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Development of a hand sanitizer with moisturizing properties for medical use.

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SUMMARY

In this work, the development of a hand sanitizer with moisturizing properties for medical use has been carried out.

Formulated product development is the process through which society and or consumer needs are identified and transformed into commercial products. This process can be divided in five main stages: identification of consumer needs, product conceptualization, quality criteria, product formulation and design of a manufacturing process.

The product being developed in this work responds to the need of medical staff to dispose of a hand sanitizer that combines maximum biocidal efficacy with superior moisturizing properties to minimize and or eliminate the skin compatibility issues of traditional formulations when used intensively in the context of nosocomial infection prevention.

To fulfill the previously identified need, the product has been conceptualized both specifying its microstructure and the delivery agent for the active ingredients of the product.

The quality criteria of a formulated product are the requirements that must be met to ensure that apart from satisfying the identified need, the product differentiates from its competition and is attractive and convincing to the end consumer. The four main quality criteria for the product being developed are: biocidal efficacy, moisturizing capabilities, emulsion stability and product rheology.

To allow the evaluation of said quality criteria, appropriate quality indexes have been discussed and in combination with an extensive research of market trends and existing hand sanitizer and moisturizer formulations a genuine and original formulation for the product has been proposed.

Finally, in the design of a manufacturing process stage, a process flowsheet indicating all the necessary unit operations and their order has been confectioned and the main equipment units have been selected and briefly analyzed.

Key words: formulated product development, consumer needs, nosocomial infections, product conceptualization, sanitizer, moisturizer, quality criteria, quality index, product formulation, manufacturing process design.

RESUM

En aquest treball s'ha conduït el desenvolupament d'un desinfectant de mans amb propietats hidratants per a ús mèdic. El desenvolupament de productes formulats és un procés mitjançant el qual, les necessitats de la societat o del consumidor són identificades i transformades en productes comercials. Aquest procés es pot dividir en cinc etapes principals: identificació de les necessitats del consumidor, conceptualització del producte, factors de qualitat, formulació del producte i disseny d'un procés de fabricació.

El producte que s'ha desenvolupat en aquest treball respon a la necessitat del personal mèdic de disposar d'un desinfectant de mans que combini una màxima eficàcia biocida amb propietats hidratants per tal de minimitzar o eliminar els problemes de compatibilitat amb la pell de formulacions tradicionals quan s'usen intensivament en l'àmbit de la prevenció d'infeccions nosocomials. Per a satisfer la necessitat detectada anteriorment, el producte ha estat conceptualitzat especificant la seva microestructura i el millor agent de lliurament per als ingredients actius del producte.

Els factors de qualitat d'un producte formulat són els requeriments que ha de complir per assegurar que a part de satisfer la necessitat detectada, el producte es diferencia de la competència i resulta atractiu i convincent per al consumidor final. Els quatre principals factors de qualitat per al producte que s'ha desenvolupat són: eficàcia biocida, propietats hidratants, estabilitat de l'emulsió i reologia del producte. Per a poder avaluar l'eficàcia dels esmentats factors de qualitat s'han discutit i estudiat els apropiats índex de qualitat que junt amb un exhaustiu estudi dels mercats i de formulacions de desinfectants i hidratants ja existents ha permès proposar una formulació genuïna i original per al producte.

Finalment, s'ha dissenyat un procés de fabricació tot confeccionant un diagrama de flux amb les operacions unitàries involucrades i el seu ordre, els equips necessaris i un breu estudi del disseny dels mateixos.

Paraules clau: desenvolupament del producte, necessitats del consumidor, infeccions nosocomials, conceptualització del producte, desinfectant, hidratant, factor de qualitat, índex de qualitat, formulació del producte, disseny d'un procés de fabricació.

1. INTRODUCTION

1. INTRODUCTION

A health care associated infection, also known as a nosocomial infection is an infection that is acquired in a hospital or health care facility. These infections can occur during healthcare delivery for other diseases and even after the discharge of the patients.

Of every hundred hospitalized patients, seven in developed countries and ten in developing countries can acquire one of these healthcare associated infections (G.M. Raja, K. Annadurai, 2014). While any patient has risk of suffering a nosocomial infection, populations at stake are patients in Intensive Care Units, burnt units, undergoing organ transplant and neonates. According to the Extended Prevalence of Infection in Intensive Care (EPIC III) study performed in 2017, the proportion of infected patients within the Intensive Care Units are often as high as 51% (J.L. Vincent et al, 2009). Extensive studies in USA and Europe show that health care associated infections incidence intensity ranges from 13 to 20 episodes per thousand patient-days (B. Allegranzi, 2011). Which in turn means that each year nosocomial infection cause or contribute to 99.000 deaths in the United States and 25.000 in Europe.

While nosocomial or health care associated infections can't be completely eradicated prevention is key to minimize its numbers and effects. It's proven that thorough handwashing and/or use of alcohol rubs or hand sanitizers by all medical personnel before and after each patient contact is one of the most effective ways to control nosocomial infections as the spread of these infections among patients are connected to health staff hand contamination in more than the 40% of cases (McBryde, Bradley, Whitby and McElvain, 2004).

Washing the hands as promptly and as thoroughly as possible between patient contacts and after contact with blood, body fluids, secretions, excretions and equipment or articles contaminated by them is frequently called the most important measure to reduce the risks of transmitting potentially pathogenic skin microorganisms from one person to another or from one site to another on the same patient and in turn preventing nosocomial infections.

Two categories of microorganisms can be present on health care worker's hands: transient flora and resident flora.

Transient flora is represented by the microorganisms taken by the staff from the environment. The bacteria and other pathogens present in it are capable of surviving and proliferating on the human skin.

The resident flora is represented by the permanent microorganisms living in the skin surface more specifically on the stratum corneum or immediately under it. While these microorganisms have low pathogenicity, they provide the perfect environment for the colonization and proliferation of pathogens from the transient flora.

The type of pathogens that can cause nosocomial infections are bacteria, viruses, yeasts and fungi. The goal of hand hygiene and disinfection is to eliminate the transient flora with a careful and proper performance of hand washing using different kinds of soap (normal and antiseptics) and/or hand sanitizers.

The main problems found in the practice of hand hygiene and disinfection via hand wash with soap relates to the lack of available sinks and the time-consuming performance of the mentioned. An easy way to solve this problem is by using alcohol based hand sanitizers due to their faster and more convenient application compared to traditional hand wash.

The most common type of alcohol-based hand sanitizers are the ones that contain an aqueous solution of ethanol, propanol or a mixture of both.

They are very effective against gram positive and negative bacteria including multi resistant pathogens, fungi and lipid-walled viruses such as VIH and hepatitis A.

Alcohol's antimicrobial or antiseptic activity is related to its ability to denature proteins (Larson and Morton, 1991). Denaturation occurs when the bonding interactions responsible for the secondary protein structure (hydrogen bonds to amides) and the tertiary protein structures (hydrogen bonding, salt bridges, di-sulfide bonds and non-polar hydrophobic interactions) are disturbed.

The disturbance of the mentioned structures effectively destroys the proteins and enzymes inside the pathogen's cells resulting in its deactivation and/or death.

According to (Boyce and Pittet, 2002) 60-95% concentrated aqueous alcohol solutions are the most effective due to the ease of this solutions to penetrate the pathogen's cellular walls and denature the protein and enzymes inside. More concentrated solutions merely coagulate the cell's outer wall preventing the ingress of any alcohol.

While there is strong evidence that alcohol based products have excellent bactericidal properties and when properly used can be a very important part in the prevention of nosocomial infections one shortcoming of using this type of products is skin compatibility.

Human skin contains in its outer layers a variety of oils and greases that provide lubricity and form a protective layer against external agents. Alcohol is a great solvent and as described by (Boyce and Pittet ,2002; Pratt et al, 2001) can dissolve the previously mentioned oils and greases and effectively eliminate the skin's protective layer causing dryness and irritation.

It becomes evident then that it exists a need for an alcohol based hand sanitizer with added emollients and humectants to its formulation that provide moisturizing properties and prevent and/or eliminate the drying and irritant effect of alcohol in the skin of healthcare personnel.

2. OBJECTIVES

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The final goal of this paper will be the development of a hand sanitizer with moisturizing properties for medical use in other words the fulfilment of the detected need. Product development is the process through which the needs of society or consumers are identified and transformed into commercial products. This procedure can be divided into four stages that will constitute the following chapters in this work.

Product Conceptualization:

The conceptualization of the product is essential since it refers to the idea or concept that is generated as a response to meet the need or needs detected in society or consumers. In this chapter, a thorough analysis of the product to be developed will be carried out so that It can be conceptualized by defining its physical properties and characteristics, the mode of application or consumption, and most importantly the necessary requirements to ensure that the need or needs are successfully fulfilled.

Quality criteria:

In this chapter and once the product has been conceptualized and its characteristics have been defined it will be necessary to identify its quality criteria. The quality criteria of a formulated product are the requirements that must be met to ensure that apart from satisfying the detected need, the product differentiates from its competitors and is attractive and convincing to the end user.

