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Review Paper

Pre-Formulation Study on The Preparation of Skin Cosmetics

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Abstract
Cosmetics have been a trend necessary for all people. The increasing need of the community in the use of cosmetics becomes the basis of the formulation of this article. Pre-formulation study for cosmetics is important to ensure that the final preparation of the cosmetics is safe to use and has maintained quality. A pre-formulation study for cosmetics is a study of physicochemical characteristics associated with the substances used in the formulation of cosmetics preparation to produce a quality cosmetic product. The pre-formulation study described here includes evaluation of sensitivity and irritability, organoleptic, formulation compatibility, thermal effect, partition coefficient, stability, particle size, wettability, hygroscopicity, type of preparation, and pH. This review article is compiled by searching for literature associated with the topic studied. Taken together, this review suggests that the pre-formulation study described recommended to be performed during the information searching step related to the physicochemical properties of ingredients used for cosmetic preparations. All of the topic studied is beneficial to determine the quality of the ingredients within the preparation before formulation, therefore, the production of cosmetic preparation can be more effective because it directs the choice of ingredients and optimum ingredient composition.

Keywords
Cosmetics, Topical, Physicochemical Properties, Pre-Formulation, Quality, Evaluation

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1. INTRODUCTION

Pre-formulation studies are not only important for medicinal preparations but also for cosmetics. Currently, pre-formulation studies related to cosmetic preparations, especially skin cosmetics, have not been widely compared to studies on drug pre-formulation. So far, no pre-formulation reviews discussing cosmetics have been published. The design of an appropriate skin cosmetics preparation requires pre-formulation studies to consider the physical, chemical, and biological characteristics of the materials that will be used to make cosmetic products. With the review regarding the pre-formulation study on skin cosmetics preparations, readers will find it easier to obtain various information related to cosmetic pre-formulation and get a better understanding of the various studies that have been reviewed. This review examines various aspects of cosmetic pre-formulation so that it is expected to be able to provide benefits as a consideration in preformulating specifically on cosmetics, thereby capable of producing optimal cosmetics and providing a thorough understanding.

The desire to always look attractive has become a trend in today's society. Through an attractive appearance, someone may increase self-confidence. Cosmetics are chosen to support one's performance. However, in reality there are many cosmetic products that can actually endanger the users. Studies showed that the hazardous material in cosmetics may lead to cases of breast cancer (Cardoso et al., 2016). On a mild scale, allergies caused by the use of harmful cosmetics irritate the skin of the user (Khan and Alam, 2019). Therefore, screening the ingredients of cosmetic products before use is an important step. This work is expected to become a basis for producers in making cosmetics to determine what aspects that need attention. Pre-formulation studies can be carried out before the cosmetic manufacturing process to ensure the feasibility of a safe product for long-term use.

1.1 Cosmetics

Recently, cosmetics have been a necessity for men and women. The need for cosmetics is often associated with the assumption relating to physical attractiveness. In general, cosmetics are ingredients used to adorn the face area such as cheeks, lips, even the eyes. They contain many chemical ingredients that can skin contact, enter the body through inhalation, or, for lipsticks, accidentally swallowed (Park et al., 2015). Daily use of cosmetics may lead to a local skin problem, which is a systemic effect from the absorption of those chemical ingredients into

the skin (Mesko et al., 2020). The need for cosmetics in all kinds of people resulted in cosmetic manufacturers compete to gain a place in the market. However, many manufacturers produce cosmetics not up to standard. Continuous use of harmful cosmetics can jeopardize health.

1.2 Preparation of Topical Cosmetics

If used as a cleanser, to beautify the skin or hair seen from the perspective of esthetics, then preparation is called cosmetics. However, if the objective is not only to beautify, but also affect the body therapeutically, then it is considered a drug. The FDA (Food Drug Administration) has explained that cosmetics are different than drugs. A drug is a substance, or a combination of substances, intended for the diagnosis, alleviate, cure or prevent a disease or to affect the function of the body. Meanwhile, cosmetic is a substance, or a combination of substances, used smeared, poured, dipped, sprayed, or inserted into or on the body to clean, beautify, increase attractiveness, or improve the appearance without affecting the structure or function of the body (Turnbull, 2018).

