases.

The subsequent ingredient in the formulation is cetyl alcohol which accounts for 5% weight in the formulation while its safe-to-use percent is at 50%. The value of 5% was chosen since its function as an emollient, emulsifier, and thickener are already being represented by other chemicals. It was added to the lotion because of its multiple actions in the formulation in addition to being an endorsement of other ingredients having the same properties.

The next ingredient is isostearic acid which accounts for 5% in the formulation while its safe-to-use percentage is 26%. The value of 5% was chosen since its action as a thickener is not needed as high as the maximum percentage since most of the formulation is composed of insoluble materials that will contribute to the thickness of the formula.
The following ingredient is phenoxyethanol which accounts for 4.936% weight which is close to the safe-to-use percentage of 5%. Ceramide, γ-linoleic acid, and cholesterol are the three SC barrier lipids. The composition of these components in the lipid matrix is crucial to its efficiency. The ratio of ceramide to cholesterol to free fatty acids is 3:1:1 is desired in the lotion. The specific percentages were chosen on economic analysis and the natural presence of the ingredients in the skin.

The last ingredient in the formulation is maleic acid which accounts for 0.004% in the formulation which is the maximum safe-to-use percentage. Although the necessary value for the pH adjuster varies from each batch, the maximum was chosen since all of it might be needed in addition to the fact that maleic acid is a component of the lipid lamellae.

Table 6: Composition of After Shower Lotion

Material	Weight %
Deionized Water	60
Dimethicone	10
Lanolin	8
PEG	7
Cetyl Alcohol	5
Isostearic Acid	5
Phenoxyethanol	4.936
Ceramide	0.03
γ-linoleic acid	0.01
Cholesterol	0.01
Palm Oil	0.01
Maleic Acid	0.004

2.4 Diffusion in the Skin

Once a substance is applied to the surface of the skin, it begins to diffuse into the skin. This diffusion must be considered when formulating moisturizing lotions and other cosmetics. The knowledge of diffusion will help the understanding of how the chemicals are transported into the skin and how water leaves the skin. Using a mathematical model, we can compare the amount of a chemical diffusing into the skin to the amount of the chemical applied.

2.4.1 Diffusion Background

The skin is a complex organ that serves to protect humans from chemical, physical, and biological intrusion while retaining moisture and providing thermal regulation. It also serves as a protection for internal organs. There are two main types of diffusion through the skin, the percutaneous diffusion and the transepidermal water loss (TEWL).

Percutaneous diffusion defines the rate and the extent that a chemical is absorbed into and through the skin into the systematic circulation.[70] Percutaneous diffusion is divided into three types of diffusion: (1) intercellular diffusion through the lipid lamellae, (2)

transcellular diffusion through both the corneocytes and lipid lamellae, and (3) diffusion through the appendages (hair follicles and sweat ducts).[70]

Transepidermal water loss (TEWL) is the insensible diffusion of water from the body through the skin into the outside environment.[70] There are two kinds of diffusion, passive and active. The passive diffusion occurs through the insensible water loss and accounts for about 300-400mL/day.[70] The active component is the release of water through sweat glands for heat dissipation or nervous response.

The passage through the stratum corneum is the rate-limiting step in percutaneous and transepidermal water loss. Passage through the deeper dermal layers and systematic uptake occurs relatively quickly and easy.[54] It is therefore important to model the passage of active ingredients into the skin in order to make a better product for the customer.

2.4.2 Diffusion Model

The diffusion model proposed by sandia.gov was used to model the diffusion of actives through the skin. Here, percutaneous diffusion is modeled taking into account the intercellular and extracellular diffusions through the skin. The diffusion through the appendages was ignored since it only accounts for 0.1% of the total surface area of the skin (Scheuplein, 1967). In addition, transepidermal water loss is not included in the model since the water loss is constant through the skin accounting for 300-400mL/day which is a very small portion of the water contained by the body (60% of adult human body).[70]

The skin allows three potential ways to passively transport the moisturizing components through the SC: intercellular diffusion through the lipid lamellae, transcellular diffusion through both the corneocytes and lipid lamellae, and diffusion through appendages (hair follicles and sweat ducts).[43] According to Clifford Ho, the second pathway, the transcellular diffusion, and the third pathway, yields insignificant results.[43] In this paper the third pathway, diffusion through the appendages, is not considered because the transepidermal water loss is very minor.