Product formulation:

At this stage of the procedure, a thorough analysis will be made to determine what ingredients or compounds should form the product and what microstructure must present so it meets the quality criteria identified previously. Intensive research will be carried out on the products available on the market and a new and genuine formulation that meets the imposed requirements and it allows the product to be differentiated from competition will be proposed.

It will be necessary to choose what type of alcohol to use, the concentration of alcohol needed, which emollient and humectants should be used and in which proportions, etc.

Design of a manufacturing process:

Here, an industrial process will be designed to produce the formulated products from its raw materials. Unit operations will be analyzed, its order will be decided and necessary equipment will be proposed.

Conclusions:

In this final chapter the most important results and conclusions of this development will be summarized and discussed.

3. PRODUCT CONCEPTUALIZATION

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Clearly, the very first step towards manufacturing a product is defining the product itself. In doing this, the consumer needs and market trends need to be captured.

Market trends may not present themselves so obviously. Therefore, innovation and creativity are among the key ingredients for success in product development. It is often the case that the development of a ground-breaking product begins with a creative inventor's desire to make life simpler followed by tireless efforts to realize the idea.

Market research among potential customers is also useful in conceptualizing the product and confirming the need.

In summary, product conceptualization involves the selection of the appropriate form in which the key ingredients should be delivered, including product packaging.

In the case contemplated in this work, the detected need has been the development of a hand sanitizer with moisturizing properties for medical use. As the name implies, the market target of the product will be the health care sector including primary care centers, hospitals and sanitary staff.

First, we must realize that the product that is being conceptualized has two primary functions (sanitize and moisturize), that will have to be carried out by two key ingredients

For the sanitizing function of the product, the key ingredient will be an aqueous solution of alcohol with a concentration that will be comprised between 60 and 95% by volume (Boyce and Pittet, 2002). Due to the irritating and drying effect of highly concentrated alcohol aqueous solutions, traditional formulations tend to use low concentrations of alcohol to try to minimize its effect but that solution it's not considered to be optimal as it effectively reduces the sanitizing capabilities of the product.

The present disclosure will opt for a sanitizer with the highest concentration of alcohol possible to ensure great sanitizing capabilities while the moisturizing function will be performed by a moisturizer.

Moisturizers are complex mixtures of chemical agents including occlusive compounds, humectants and emollients specially designed to make the external layers of the skin (epidermis) softer and more pliable and to increase its water content by reducing evaporation.

As it will be discussed further in this work, conventional moisturizing hand sanitizer formulations tend to add moisturizers directly to the alcohol-water solution. Commonly used moisturizers are usually hydrophobic compounds that lead to a very limited stability due to its water repelling behavior.

As a result, the added moisturizers or skin protectants don't remain evenly distributed throughout the sanitizer rendering its moisturizing ability ineffective. Additionally, the instability of this conventional formulations causes the formation of large oil layers on the skin causing it to feel greasy and not aesthetically pleasing. Finally, the incorporation of said moisturizers directly into the sanitizer requires additional processing steps which add to the complexity and cost of the manufacturing process.

The fact that some compounds that will be present in the formulation are hydrophilic and others are hydrophobic (mostly the moisturizing compounds) calls for an emulsion as the proper delivery vehicle.

Hydrophilic compounds are those whose interactions with water and other polar substances are more thermodynamically favorable than their interactions with oil or other hydrophobic or non-polar solvents.

Hydrophobic compounds in contraposition are those whose interactions with oil or other non-polar solvents are more thermodynamically favorable than their interactions with water or other polar solvents.

An emulsion is a heterogenous mixture of two or more immiscible liquids like per example oil and water. In an emulsion, one liquid (the dispersed phase) is dispersed in the other (the continuous phase).

To avoid the greasy feeling when the sanitizer is applied to the skin an O/W (oil in water) emulsion will be chosen. Which means that the dispersed phase will be oil and the continuous phase will be water.

The lipophilic moisturizing agents will be emulsified by themselves with a minimal fraction of water in the form of a high internal phase emulsion (emulsion with a dispersed phase fraction greater than 74%).

As it will be discussed later, by pre-emulsifying the lipophilic moisturizing compounds in form of a high internal phase emulsion the sanitizer will have superior stability and costs of the manufacturing process will be greatly reduced.

For the final product, the high internal phase emulsion will be diluted in the alcohol-water mixture. Additional hydrophilic moisturizing compounds may be added at this stage and other compounds such as thickeners will be used to fine tune the rheology of the final emulsion and to further improve its stability and shelf life.

Now that the selection of the appropriate form in which the key ingredients should be delivered has been disclosed, the only step remaining in the conceptualization of the product is defining the packaging of said product.

For a more casual use of the sanitizer such as in primary attention, pediatrics, physicians and nursery the preferred packaging solution according to (Christianto Wibowo, Ka M. Ng, 2002) will be plastic bottles with pump caps for dispensing. These containers will have a maximum volume of 500ml due to its casual use and to promote convenience of use and ease of handling.

For more intensive applications and environments where a high level of hygiene and disinfection is required such as surgery rooms, intensive care units, and emergencies traditional delivery methods such as manual dispensers, or the previously mentioned bottles are not ideal because they involve direct contact between the container and the healthcare staff hands.

Over time, this contact between the hands of the professionals and the containers leads to the development of a local flora of microorganisms in the container's surface that could be responsible for a nosocomial infection.

The preferred method for minimizing that risk is the use of hand free operated hand sanitizer dispensers. These consist of a container in which the sanitizer is stored and an automated dispensing pump that is activated when the movement of the hands beneath the apparatus is sensed.

Again, according to (Christianto Wibowo, Ka M. Ng, 2002) the best packaging solution for this case will be a sealed plastic bag or sachet to refill the hand free sanitizer dispensers.

4. QUALITY CRITERIA

4. QUALITY CRITERIA

As mentioned in chapter 2 the quality criteria of a formulated product are the requirements that must be met to ensure that apart from satisfying the detected need, the product differentiates from its competitors and is attractive and convincing to the end consumer.

To quantify each quality criteria, the concept of quality index should be introduced. Quality indexes are properties that can be measured and/or tested and allow evaluation of said quality criteria.

4.1. BIOCIDAL EFFICACY OF THE SANITIZER

The final and most important goal of a hand sanitizer is to have adequate effectiveness as a biocidal. While alcohol-based hand sanitizers are very effective against many kinds of microorganisms, the type of alcohol chosen in its formulation, the concentration of said alcohol and the application times of the sanitizer have a dramatic effect in the final biocidal performance of the product.

It becomes evident that the sanitizer being developed will have to be tested against a standard.

A standard, also known as technical standard is a stablished norm or requirement regarding technical systems or products. It's usually a formal document that stablishes uniform engineering or technical criteria methods, processes and practices.

A standard may be developed privately or unilaterally by corporations, regulatory bodies and standards organizations. Standards organizations often have more diverse input and develop standards that might become mandatory if adopted by a government i.e. through legislation.

One of the most important standards organizations is the European Committee for Standardization whose goal is to foster the economy of the European Union in global trading, the welfare of European citizens and the environment by providing an efficient infrastructure to interested parties for the development, maintenance and distribution of coherent sets of standards and specifications.

One of the most important standards for evaluating the biocidal efficacy of a hand sanitizer are the EN 1500 for hygienic hand disinfection and the EN 12791 for surgical hand disinfection.

4.1.1 EN 1500

The EN 1500 is an European Standard test method that evaluates the efficacy of a hand sanitizer to achieve hygienic disinfection by measuring the number of viable bacteria remaining on the fingertips after contamination and posterior hand rub with the sanitizer. A hand rub is defined as a treatment which involves rubbing the hands without the addition of water. This method specifically simulates conditions for stablishing if a sanitizer decreases or eliminates the transient flora from the hands.

Procedure

In this test, subjects with healthy hands are randomly assigned either to a reference control product or the sanitizer under evaluation. Following an initial cleansing wash with soap to remove natural transient microorganisms the subject's hands are dried thoroughly with a paper towel.

Typically, a prepared pure culture of a non-pathogenic strain of E. Coli is used as the inoculum for this test method. Subjects immerse their hands in a volume of the inoculum up to the mid carpels for 5 seconds with their fingers spread apart.

The hands are then allowed to air dry for 3 minutes, then the fingertips are sampled by rubbing them into a petri dish with sterile tryptic soy broth (TSB) for pre-values of viable bacteria present on the hands.

Immediately after pre-value sampling the hands a re-inoculated then subjected to either the reference hand rub procedure with 2-propanol 60% v/V or the sanitizer under evaluation.

The fingertips are then sampled again for post-values in the same manner as the pre-values this time with TSP containing a chemical neutralizer. The samples are then diluted appropriately and placed onto a tryptic soy agar (TSA) medium where they are allowed to incubate 18-24 hours at 36 ºC, counted and then re-incubated for an additional 24 hours to detect any potential slow growing.

Finally, the pre- and post-values recovered from the fingertips are evaluated against one another resulting in a ratio called the logarithmic reduction factor. This reduction factor provides a quantitative measure of the biocidal efficacy. Then the reduction factor of both the reference treatment and the evaluated sanitizer are compared.

To pass this test, the sanitizer must present a logarithmic reduction equal or better than the one for the reference treatment of 2-propanol 60% v/v.