The topical formulation is aimed to target skin uses in various cosmetics, protection, and therapeutical use (Hadgraft and Lane, 2016). Most cosmetic preparations are formulated through emulsification. However, this method is thermodynamically unstable. Polymers, carbomers or fatty alcohol are added to the cosmetic to stabilize the preparation. Any damage to the preparation can change the composition of the cosmetics and cause health problems and reduce product appeal. The use of preservative and antimicrobial agents can be an alternative to cope with this problem. Although many preservatives work on the microbial cell membrane, the mechanism can affect the stability of the cosmetic, thus the addition of preservatives should be considered (Hayase, 2017).

1.3 Anatomy of the Human Skin

Skin is an organ with important functions to the body, including protection, thermoregulation, and immune response. The cross-section of human skin anatomy can be seen in Figure 1. The outer skin layer is an epidermis, a tissue that continuously undergoes regeneration. Epidermal regeneration occurs because the epidermis does not contain vascularization, thus no nutrition to maintain tissue survivability. There are five layers of the epidermis. The order from the outer layer to the inner layer is the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and germinative or basal layer (Karadzovska et al., 2013; Mathes et al., 2014; Notman and Anwar, 2013). The cells in the stratum corneum are known as corneocytes. These cells are solid, functionally dead, nucleated, and filled with keratin. The composition of the stratum corneum is analogous to the wall of "brick and mortar". The inner structure, the lipid cells in between are like mortars and corneocytes are like bricks. Lipid forms several bilayers arranged surrounding the corneocytes. Between lipid, cells lie a combination of cholesterol, ceramide, fatty acid, cholesteryl ester, and a small amount of cholesterol sulfate (Anissimov et al., 2013; Barry, 2001; El Maghraby et al., 2008; Hansen et al., 2013). The stratum corneum is composed of 15 to 20 layers of corneocytes. In a dry state, it has a thickness of 10 to 15 µm. While hydrated, the stratum corneum swells and can reach 40 µm, which showed increased permeability. This provides a characteristic of barrier and resistance to water. The corneum layer is known as the main layer restricting the absorption of chemical substances through the skin (Anissimov et al., 2013; Cevc and Vierl, 2010; El Maghraby et al., 2008; Hansen et al., 2013). There is a study that the elevation of stratum corneum drastically increases skin permeability, while the elevation of all epidermis increases skin permeability to 1 to 2 times. Therefore, each layer of the skin affects permeability to a certain degree (Andrews et al., 2013).

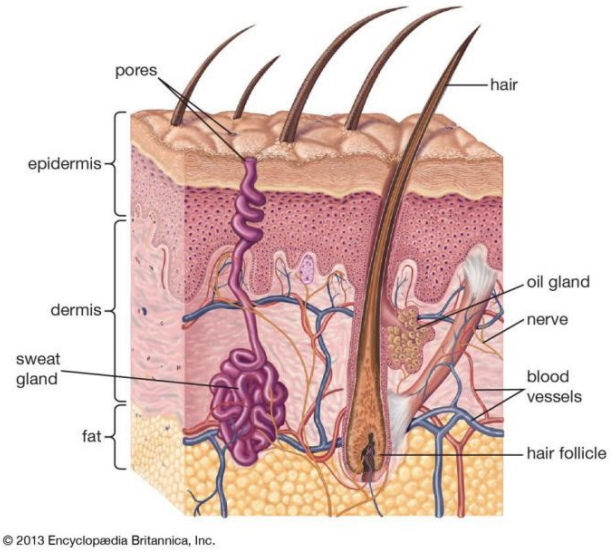

Figure 1. Cross-section of the Human Skin (Waugh and Grant, 2014)

Figure 2 describes the structure of the skin anatomy (the middle figure is a 3D structure of human skin episcopically). Hypodermis (white); reticular dermis (yellow); papillary dermis (blue); epidermis (pink). The scale bar represents 200 μm. Figure 2(a) Skin surface topography in a different part of the body. The form of different skin subunits. (i) the volar surface of the finger, (ii) back of the hand, (iii) stomach. Figure 2(b) (i) Illustration of the epidermis; formation of hexagonal-shaped corneocytes group from the basal epithelia replication. (ii) Cross-section through the human epidermis. Ceramide-rich epidermal layer looks clear above and the dermis looks white because of high collagen. Figure 2(c) (i) skin cross-section to the reticular dermis level. (ii) An episcopic image of the dermis showed intertwined orientation of collagen fibers. The scale represents 200 μm. Figure 2(d) Flexible and lose microvacuolar collagen tissue. Figure 2(e) Hypodermal fat image as seen through different images. (i) Hypodermal fat as seen from endoscopic surgery in living tissues that shows yellow lumps of fat. (ii) hypodermal fat as seen from excitation of two fluorescence