After extensive research, the model developed by Clifford Ho was selected. He modeled the intercellular diffusion as a three-phase continuum in which the corneocytes are the immobile protein phase, which can provide reversible interactions (adsorption and desorption) with chemicals in the mobile phases which are the lipid (or oil) and aqueous

(water) phases in between the corneocytes.[43] Their model is based upon Fick's Law concerning the mobile regions, resulting in the following equation:

$$\frac{\partial}{\partial t}\left(C_o\phi_o + C_w\phi_w + C_p\phi_p\right) = \frac{\partial}{\partial x}\left(D_o\tau_o\phi_o\frac{\partial C_o}{\partial x} + D_w\tau_w\phi_w\frac{\partial C_w}{\partial x}\right) \qquad \text{(Eq. 1)}$$

where C is the concentration of the chemical present in the phases (kg/m^3-phase), D is the molecular diffusion coefficients (m^2/s), φ is the porosity of given phase (m^3-phase, m^3-total), τ is the tortuosity coefficient (inverse of tortuosity) that expresses ratio of linear path length to actual path length, and the subscripts o,w, and p represent the oil, water and protein phases, respectively.[43]

The model also assumed that local equilibrium exists and that the separation between the phases could be conveyed by the following expressions:

$$C_o = K_{ow}C_w \quad \text{(Eq. 2)}$$

$$C_w = K_{wp}C_p \quad \text{(Eq. 3)}$$

$$C_p = K_{op}C_p \quad \text{(Eq. 4)}$$

where K represents the partitioning coefficients of the individual phases.[43]

Since the protein phase has been determined to be hydrophilic, Ho assumed that the water-protein partition coefficient, K_{wp}, is approximately equal to 1.[43] As a result of this assumption, the concentrations of the water and protein are equal *($C_w = C_p$)* and the partition coefficients of the oil-protein and oil-water phases are equal *($K_{op}=K_{ow}$)*.[43] Thus, their model was reduced to

$$\frac{\partial C_w}{\partial t} = \frac{D_{sc}}{R_{sc}}\frac{\partial^2 C_w}{\partial x^2} \qquad \text{(Eq. 5)}$$

where

$$D_{sc} = D_o\tau_o\phi_o K_{ow} + D_w\tau_w\phi_w \quad \text{(Eq. 6)}$$

$$R_{sc} = K_{ow}\phi_o + \phi_w + \phi_p \quad \text{(Eq. 7)}$$

D_{sc} represents the effective diffusion coefficient and R_{sc} represents the retardation factor.[43]

The Wilke-Chang correlation was used to determine the diffusion coefficients for chemical diffusion into the oil and water phases (i.e. D_o and D_w):

$$\frac{D_{AB}\mu_B}{T} = \frac{7.4x10^{-8}\left(\Phi_B M_B\right)^{1/2}}{V_A^{0.6}} \qquad \text{(Eq. 8)}$$

where D_{AB} is the diffusion coefficient, μ_B is the viscosity of the solvent, T is the temperature, Φ_B is the association parameter of the solvent, M_B is the molecular weight of the solvent and V_A is the molar volume of the solute.[77] For chemicals in which no molar volume was available, estimations were made using the molecular formula and Table 24.5.[77] The variables used are found in the following table, Table 7.

Table 7: Phase-oriented Variables for Diffusion Coefficient

μ_B	Viscosity (cp)	Water Oil	1.701 35.0
T	Absolute Temperature (K)		298.15
M_B	Molecular Weight (g/mol)	Water Oil	18.0 515.7
Φ_B	Association Parameter	Water Oil	2.26 1

The SC surface was assumed to maintain a constant concentration in the water phase and that the concentration is zero at a distance L_{sc} from the surface due to the bloodstream.[43] Additionally, the initial SC concentration is assumed to be zero.[43] These boundary and initial conditions are represented by the following equations:[43]

$$C_w(0,t) = C_w^o \quad \text{(Eq. 9)}$$

$$C_w(L_{sc},t) = 0 \quad \text{(Eq. 10)}$$

$$C_w(x,0) = 0 \quad \text{(Eq. 11)}$$

Using Eq. 6 -11, Eq. 5 becomes

$$\frac{C_w}{C_w^o} = 1 - \frac{x}{L_{sc}} - \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{1}{n}\sin\left(\frac{n\pi x}{L_{sc}}\right)e^{-\left(\frac{D_{sc}n^2\pi^2 t}{R_{sc}{L_{sc}}^2}\right)} \quad \text{(Eq. 12)}$$

which represents the water phase concentration dependent on time and location in the skin.[43]

The model was used in order to estimate how much the active ingredients were penetrating into the skin if the concentration at the surface and time of interaction between the active and the skin were specified. The concentrations at the top were decided upon on maximums recommended by the Cosmetic Ingredient Review which are the maximums used by the Food and Drug Administration department. The time of contact between the skin and the actives was chosen on what the customer would prefer as a small period of time of

application before continuing everyday tasks. The values of the concentration ratios of the active ingredients are found in the following table.