4.1.2. EN 12791

The EN 12791 is a standard method that evaluates the biocidal efficacy of a hand sanitizer to achieve surgical disinfection. While the methodology and procedures of this test differ slightly from the EN 1500 the basic principle is the same.

A reference treatment and the sanitizer under evaluation are compared using the logarithmic reduction factor of both. To pass this test, the sanitizer as with the EN 1500 must present a reduction factor equal or better than the reference treatment that in this case is 1-propanol 60% v/v.

Due to the bibliographical nature of this work, the sanitizer being developed will not be tested in the "real world", instead, to ensure that the proposed formulation complies and even exceeds the previously mentioned standards the following studies will be used to determine the best type of alcohol to use, the optimal concentration of said alcohol and the necessary application times to reach the desired biocidal efficacy.

STUDY 1: EFFICACY OF ALCOHOL-BASED HAND GELS (A. Kramer, P. Rudolph, G. Kampf and D. Pittet, 2002]

The aim of this study was to determine the biocidal efficacy of several hand gels according to EN 1500 standard with 3ml of sanitizer during 30 seconds of application which resembles current clinical practice.

Methodology

After a thorough hand wash with non-medicated soap, hands were placed in a suspension of E-coli for 5 seconds and allowed to air dry for 3 minutes afterwards. Pre-values were obtained from all fingertips. 3ml of hand gel were applied for 30 seconds or 2x3ml of reference alcohol were applied for 2x30 seconds (cross over design).

After the treatment of the hands, fingertips were sampled once more. Pre-values and post-values were obtained by rubbing the fingertips for one minute in nutrient broth containing validated neutralizing agents followed by serial dilution. Aliquots were spread on tryptic soy agar (TSA). After incubation of the plates, the total colony counts were determined per subject and time point. All values were expressed on a logarithmic reduction scale or reduction.

Results

Active ingredients	Main reduction factor of product	Main reduction factor of reference alcohol	Efficacy compared to reference %
2-propanol 45% and 1-propanol 30% w/w	4,26	4,10	103,9
Ethanol 57% v/v	2,68	3,78	70,9
Ethanol 60% v/v	3,07	4,12	74,5
2-propanol 60% v/v plus other antiseptic ingredients	4,07	4,96	82,1
Ethanol 62% v/v	3,07	4,10	74,9
Ethanol 70% v/V	3,36	4,26	78,9
Industrial methylated spirits 70% v/v	3,58	4,68	76,5

Table 1: Comparative efficacy of alcohol-based hand sanitizers according to EN 1500 standard.

Conclusion

From the tested products the one with the greatest biocidal efficacy meeting and even exceeding the EN 1500 standard in 30 seconds of application is the one which has as active ingredient a mixture of 45% 2-propanol and 30% 1-propanol v/v.

STUDY 2: SURGICAL HAND DISINFECTION WITH A PROPANOL-BASED HAND RUB: EQUIVALENCE OF SHORTER APPLICATION TIMES (G. Kampf, C. Ostermeyer and P, Keeg, 2005)

This study has investigated the efficacy of a propanol-based hand rub for surgical hand disinfection according to EN 12791 with an application time under 3 minutes.

Methodology

This cross over study examined the efficacy of propanol-based hand rub with a hand sanitizer containing 45% 2-propanol and 30% 1-propanol w/w for different application times. For the 20 test subjects carried out a surgical hand disinfection in accordance with EN 12791. The hand sanitizer was applied to the hands for 3, 2, 1.5, and 1 minutes respectively. The fingers were rubbed in tryptic soy broth for 1 minute to determine the pre-values and immediate values.

Results:

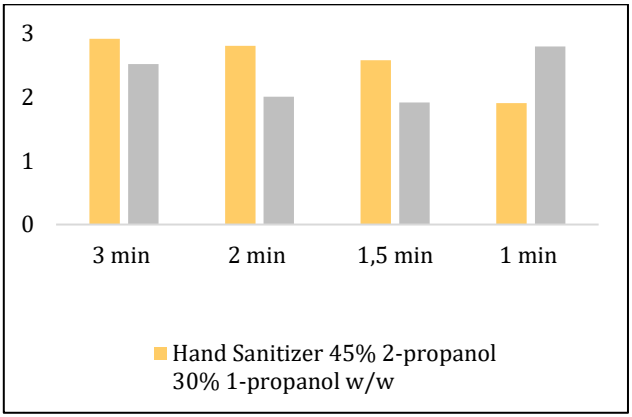

Figure 1: Immediate effect of a hand sanitizer containing 45% 2-propanol and 30% 1-propanol w/w for surgical disinfection EN 12791 with different application times.

Conclusion

To achieve EN 12791 levels of biocidal efficacy for surgical disinfection with a hand sanitizer containing a mixture containing 45% 2-propanol and 30% 1-propanol w/w as active ingredient, the duration of the application must be greater than 1 minute. For longer times of application (1.5, 2 and 3 minutes) this formulation exceeds the efficacy of EN 12791 faster than the reference disinfection.

Finally, the conclusion once the results of the previous studies have been contemplated is that the best biocidal active ingredient for a hand sanitizer is a mixture of 45% 2-propanol and 30% 1-propanol w/w.

To achieve hygienic disinfection in compliance to EN 1500 standard, the application can be as short as 30 seconds.

If surgical disinfection is desired, in accordance to EN 12791 standard the application time must be at least 60 seconds.

With this important conclusions and information, the formulation of the sanitizer being developed in this work is guaranteed to reliably fulfill the previously mentioned claims.

4.2. MOISTURIZING CAPABILITIES

As mentioned in previous chapters, one of the two main functions of the product being developed is its moisturizing capabilities.

Moisturizers are complex mixtures of chemical compounds designed to make the external layers of the skin (epidermis) softer, moister and more pliable. According to their physical properties and their mechanism of action moisturizers can be classified as:

- Emollients
- Humectants
- Occlusives

Emollients:

Emollients are mainly lipids and oils which hydrate and improve the skin softness, flexibility and smoothness. Intracellular lipids comprising multilamellar structures, which are in the stratum corneum (outermost layer of epidermis), play a major role in skin architecture.

In the stratum corneum, ceramides are the major lipid constituents and along with neutral lipids form broad laminated intercellular sheets which act as a barrier to external agents from the environment (S. Rathi, 2006). Natural ceramides are too expensive for commercial products hence several pseudo-ceramides are used as emollient agents (M. Loden and H. Maibach, 1999).

Lipophilic compounds get easily incorporated into liposomes and make the skin texture softer and smoother via their effects on skin barrier functions, eicosanoid production, membrane fluidity and cell signaling (M. Loden, 2005).

Squalene as an emollient:

Squalene is one of the most common lipids produced by human skin cells and is a component of human sebum. It is an isoprenoid compound and acts as an intermediate metabolite in the synthesis of cholesterol and acts as a quencher of singlet oxygen thus protecting skin surface from lipid peroxidation due to exposure to ultraviolet rays and other sources of ionizing radiation.

An added boon of squalene is that even though it is technically an oil, it does not have an oily feel, is odorless, antibacterial and safe for sensitive skins (G.S. Kelly, 1999).

In the following table, some examples of typical emollient agents are listed:

Dry emollients	Fatty emollients	Astringent emollients	Protective emollients
Deacyl oleate, isopropyl palmitate, isostearyl alcohol…	Castor oil, glyceryl stearate, jojoba oil, octyl stearate, propylene glycol…	Cyclomethicone, dimethicone, isopropyl mystirate, octyl octanoate…	Di.isopropyl dilinoleate, isopropyl isostearate…

Table 2: List of common emollient agents.

Humectants:

Humectants are basically hygroscopic compounds that draw water from the dermis into the epidermis and attract moisture from the environment. Various examples of humectant agents are:

- Glycerin
- Alpha hydroxyl acids
- Propylene glycol
- Butylene glycol
- Hyaluronic acid
- Urea
- Panthenol
- Gelatin
- Sorbitol

However, humectant agents are double edged weapons as they increase trans-epidermal water loss (TEWL) by enhancing water absorption form the dermis into the dermis where it can be easily lost to the environment by transpiration. It is for that reason that they are mostly combined with occlusive agents (J.N. Kraft and C.W. Lynde, 2005).

Occlusive agents:

Occlusive agents are substances (usually oils) that physically block trans-epidermal water loss (TEWL) by creating a hydrophilic barrier over the skin. They also incorporate to the matrix between corneocytes and diffuse into the intracellular lipid domains thus contributing to their efficacy.

In the following table, some examples of occlusive agents are listed:

Type	Examples
Hydrocarbons	Petrolatum, paraffin, mineral oil, caprylic triglycerides, squalene…
Fatty acids	Lanolin acid, stearic acid…
Fatty alcohols	Ceteyl alcohol, stearic acid…
Phospholipids	Lecithin
Polyhydric alcohols	Propylene glycol
Sterols	Cholesterol

Vegetable waxes	Carnauba, candelilla…
Wax esters	Beeswax, lanolin, stearyl stearate…

Table 3: List of various occlusive agents.