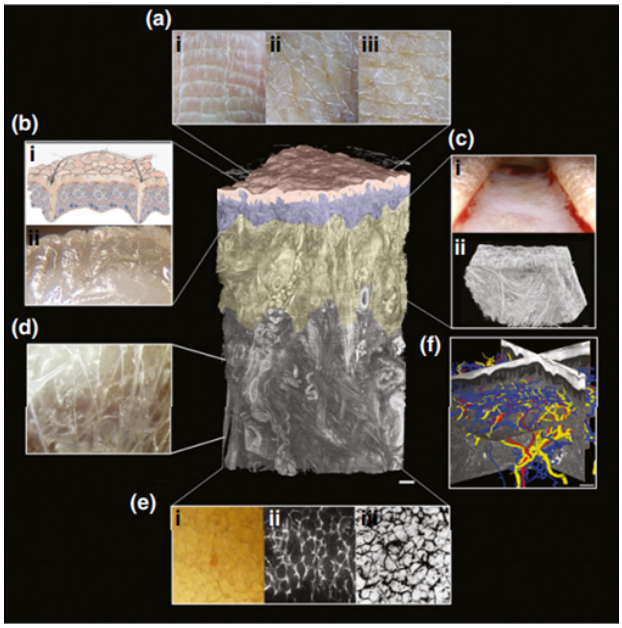

Figure 2. Anatomy of the Human Skin Episcopically (Wong et al., 2016)

photons which shows fibroelastic fibers. (iii) Hypodermal fat as seen from lymphatic injection using India ink. Figure 2(f) 3D image from skin vascularization using episcopy.

2. PRE-FORMULATION OF COSMETICS PREPARATION

2.1 Sensitivity Test and Irritability

Dermatitis contact allergy (DCA) is a hypersensitivity reaction caused by repeated exposure to irritable cosmetics ingredients. The ability of cosmetic ingredients to irritate the skin is often tested on animals (Vukmanović and Sadrieh, 2017). One of the safety assessments of cosmetics is the irritation test, which is performed before use on humans to prevent hypersensitivity reactions. A cream base can cause adverse effects on the skin, including primary irritation, sensitization reaction, photoallergy, and phototoxicity. Skin irritation is an inflammatory process mediated by non-immune factors. This can be observed subjectively or objectively. The test can be performed in vivo on living skin, in certain areas or conditions of humans (Vinardell and Mitjans, 2008).

The ability to irritate skin from a cosmetic preparation can be tested with a primary skin irritation test. A male rabbit aged 2-4 months, healthy, and without wounds can be chosen. The back fur can be trimmed to 2.54 x 2.54 cm and marked by a marker, then left for 24 hours. Before administration of cosmetic, the skin is cleaned with distilled water and cotton, then 0.5 grams of cosmetic is applied and covered with sterile gauze and let stand for 24 hours. Observation includes indicators of irritation, erythema, and edema for 24, 48, and 72 hours (Wu et al., 2009).

An old paradigm considered in vivo test on genotoxicity has a dependency on animal models. The most recent regulation in Europe, such as the 7th amendments to the Guideline of Cosmetics, prohibits the use of in vivo genotoxicity tests. Furthermore, programs such as Registration, Evaluation, Authorization, and Restriction of Chemical Substances (REACH) in Europe heavily relies on in vitro model, which has several advantages, including cheaper and time saving compared to in vivo method (Mun et al., 2009). In a cosmetic pre-formulation test on substances with the potential to irritate the skin, might be available as raw material impurities or a byproduct from the manufacturing process of the cosmetic. The most common allergic reaction is due to fragrance and preservatives contained in a product (Peiser et al., 2012).

The prevalence of individual sensitivity toward an allergen can be increased with use. For example, individuals who often use cosmetics that contains nickel have an increased risk of allergy (Nguyen et al., 2008). DCA is a delayed-type hypersensitivity reaction, in which the development follows a phase of afferent (often known as sensitization or induction) maturation of skin dendritic cells, involving activation and migration to the lymph glands, which stimulates antigen-specific T-cells (Vocanson et al., 2009). A study developed a method of in vitro T-cell essay as an alternative to test for metal content to substitute for the use of animals. This test is based on the understanding of said mechanism (Vukmanović and Sadrieh, 2017).