Table 8: Active Ingredients and Calculated Concentration Ratios

		C_w/C_w^o
Pre-Shower Lotion		
Ammonium Lactate	$CH_3CHOHCOONH_4$	0.862
Shower Gel		
Sodium PCA	C_4O_3NHNa	0.607
Lactic Acid	$C_3H_6O_3$	0.415
Urea	CH_4N_2O	0.391
Citric Acid	$C_6H_8O_7$	0.296
Urocanic Acid	$C_6H_6N_2O_2$	0.604
Post-Shower Lotion		
Cholesterol	$C_{27}H_{46}O$	0.445
Linoleic Acid	$C_{18}H_{30}O_2$	0.497
Ceramide	$C_{30}H_{59}NO$	0.358
Dimethicone	$C_{16}H_{48}O_6Si_7$	0.394
Lanolin	$C_{44}H_{89}O_2$	0.307

Using the formulation that Hemina created and the diffusion model, the concentrations of the active ingredients within in the skin were determined. The values are summarized in the following tables for each of the products.

Table 9: Pre-Shower Active Concentration

	Surface, C_w^o (g/L)	Within the Skin, C_w (g/L)
Ammonium Lactate	101.4	87.4

Table 10: Shower Gel Active Concentration

	Surface, C_w^o (g/L)	Within the Skin, C_w (g/L)
Sodium PCA	20.3	87.4
Lactic Acid	50.7	21
Urocanic Acid	20.3	12.254
Citric Acid	20.3	6
Urea	40.6	15.9

Table 11: Post-Shower Active Concentration

	Surface, C_w^o (g/L)	Within the Skin, C_w (g/L)
Lanolin	81.2	24.9
Dimethicone	101.4	40
Ceramide	0.1014	0.0363
γ-linoleic Acid	0.1014	0.0504
Cholesterol	0.1014	0.0451

2.4.3 Delivery System

Delivery systems are crucial to the diffusion of chemicals into the skin. A range of current delivery systems are used to enhance the diffusion of active ingredients through the skin. The technologies analyzed for the production of Hemina, Inc.'s package included liposomes, nanospheres or microspheres, encapsulations, multiple emulsions and microemulsions. Liposomes and microemulsion were chosen since they can be inexpensively manufactured compared to the necessary equipment required for the other technologies. A small description of the delivery systems technologies considered is described below.

2.4.3.1 Liposomes

Liposomes (100-200nm), formed from phospholipids, store water-soluble substances in its interior as biological cells.[55] Since liposomes can uptake endocytosis (can fuse with the cell wall), they enhance penetration of the encapsulated active ingredients through the stratum corneum. Another benefit includes the delivery of active ingredients to all tissues and organs due to its exhibition of short circulation half-time due to phagocytosis (non-targeted). In addition, they are advantageous because of their low toxicity, biodegradability, and the ability to replace surfactants and emulsifiers.[16] Figure 3 shows the liposome vehicle structure.

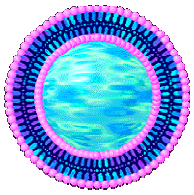

Figure 3: Liposome Vehicle Structure[16]

2.4.3.2 Nanospheres & Microspheres

Nanospheres (10nm-10µm) and microspheres (1-10µm) are tough protein polysaccharide matrices that encircle and trap the active ingredient. Figure 4 shows the nanospheres structure.

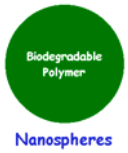

Figure 4: Nanosphere Vehicle[16]

2.4.3.3 Nanocapsules & Microcapsules

Nanocapsules, which are about 130-160 nm in size, and microcapsules, which are about 0.20-90nm in size, enclose the active ingredients or the actives dispersion in a matrix by a polymer membrane or outer layer.[16] Figure 5 shows the structure of the nanocapsules.

Figure 5: Nanocapsule Vehicle[16]

2.4.3.4 Multiple Emulsions

Multiple emulsions, approximately 5-50nm in size, have either the form of oil-in-water-in-oil emulsion which equates to an oil-in-water emulsion (i.e. O/W/O=O/W) or of water-in-oil-in-water equating to a water-in-oil emulsion (i.e. W/O/W= W/O). The compartmentalization of actives occurs in three phases.[55]

2.4.3.5 Microemulsions & Nanoemulsions

Microemulsions, which are greater than 0.5nm in size and nanoemulsions which are between 100 and 200µm, have an emulsion form of oil-in-water (O/W) or water-in-oil

(W/O). These are believed to allow an effective transport through the skin due to the small size of its droplets with high surface area.[55]