Moisturizers are often mixtures of the previously mentioned moisturizing agents. Their choice, quantity and proportion have great impact in the final moisturizing performance of said product.

It becomes necessary then to quantify the performance of a moisturizer in function of the previously mentioned attributes by reviewing the following experimental studies using five different moisturizing lotion formulations (F. Anthony Simion, Eric S. Abrutyn and Zoe D. Draleos, 2005):

Glycerin-rich lotion (Lotion GR)	Hydrocarbon lotion (Lotion H)	Waxy lotion (Lotion W)	Butylene glycol lotion (Lotion B)	Low-glycerin lotion (Lotion LG)
Glycerin *	Petrolatum	Emulsifying wax	Butylene Glycol	Glycerin
Petrolatum	Mineral oil	Glycerin	Mineral oil	Stearic acid
Isopropyl palmitate	Ceresin	Octyl isononanoate	Petrolatum	Glycol stearate
	Lanolin alcohol	Dimethicone	Glycerin	Sunflower seed oil
			Cetyl alcohol	

* Lotion GR contains more than 15% glycerin, whereas lotions W, B, and LG contain less than 8% glycerin. Lotion H does not contain glycerin.

Figure 2: Table of moisturizing lotion formulations used in study [19].

4.2.1. Sensory testing:

In sensory testing, consumers are employed to function as instruments to measure product differences, characteristics and preference levels.

In this test, up to 30 competent panelists where conducted to try each formulation [figure 2] for a determined amount of time and with a specified method and frequency of application.

The results of this test are represented in the following graph:

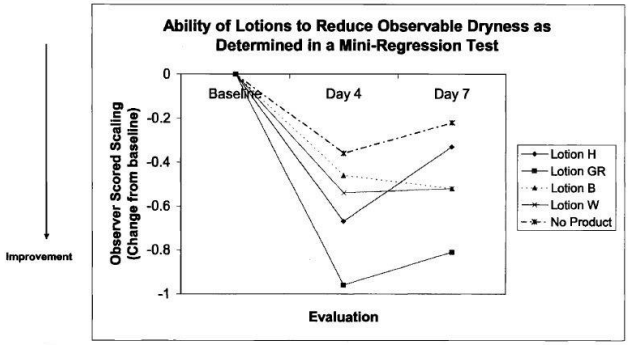

Figure 3: Results for sensory testing of different moisturizing lotion formulations.

4.2.2 Squamometry:

Squamometry is a combination of sampling corneocytes by adhesive coated discs followed by color measurements of the previously stained cells.

Corneocytes are terminally differentiated keratinocycles and compose most of the stratum corneum. They are regularly replaced by desquamation and renewal from lower epidermal layers making them an essential part of the skin barrier properties.

After sampling, harvested cells (corneocytes) are stained and reviewed visually by light microscopy. The evaluated intensity of staining is related to the level of skin surface alterations and dryness using a chroma C* color scale.

For the formulations tested [figure 4], the results where:

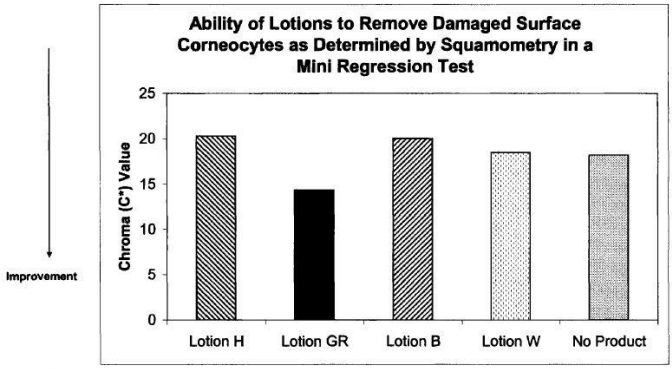

Figure 4: Squamometry results of different moisturizing lotion formulations.

4.2.3. Desquamation index:

Dry skin has a scaly surface and is rough to the touch. The degree of dryness is closely related to the amount and size of the superficial scales (F. Anthony Simion, Eric S. Abrutyn and Zoe D. Draleos, 2005).

For testing, transparent self-adhesive and flexible discs are pressed onto the skin and then repealed to include the loose scales of the upper skin layer. Then, every disc is photographed and analyzed by a standardized procedure that includes densiometric and light refraction analysis of the adherent scales.

Finally, a specialized software calculates the desquamation index that as mentioned is directly related to the skin dryness.

For the tested formulations [figure 5] the desquamation indexes where:

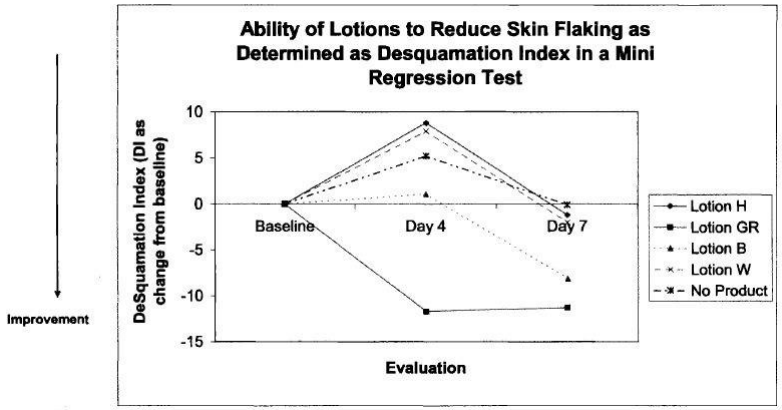

Figure 5: Desquamation indexes for different moisturizing lotion formulations.

4.2.4. Skin conductance:

In this test, electrical conductance (ability of electric charge to flow through a certain path) of the skin is measured by applying a small electrical current to two different points of the skin surface and calculating the resistance across said points. Then, conductivity can be determined knowing that is the inverse of resistance.

Due to moist skin having lower electric conductance than dry skin, a comparative scale can be developed to quantify skin dryness. The conductance values for the tested formulations [figure 6] where:

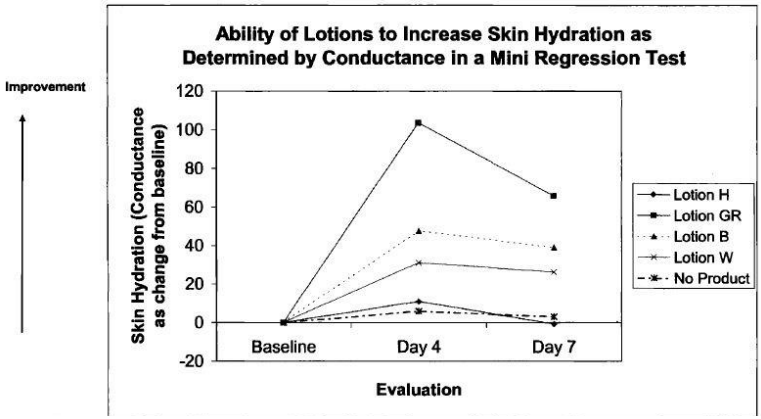

Figure 6: Conductance values for different moisturizing lotion formulations.

According to the results of the previously reviewed tests, the most effective moisturizing lotion formulation was the GR (glycerin rich) lotion.

4.3. EMULSION STABILITY

As mentioned in a previous chapter, the sanitizer being developed in this work has been conceptualized as an oil in water emulsion. The oil phase containing part of the moisturizing agents and the water phase containing the rest of the moisturizers, the biocidal active ingredient in the form of a mixture of 45% 2-propanol and 30% 1-propanol w/w and other compounds such as thickeners to fine tune its rheology.

Before exploring and studying the factors that affect an emulsion stability it will be convenient to first explain what an emulsion is.

An emulsion is thermodynamically unstable dispersion of several immiscible liquids. The most common type of emulsion are the ones containing 2 phases one of which is constituted by a polar compound (usually water) and the other by a non-polar compound (usually oil). One of those phases is called the dispersed phase which as the name implies is dispersed in the form of varying

size droplets in the other phase called the continuous phase. An oil in water emulsion then consists of an oil (non-polar) phase dispersed in water (polar).

To form a stable oil in water emulsion, the interfacial tension present in the interphase between the oil and water phases must be overcome. While high rate mixing can reduce the mentioned interfacial tension enough to emulsify the mixture, to provide the emulsion with long term stability an emulsifying agent must be added.

The most common type of emulsifying agents what we call surfactants. Surfactant are amphiphilic compounds that lower the interfacial tension by adsorbing in the interface of the system.

Amphiphilic compounds are the ones that contain both hydrophilic groups (their tails) and hydrophilic groups (their heads).

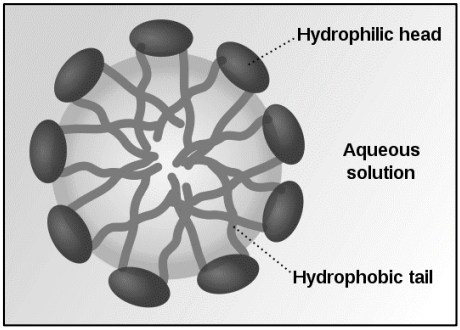

Figure 7: Representation of a surfactant.