Basketter et al. (2014), classified ingredients that can induce skin sensitivity into 6 categories. This was obtained from a literature study concerning several data and reports on specific ingredients that affected skin sensitivity. Table 1 describes the reason for the classification. This can be the basis to form inclusion criteria for ingredients that need skin sensitivity tests due to the possibility to cause DCA.

Currently, there are five methods approved for in vitro assay development, substituting the use of animal models. First, the Direct Peptide Reactivity Assay (DPRA) is a chemical testing method that targets key events (KE) 1 (a covalent bond with skin protein) with the calculation of reduction of peptide synthesis. Second, KeratinoSens™ in vitro test, which is based on the activation of Keap1-Nrf2-ARE pathway that targets KE2 (keratinocyte response). There are three in vitro tests based on the measurement of dendritic cell activation biomarker, which targets KE3 (dendritic cell activation), which are the human cell line activation test (h-CLAT) on human cell line, U937 cell line activation test (U-SENS™), and Luc test on IL-8. It should be noted that although efforts have been given to conduct tests without animals, there is no available method to target the KE4 test, which is related to T-cell proliferation to assess skin sensitivity (Hoffmann et al., 2018).

2.2 Organoleptic

The organoleptic parameter of cosmetic ingredients is evaluated using observation on the aspects of visual, color, odor, and touch sensitivity (Oliveira et al., 2017). An organoleptic is a test based on the sensing process. Sensing means reaction or stimulus that provides an impression of an object (Ana

Table 1. Ingredients that cause Skin Sensitivity and their Degree (Basketter et al., 2014)

Category	Clinical Data	Example of Substance
1	The group with the highest potential of causing skin sensitivity. Testing data on human (no observed effect level [NOEL]) was taken to induce sensitivity with the human repeated insult patch test (HRIPT)	Dinitrochlorobenzene, methylchloroisothiazolinone (MCI) /methylisothiazolinone, and p-phenylenediamine)
2	The group with a lower potential than the first category. Use in high concentration and intensity can cause higher sensitivity risk	Formaldehyde, isoeugenol, methyldibromo glutaronitrile
3	This group contains a substance generally known as an allergen, however, its use in lower concentration only resulted in minor effects	Abietic acid, eugenol, imidazolidinyl urea
4	This group rarely cause allergy. An adverse effect may occur from long-term use	
5	This group has a very low chance to cause sensitivity, except in certain conditions, such as topical routine use	Hexylcinnamal, isopropanol, propylene glycol
6	This group has no clinical evidence of causing skin sensitivity	Xylene, glycerol, sodium lauryl sulfate

et al., 2017). Several studies indicated that an organoleptic study is conducted on several panelists who understand the characteristics of the preparation to be made. The panelists were given a form containing the characteristics of the preparation and asked to provide an assessment within a certain range (Benvenuti et al., 2016; Góral et al., 2018).

Organoleptic testing is a simple test and describes the daily condition of the user of the preparation. This test does not require extra equipment and offers a low cost. The main disadvantage of this method is low reproductivity because of inter- and intra-examiner variability. This can be overcome with training and calibration of the chosen examiners (De Mesquita-Guimarães et al., 2017). Cosmetic preparation must have a good organoleptic character because it is highly related to user acceptability.

2.3 Formula Compatibility

To maintain the property and final product of cosmetic preparation, compatibility must be an aspect to be considered in the formulation to produce a final product that fulfills an esthetic function, maintain the chemical substances, microbiological and physical properties within the preparation (Bogdan et al., 2019). Compatibility tests between cosmetic ingredients can be performed using the Fourier Transform Infra-Red (FT-IR) method. FT-IR test can be performed by comparing the FT-IR spectrum of a single ingredient with the combination of the ingredient with other substances (Sharadha et al., 2020). From the result of FT-IR, we can analyze the correlation between the components used, whether they are compatible or not. If the peak of the spectrum from a single ingredient is stable after added to other ingredients, then those ingredients are compatible. Several aspects such as molecular weight, solution concentration, temperature, salinity, and pH can also affect compatibility (Song et al., 2020).

There is a study that tested the compatibility of ingredients using the FT-IR method, as described in Figure 3 (Pramod et al., 2015). The image showed that the compatibility between ingredients can be seen by comparing the spectrum of a single ingredient with the combination of said ingredient with other substances and showed a stable result with no interaction between components. The result of FT-IR produces more information if combined with the DSC technique (Fernandes et al., 2009).