As seen in figure 7, the surfactant adsorbs into the interface orientin it's hydrophilic towards the aqueous phase and its hydrophobic tails towards the oil droplet.

According to the Bancroft's rule, the final structure of an emulsion obtained using a surfactant depends greatly in the nature of said surfactant. If the surfactant is more soluble in the polar phase (water) then an oil in water emulsion will be formed. In contraposition, if the surfactant is more soluble in the non-polar phase (oil) then the resulting emulsion will be a water in oil emulsion.

To quantify the hydrophilic/lipophilic nature of a surfactant, in 1949 Griffin proposed the HLB (Hydrophilic Lipophilic Balance) scale. This scale is a great tool to decide which surfactant to be used depending on the type of emulsion desired and it has an important effect in the stability of said emulsion.

HLB value	Application
3-6	Water in oil emulsions
7-9	Humectant agents
8-18	Oil in water emulsions
13-16	Detergents
15-18	Solubilizing agents

Table 4: Application of surfactant depending their HLB value.

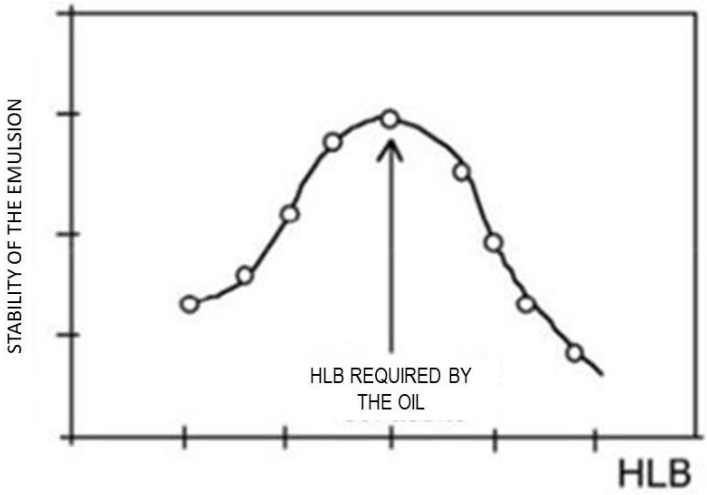

Figure 8: Stability of an O/W emulsion in function of the HLB value.

As seen in Figure 8, emulsions have a maximum of stability when the HLB of the surfactant use coincides with the required HLB of the oil.

Once formed, the stability of the emulsion depends of the following mechanisms:

- Sedimentation, also known as creaming.
- Flocculation.
- Coalescence.
- Ostwald Ripening.

4.3.1. Sedimentation

Sedimentation, also known as creaming is a procedure caused by the action of gravity that produces a vertical concentration gradient of the droplets without varying their size.

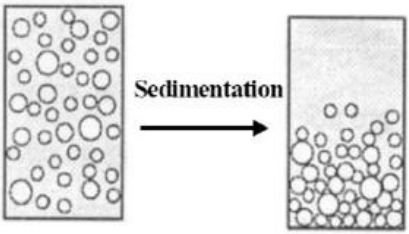

Figure 9: Sedimentation process.

For an isolated droplet, the creaming or sedimentation speed is defined by the following equation:

$$v = 2a^2 \cdot \frac{(\rho_o - \rho) \cdot g}{9 \cdot \gamma} \quad [eq.1]$$

v is the speed or rate of sedimentation, a is the droplet radius, ρ_o and ρ are the respective densities of the continuous and dispersed phases, g is the acceleration of earth's gravity and γ is the absolute viscosity of the continuous phase.

According to this, to maximize the stability of the emulsion against sedimentation or creaming, the droplet size will be kept to a minimum and the viscosity of the continuous phase should be kept to a maximum i.e. by using thickening agents.

4.3.2. Flocculation

Flocculation is the process by which the droplets adhere to themselves without their size being affected.

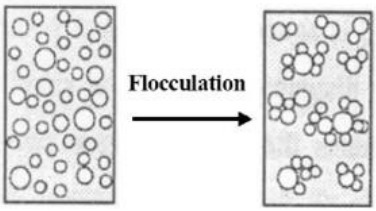

Figure 10: Flocculation process.

According to the DLVO theory, this process is controlled by a total potential of interaction- This potential is the sum of Van der Waals attractive forces and Double Layer repulsive forces (Jan W. Gooch, 2007)

$$V = V_A + V_R \quad [eq.2]$$

Van der Waals attractive forces

Van der Waals force is the total name of dipole-dipole force, dipole-induced force and dispersion forces (Jacob N. Israelachvili, 2007) in which dispersion forces are the most important as they're always present.

According to the Derjaguin approximation (B.V. Derjaguin, 1934) the Van der Waals interaction potential between 2 spherical particles or droplets is described by the following equation:

$$V_A = -\frac{A}{6 \cdot D} \cdot \frac{R_1 \cdot R_2}{(R_1 + R_2)} \quad [eq.3]$$

A is the Hamaker constant, R_1 and R_2 are the radius of both particles or droplets and D is the distance between them.

Double Layer repulsive forces

Double layer forces occur between charged objects across liquids. This force acts over distances that are comparative to the Debye length which is on the order of 0,1 to 1 nanometers. The strength of this forces increases with the magnitude of the surface charge density according to the following expression:

$$V_R = \frac{64 \cdot \pi \cdot k_B \cdot T \cdot R \cdot \rho_\infty \cdot \gamma^2}{k^2} \cdot e^{-k \cdot D} \quad [eq.4]$$

R is the radius of the spherical particles, T is the temperature, and k is defined as:

$$k = \sqrt{\sum \frac{\rho_{\infty i} \cdot e^2 \cdot z_i^2}{\epsilon_r \cdot \epsilon_o \cdot k_B \cdot T}} \quad [eq.5]$$

ρ_∞ is the number density of ion i in the bulk solution, z is the valency of said ion, ϵ_o is the vacuum permittivity, ϵ_r is the relative static permittivity and k_B is the Boltzmann constant.

In summary then, according to DLVO theory, the best way to provide the emulsion with maximum stability against flocculation is by minimizing the attractive forces of the system by both minimizing the droplet size and maximizing the distance between them. While it's not possible to maximize the distance between the droplets once the emulsion has been formed, increasing its viscosity (by adding a thickener to the aqueous phase) will provide an immobilization effect preventing the droplets from easily coming closer together and potentially decreasing the stability of the system due to the increase of attractive forces.

4.3.3. Coalescence

Coalescence is the process by which two or more droplets merge during contact forming a new and individual bigger one.

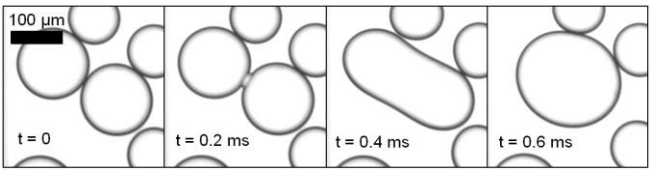

Figure 11: Coalescence process.

The evolution of emulsion stability through coalescence can be characterized by a kinetic parameter w describing the number of coalescence events per unit time and per unit surface area of the droplets. Following the mean field description of Arrhenius w can be expressed as:

$$w = w_o \cdot \exp\left(-\frac{E_a}{K_b} \cdot T\right) \quad [eq.6]$$

Where $K_b \cdot T$ is the thermal energy and w_o is the attempt frequency of the hole nucleation process.

Owing to the intrinsic complexity of the destruction scenario of the emulsion by coalescence, the measurements of w_o and E_a are scarce.

Although the most exact way of understanding this evolution is only possible through a quantitative and usually experimental determination of w, for simple emulsions stabilized by surfactants (D.S. Tawfik and A.D. Griffiths, 1998) stated that the emulsion is modeled as a stack of monodisperse cells with characteristic size D.

The total number of droplets per unit of volume n is related to the volume fraction Φ of the dispersed phase through the following relationship:

$$\phi = n \cdot \pi \cdot \frac{D^3}{6} \quad [eq.7]$$

Because coalescence is a completely random process, the total number of coalescence events per unit time is assumed to be proportional to the total surface area A of the droplets.

$$\frac{-dn}{dt} = w \cdot A = W \cdot n \cdot \pi \cdot D^2 \quad [eq.8]$$

In eq. 8, w is defined as a coalescence frequency per unit surface area of the droplets. Considering eq.7 and eq. 8 and assuming that w is constant (independent of D), it can be concluded that the droplet's mean size in the emulsion increases with time according to the following law:

$$\frac{1}{D_o^2} - \frac{1}{D^2} = \frac{2\pi}{3} \cdot w \cdot t \quad [eq.9]$$

Where D_o is the initial droplet diameter. This model predicts divergence of the diameter after a finite time τ given by:

$$\tau = \frac{3}{2\pi \cdot w \cdot D_D^2} \quad [eq.10]$$

According to this model, to maximize the stability of an emulsion against coalescence the initial droplet diameter D_o should be minimized.

4.3.4 Ostwald Ripening

Ostwald ripening is an emulsion destabilizing mechanism that consists of a diffusive transfer of the dispersed phase from the smaller droplets to the larger ones due to their internal pressure (Laplace pressure) difference.

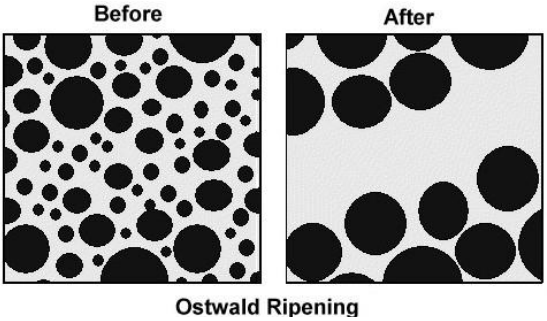

Figure 12: Ostwald Ripening.

LIfshitz, Slezov and Wagner stated that the speed or rate of droplet enlargement due to Ostwald Ripening can be determined using the following expression:

$$w = \frac{dac^3}{dt} = \frac{8c(\infty) \cdot \gamma \cdot D \cdot V_m}{9RT} \cdot f(\phi) \quad [eq. 11]$$

Where t is the time, a_c is the average droplet radius, D is the molecular diffusion coefficient of the dispersed phase in the continuous one, V_m is the molar volume of oil, γ is the interfacial tension, $c(\infty)$ is the molecular solubility of the dispersed phase in the continuous one and $f(\phi)$ is a correlation factor that accounts for the dispersed volume fraction that equals 1 when Φ tends to 0.

As seen in eq. 11, to provide an emulsion with maximum stability against droplet enlargement due to Ostwald Ripening, the average droplet radius should be minimized and the dispersed phase volume fraction Φ should be as low as the product selected microstructure allows.

4.4. RHEOLOGY

While the primary concern when developing a formulated product is always functionality (in this work biocidal efficacy, emulsion stability and moisturizing properties), perception-related quality factors such as ease of application, appearance and texture among others are often crucial in consumer satisfaction. Most of the previously mentioned perception-related quality factors depend on the rheology of the product, in this case, a hand sanitizing and moisturizing lotion (liquid-like cream). So, it becomes important to translate this perception-related quality factors into rheological requirements.

Although psychophysical models relating rheological and sensorial attributes have been developed (Breuer, 1993), the use of experimental heuristics such as the ones summarized in the following list (Christianto Wibowo and Ka M. Ng, 2001) are still the preferred method of specifying these characteristics.

- Can be poured easily
- Spreads easily when rubbed on the skin
- Does not flow readily under gravity but easy to stir
- Should give a uniform coating when applied to a surface
- Should not flow by itself but can be squeezed out of a container
- Feels smooth
- Does not feel oily
- Appears transparent, opaque or pearlescent
- Does not cause irritation

For the product being developed in this work the following perception-related quality factors have been determined and categorized in two main groups:

EASE OF APPLICATION	SENSORIAL PERCEPTION
Spreads easily when rubbed on the skin. Should not readily flow by gravity but can be easily poured out of a container.	Feels smooth. Does not feel oily. Appears transparent.

Table 5: Selected perception-related quality factors for the product.

Spreads easily when rubbed on the skin:

The most important factors that determine the ability of the product to be easily spreadable are its rheological behavior, its viscosity in repose and its viscosity at the application shear rate (Christianto Wibowo and Ka M. Ng, 2001).

According to (Miner, 1993) for a lotion to be easily spreadable it should have low viscosity at high shear rates (when applied) which mean it should present a pseudo-plastic (also known as shear-thinning) rheological behavior.

Two of the most popular models to describe pseudo-plastic behavior are the power law or Herschel-Bulk-Ley model and the stretched exponential model (Barnes, 1997).

For a pseudo-plastic (shear-thinning) behavior ($n < 1$) the Herschel-Bulk-Ley model allows to determine the final viscosity μ_∞ according to the following expression:

$$\mu_\infty = \frac{\tau_o}{\gamma} + K \cdot \gamma^{n-1} \qquad [eq.12]$$

Where τ_o is the yield value, γ is the shear rate and K is the pre-exponential factor of a non-Newtonian fluid viscosity.

The stretched exponential model describes the change of viscosity with time after a variation of an applied shear rate and for a pseudo-plastic (shear-thinning) behavior ($n < 1$) the viscosity μ can be expressed as:

$$\mu = \mu_\infty + (\mu_o - \mu_\infty) \cdot \left\{1 - exp\left[-\left(\frac{t}{t_r}\right)^a\right]\right\} \qquad [eq.13]$$

Where μ_∞ and μ_o are respectively the final and initial viscosities, t is the time, t_r is the relaxation time and a is a dimensionless constant.

Due to the hand sanitizing and moisturizing lotion being developed in this work is an oil in water emulsion, the viscosity can also be determined according to its dispersed phase volume fraction ϕ.

- For dilute emulsions with $\phi < 0{,}62$ (Krieger and Dougherty, 1959)

$$\mu_e = \mu_c \cdot \left(1 - \frac{\phi}{\phi_{crit}}\right)^{-k \cdot \phi_{crit}} \qquad [eq.14]$$

Where μ_e is the emulsion's viscosity, μ_c is the viscosity of the continuous phase, ϕ_{crit} is the critical dispersed phase volume fraction and k is a dimensionless constant.

- For dilute emulsions with $\phi < 0{,}70$ (Pal, 1995)

$$\mu_e = \mu_c \cdot \left[1 + \frac{(5k+2)}{2\cdot(k+1)} \cdot \phi + \frac{(5k+2)^2}{10\cdot(k+1)^2} \cdot \phi^2\right] \cdot \left[\frac{1 + \lambda_1 \cdot \lambda_2 \cdot N_{Ca}^2}{1 + \lambda_1^2 \cdot N_{Ca}^2}\right] \qquad [eq.15]$$

$$\lambda_1 = \frac{(19k+16)\cdot(2k+3)}{40\cdot(k+1)} \cdot \left[1 + \frac{(19k+16)}{5\cdot(k+1)\cdot(2k+3)} \cdot \phi\right] \qquad [eq.16]$$

$$\lambda_2 = \frac{(19k+16)\cdot(2k+3)}{40\cdot(k+1)} \cdot \left[1 - \frac{3\cdot(19k+16)}{10\cdot(k+1)\cdot(2k+3)} \cdot \phi\right] \qquad [eq.17]$$

Where k is the viscosity ratio and N_{Ca} is the capillary number.

- For concentrated emulsions $\phi > 0{,}74$ (Princen and Kiss, 1989)

$$\mu_e = \frac{\tau_o}{\gamma} + C(\phi) \cdot \mu_c \cdot N_{Ca}^{-0,5} \qquad [eq.18]$$

$$N_{Ca} = \frac{\mu_c \cdot d_p \cdot \gamma}{2 \cdot \sigma} \qquad [eq.20]$$

$$C(\phi) = 32 \cdot (\phi - 0{,}73) \qquad [eq.21]$$

Where d_p is the droplet diameter and σ is the interfacial tension.

According to (Brummer and Godersky, 1999) for a lotion (liquid-like cream) the maximum viscosity in repose should be between 120-500 $Pa \cdot s$ and 0,025 $Pa \cdot s$ at the application shear rate (500 s^{-1}).

To determine the viscosity at a given shear rate the shear modulus G must be considered. The shear modulus gives the relation between the shear stress τ and the shear rate γ.

$$G = \frac{\tau}{\gamma} \qquad [eq.22]$$

- For dilute emulsions $\phi < 0{,}70$ (Oldroyd, 1953)

$$G^* = G_c^* \cdot \left(\frac{1 + 3\cdot\phi\cdot H}{1 - 2\cdot\phi\cdot H}\right) \qquad [eq.23]$$

$$H = \frac{\left(\frac{8 \cdot \sigma}{d_p}\right) \cdot (5 \cdot G_d^* + 2 \cdot G_c^*) + (G_d^* - G_c^*) \cdot (19 \cdot G_d^* + 16 \cdot G_c^*)}{\left(\frac{80 \cdot \sigma}{d_p}\right) \cdot (G_d^* - G_c^*) + (2 \cdot G_d^* + 3 \cdot G_c^*) \cdot (19 \cdot G_d^* + 16 \cdot G_c^*)} \qquad [eq.24]$$

Where H is the vessel height, G is the shear modulus, G_c^* and G_d^* are respectively the complex shear modulus of the continuous and dispersed phase.

- For concentrated emulsions $\phi > 0{,}74$ (Princen and Kiss, 1986)

$$G = 1{,}769 \cdot \mu_c \cdot N_{Ca}^{-1} \cdot \phi^{\frac{1}{3}} \cdot (\phi - 0{,}712) \qquad [eq.25]$$

Should not readily flow by gravity but can be easily poured out of a container:

According to (Miner, 1993), products that are not supposed to readily flow by gravity or appear runny but are easily poured out of a container should have a yield point between 10 to 15 Pa (Christianto Wibowo and Ka M. Ng, 2001).

The yield value is the point of a stress-strain curve that indicates the limit of elastic behavior and the beginning of plastic behavior.

- For concentrated emulsions $\phi > 0{,}83$ (Princen and Kiss, 1989)

$$\tau_o = \frac{26}{d_p} \cdot \phi^{\frac{1}{3}} \cdot Y(\phi) \qquad [eq.26]$$

$$Y(\phi) = -0{,}080 - 0{,}114 \cdot \log(1 - \phi) \qquad [eq.27]$$

Where τ_o is the yield value at a given dispersed phase volume fraction.

Sensorial perception

According to (Chappat, 1994), the most important factor to obtain a lotion that feels smooth, not oily when applied and appears clear, the droplet size should be between 1 to 20 μm ((Christianto Wibowo and Ka M. Ng, 2001).

5. PRODUCT FORMULATION

5. PRODUCT FORMULATION

After the quality criteria and quality indexes of the formulated product have been determined ad quantified, the compounds or ingredients that will form said product can be chosen and a formulation can be proposed.

5.1. BIOCIDAL AGENT

As described in chapter 4.1. and as shown in Table 1, the biocidal agent with a greater biocidal efficacy being able to outperform both EN 1500 and EN 12791 European standards for hygienic and surgical hand disinfection in Shorter application times than traditional surgical hand scrubs, is a mixture of 45% 2-propanol and 30% 1-propanol by weight.

5.2. MOISTURIZING AGENTS

As studied on chapter 4.2. the best moisturizing agent mixture presenting the best quality indexes on all tests performed (sensory testing, squamometry, desquamation index and skin conductance) is a glycerin rich lotion containing glycerin as a humectant, petrolatum as an occlusive agent and isopropyl palmitate as an emollient.

For the final formulation of the product, the use of squalene instead of petrolatum has been proposed due to its better skin compatibility, moisturizing efficacy and sensorial acceptance (G.S. Kelly, 1999).

According to G. Deckner current moisturizer formulation trends recommend:

- 5-20 % Humectant agents
- 5-15 % Emollients
- 2-5 % Occlusive Agents

With this information, the proposed moisturizing agent ratio by weight for the product being developed will be:

- 10 % Glycerin (continuous phase)
- 5 % Isopropyl palmitate (dispersed phase)
- 2 % Squalene (dispersed phase)

5.3. SURFACTANT

As discussed in chapter 4.3. surfactants have a crucial role in emulsion stability and formation. To determine which surfactant or mixture of surfactants should be used first the HLB required by the oil must be calculated.

In this case, the dispersed phase of the emulsion will contain 2 oils, squalene and isopropyl palmitate.

According to (Griffin, 1959) the global HLB of a binary mixture of oils can be determined using the following expression:

$$HLB = HLB_{Squalene} \cdot X_{Squalene} + HLB_{Isopropyl\ Palmitate} \cdot X_{Isopropyl\ Palmitate} \quad eq[28]$$

Where X is the mass fraction of each oil.

Which for the mixture being studied results in an HLB of 11,6.

To match the required HLB of the oil, a mixture of surfactants will be used and their proportion will be determined using eq. [28].

The chosen surfactants are glycerol monostearate (HLB=11) and polyoxyethylene (10) cetyl ether (HLB=13).

To achieve a global HLB of 11,6 the previously mentioned surfactants must be mixed in a ratio of 0,51 glycerol monostearate and 0,45 polyoxyethylene (10) cetyl ether by weight.

Finally, according to (Griffin, 1954) the total percentage of surfactant in the product should be between 2 to 4 % by weight.

5.4. THICKENER

Thickening agents or thickeners are substances which increase the viscosity and modify the rheological behavior of a mixture (in this case an emulsion) without substantially perturbing other properties.

In chapter 4.4. it has been determined that the product being developed should present a pseudo plastic (shear thinning) rheological behavior and its viscosity in repose (shear rate 0) should be between 120 and 500 $Pa \cdot s$.

From these two requirements, the type of thickening agent will determine the rheological behavior while its quantity will determine its viscosity.

In the following figure, some types of thickening agents and their rheological behavior have been represented:

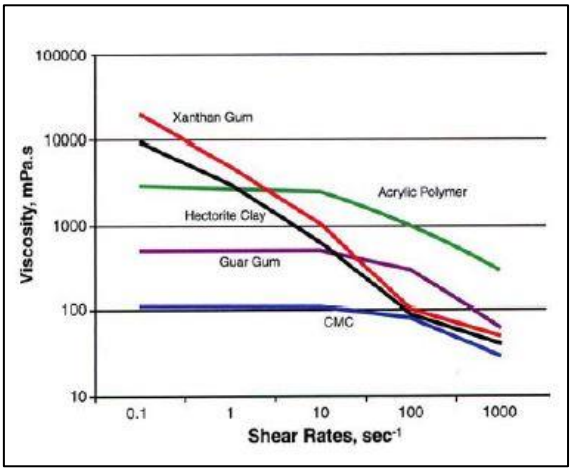

Figure 13: Rheological behavior of various thickening agents.

As shown in Figure 13, to achieve pseudo plastic (shear thinning) rheological behavior the best thickeners to use are Xanthan Gum and Acrylic polymers.

While xanthan gum exhibits an almost perfect pseudo plastic behavior, according to (J.J. Flahive III, A. Foufopoulos and M.R. Etzel, 2006) it precipitates in presence of high concentrated alcohols which means that is not suitable for the product being developed.

On the other hand, acrylic polymers also present pseudo plastic behavior while being compatible with hydro alcoholic solutions.

One of the most effective acrylic polymer thickeners are carbomers which are reticulated acrylic acid polymers that have great solubility in water and alcohol and in low concentrations and have great thickening ability (Remi Chauvin, 1995)

For the sake of this work, commercially available Carbopol 940NF carbomer has been chosen as a thickener. For this specific thickener its concentration to achieve a repose viscosity between 120-250 $Pa \cdot s$ should be between 1,5 and 4 % (Remi Chauvin, 1995).

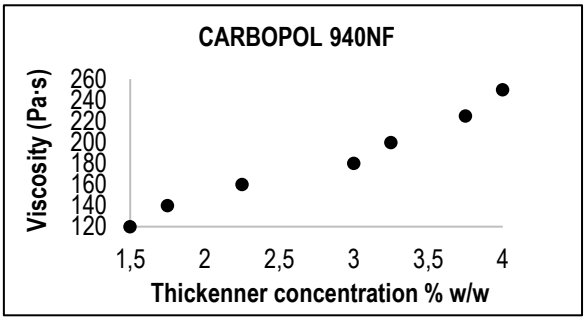

Figure 14: Viscosity at different thickener concentration values.

One particularity of carbomers is their sensitivity to pH, as shown in the following figure, Carbopol 940NF provides maximum viscosity when the pH is neutral (pH=7).

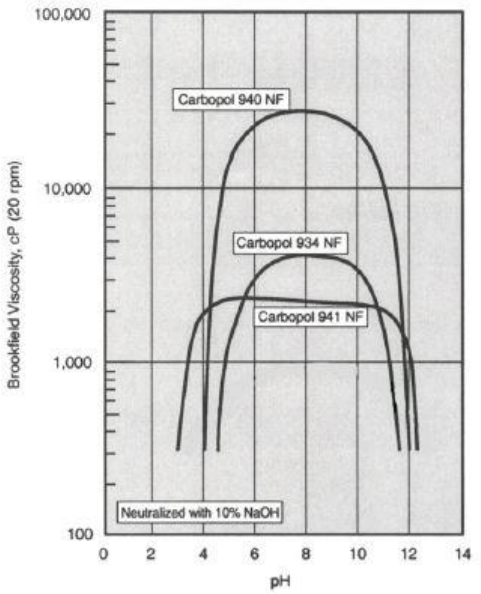

Figure 15: Viscosity of carbomers at different pH values.

This means that controlling the pH could be a great tool when manufacturing the product. Keeping the pH out of the optimum range of the carbomer i.e. keeping the viscosity at a minimum could allow much lower energy requirements and costs in the mixing and homogenization stages of the production process. Then after the mentioned energy and cost intensive stages the mixture would be neutralized until the desired viscosity is achieved.

With all of that in mind, and noting that in practice product formulations can be only definitely developed through trial and error and experimentation, a final formulation for the product being developed can be proposed:

Product	**100**
2-propanol	45
1-propanol	35
Glycerin	10
Polyoxyethylene (10) cetyl ether	1,5
Glycerol monostearate	1,3
Carbopol 940F	3,0
Squalene	2,0
Isopropyl palmitate	5,0
Water	2,2

Figure 16: Proposed final product formulation % by weight.

6. DESIGN OF A MANUFACTURING PROCESS

6. DESIGN OF A MANUFACTURING PROCESS.

After the product has been conceptualized, its quality criteria and indexes determined and quantified and a formulation has been proposed, the final stage of formulated product development is the design of a manufacturing process that for the product being developed will consist of two main stages:

- Process Flowsheet
- Equipment unit select

6.1. PROCESS FLOWSHEET

The proposed flowsheet (figure 17) can be dissected in 5 main stages:

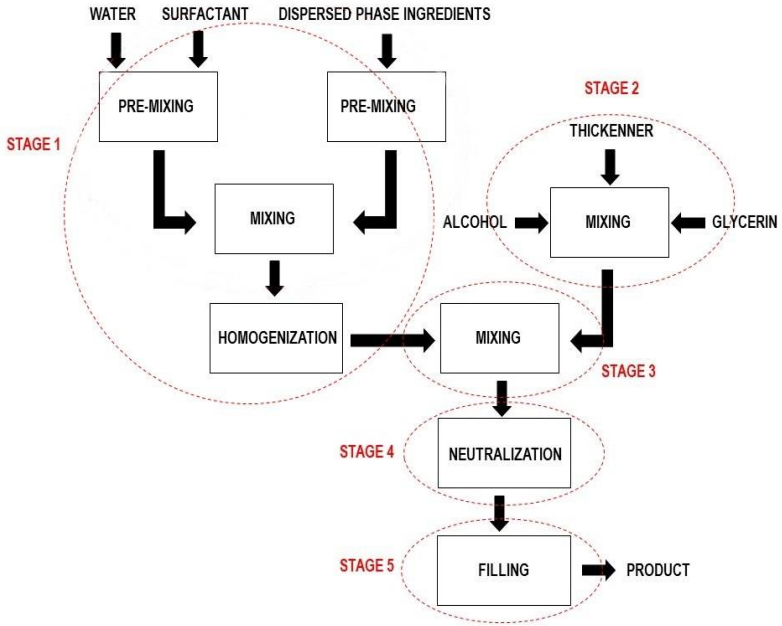

Figure 17: Process Flowsheet.

6.1.1. Stage 1: Pre- emulsion formation.

In this stage, a high internal phase pre-emulsion will be formed. To do so first, the dispersed phase ingredients (squalene and isopropyl palmitate) will be pre-mixed. At the same time, the surfactant will be pre-mixed with water (continuous phase). According to (Lin, 1968), placing the surfactant on the continuous phase will lead to the formation of an O/W emulsion with fine droplet size.

Then, the pre-mixed continuous and dispersed phase will be mixed together obtaining a pre-emulsion followed by a posterior homogenization to obtain the desired droplet size. Note that by adding all the surfactant to the continuous phase (Lin, 1968) the pre-emulsion will already have fine droplet leading to energy and cost savings in the mentioned homogenization stage.

6.1.2. Stage 2: Carbomer Hydration.

Being conducted in parallel of stage 1, in this stage the carbomer (thickener) will be hydrated by mixing it with the alcohol mixture (2-propanol and 1-propanol) and the glycerin. The mentioned hydration will be performed at pH values out of the optimum range of the carbomer to keep the viscosity to a minimum thus leading to energy and cost savings in the following mixing stage.

6.1.3. Stage 3: Final emulsion formation.

In stage 3 the final emulsion will be formed. This emulsion will be the result of diluting the high internal pre-emulsion formed in stage 1 with the mixed ingredients of stage 2. Due to the previous homogenization, said pre-emulsion will already have the desired droplet size which means that there will be no need to a second homogenization which would mean dealing with higher volumes thus increasing costs and energy consumption.

6.1.4. Stage 4: Neutralization.

Once the final emulsion has been formed, the viscosity will have to be increased to the desired value. To do so, the emulsion will be neutralized allowing the thickener to provide its maximum viscosity. This stage is quite useful as this pH depending viscosity could mean that some batches of the product could be produced with higher thickener concentrations and stored at higher than

desired viscosities thus increasing its stability and shelf life. Then when the time would come to be commercialized they could be brought back to the desired viscosity by modifying their pH.

6.1.5. Stage 5: Filling.

In this final stage the product would have to be packaged in this case filled in its final commercialization containers that as discussed in chapter 3 would be 500 ml pump cap bottles and 1L sealed sachets.

6.2. EQUIPMENT UNIT SELECTION

In the proposed manufacturing process, the main stages or unit operations that would require equipment units are:

- Mixing
- Homogenization

6.2.1. Mixing:

For the mixing stages, the most cost-effective equipment unit (figure 18) would be and agitated vessel. As the name implies this units consist of a vessel with an agitation system comprised by a motor and an impeller.

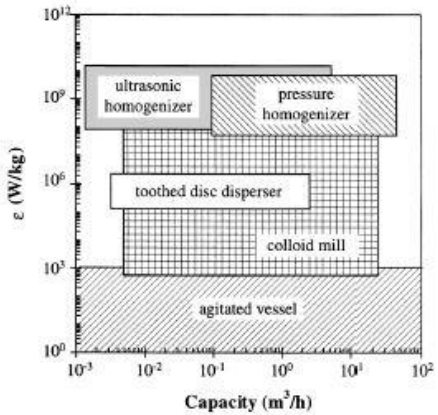

Figure 18: Capacity and energy consumption of equipment units.

According to (Zwietering, 1958) the design equations for this units are:

$$\epsilon_{av} = C_4 \cdot N^3 \cdot D^2 \cdot N_p \qquad [eq.29]$$

Where ϵ_{av} is the average power density, N is the rotational speed, D is the impeller diameter, N_p is the dimensionless power number that depends of the agitation Reynolds number and the impeller geometry and C_4 is a dimensionless constant that can be calculated with the following expression:

$$C_4 = \frac{4}{\pi} \cdot \left(\frac{D}{T}\right)^2 \cdot \left(\frac{D}{H}\right) \qquad [eq.30]$$

Where T and H are the diameter and height of the vessel.

Additionally, the critical impeller speed for complete suspension N_{cs} can be determined with the following expression:

$$N_{cs} = C_5 \cdot \left(\frac{\mu}{\rho_L}\right)^{0.1} \cdot d_p^{0.2} \cdot \left[\frac{g \cdot (\rho_s - \rho_L)}{\rho_L}\right]^{0.45} \cdot D^{-0.85} \cdot X^{0.13} \qquad [eq.31]$$

Where C_5 is a dimensionless constant, μ is the viscosity, d_p is the droplet diameter and X is the weight factor of solids in suspension.

6.2.2. Homogenization:

For the homogenization stage, the most cost-effective equipment unit (figure 18) would be a colloid mill.

Colloid mills are equipment units that are commonly used in industry to reduce droplet size and homogenize emulsions. The operate on the rotor-stator principle in which a rotor turns at high speeds (2000-18000) rpm forcing the emulsion through the gap between the mill walls and the rotor creating high levels of hydraulic shear that in turn disrupt the droplets breaking them in smaller ones.

According to (Wieringa et al, 1996) the design equations for a colloid mill are:

$$\gamma = \frac{2\pi \cdot N \cdot R_r}{b} \qquad [eq.32]$$

Where γ is the shear rate, N is the rotational speed, R_R is the colloid mill rotor radius and b is the gap width of the colloid mill.

$$N_{Fa} = \frac{2\pi \cdot N \cdot \rho_e \cdot R_R^{0.5} \cdot b^{1.5}}{\mu_e} \qquad [eq.33]$$

Where N_{Fa} is the dimensionless fragmentation number, ρ_e is the emulsion's density and μ_e is the emulsion's viscosity.

7. CONLUSIONS

7. CONCLUSIONS.

While the nature of this work is purely bibliographical, numerous conclusions, facts and taken decisions related to the development of the product can be summarized as it follows:

In the context of nosocomial infection prevention, the need of a hand sanitizer with moisturizing properties to minimize and or eliminate skin compatibility issues of traditional formulations has been identified.

The optimum product microstructure has been determined as a hydro-alcoholic hand lotion, more specifically an O/W emulsion as it is the preferred way of delivering the hydrophilic and lipophilic active ingredients of the product.

The main quality factors of the developed formulated product have been identified as: biocidal efficacy of the sanitizer, moisturizing capabilities, emulsion stability and rheology.

By quantifying said quality criteria through the study of properly chosen quality indexes it has been determined that:

- The most effective biocidal agent for the product is a mixture containing 45% 2-propanol and 30% 1-propanol by weight, being able to meet and even outperform EN1500 and EN12791 levels of biocidal efficacy for hand and surgical disinfection in shorter application times than traditional hand rubs.
- According to several skin hydration tests such as sensory testing, squamometry, desquamation index and skin conductance it has been determined that the most effective moisturizer mixture is one containing glycerin, isopropyl palmitate and petrolatum substituting the latter by squalene due to tis greater skin compatibility and more appealing sensory perception.
- Having studied the main emulsion destabilization mechanisms it has been determined that the viscosity of the continuous phase, the choice of surfactant (in this case a mixture of 51% glycerol monostearate and 45% polyoxyethylene (10) cetyl ether by weight) and the droplet size have great effect on the emulsion stability and in turn on the stability and shelf life of the product being developed.

- It also has been determined that the rheology of the product plays a major role to achieve optimum perception-related quality factors such as ease of application, appearance and sensorial perception. To do so, the product should present a pseudo plastic (shear-thinning) rheological behavior (in this case by using a carbomer as a thickener), its viscosity in repose should be between 120-500 $Pa \cdot s$ dropping to 0,025 $Pa \cdot s$ at the application shear rate (500 s^{-1}), should have a yield point of 10 to 15 Pa and the droplet size should be between 1 and 20 μm.

- Finally, a cost conscious and energy saving manufacturing process has been proposed including a process flowsheet (figure 17) in which the main unit operations and their order have been indicated and the necessary equipment units have been proposed to be an agitated vessel for the mixing operations and a colloid mill for the homogenization ones.

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