2.4 Thermal Effect

In cosmetic pre-formulation, a thermal effect analysis is performed on the compatibility of ingredients as components used in the formula. The test is conducted using a Differential Scanning Calorimeter (DSC) by inserting samples to a tightly closed aluminum pan heated at a certain temperature and rate under a nitrogen atmosphere. The melting point of the ingredients is observed as an endothermic peak in each thermogram of certain temperatures. Based on the results, there is only a physical combination of components without interaction during contact, or they interact with each other (Sharadha et al., 2020). Furthermore, thermal effect pre-formulation on the ingredients can be used to determine the temperature effect on the degradation rate of ingredients in cosmetic preparation using the Thermogravimetric (TGA) analysis (Kuehl et al., 2009). DSC and TGA thermal analyses can be conducted simultaneously using a Differential Thermal Analysis (DTA) (Lima et al., 2018).

The thermogram of cosmetic ingredients can be seen using DSC and TGA. The endothermic and exothermic peaks are

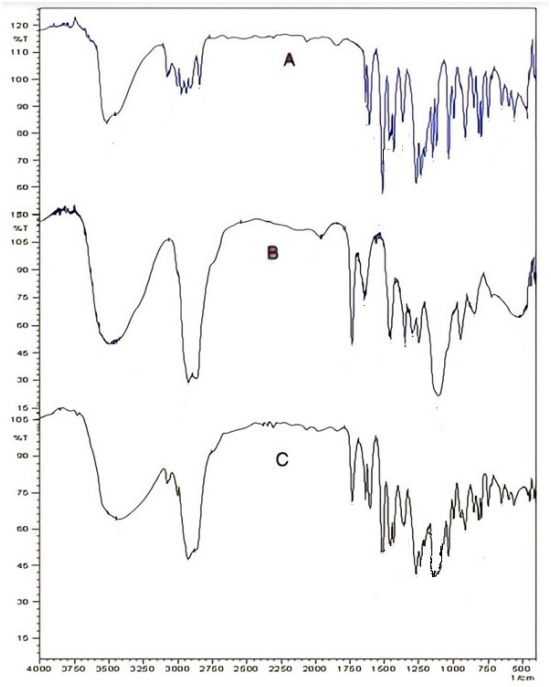

Figure 3. FT-IR Spectra. Spectra A = Eugenol, Spectra B = Tween 80, Spectra C = Combination between Tween 80 and Eugenol

obtained due to melting, decomposition, or loss of sample moisture. In DSC, the extent of the peak shows the loss of crystallinity (Mahant et al., 2020). Another study indicated that the thermogram of a microsponge using curcumin was similar to the formulation of an empty micro sponge (Arya and Pathak, 2014). This showed a loss of a prominent peak, which indicated uniform molecular dispersion within the microsponge.

2.5 Partition Coefficient

Partition coefficient determination in cosmetic pre-formulation studies was conducted to select ingredients with desired permeability to prepare the topical formulations. The partition coefficient testing can be explained using a shake-flask method (De Mello et al., 2004). Glutathione (GSH) is a broad antioxidant of the thiol-tripeptide group, highly hydrophilic, which has limitations for topical preparations. Nugrahaeni et al. (2018) determine the apparent partition coefficient of glutathione; glutathione with additional surfactant at different HLB values of HLB 4.3; 5.5; 7; 11 and the result is glutathione with surfactant HLB 7 has the highest log P of 2.23, the penetration test results can decreased MMP-1 expression therefore it is recommended to use efficiently as a topical agent.

The partition coefficient pre-formulation was performed on a new molecule with the structure of (3)-2-(4-tert-butylbenzylidene) hydrazinecarbothioamide (QNT3-18) and 4-tertbutylphenylthiourea (QNT3-20) that suspected to inhibit melanogenesis through the tyrosinase inhibition. The partition coefficient (log P) value of the quotient between water and octanol concentration from QNT3-18 and QNT3-20 molecules is 3.9 and 2.6, respectively. This showed that QNT3-18 had more hydrophobicity compared to QNT3-20. Therefore, QNT3-18 diffused more into the skin than QNT3-20 (Ki et al., 2013).

Pre-formulation studies of N-nitrosodiethanolamine (NDELA), an impurity in many cosmetic products has been evaluated. NDELA penetrated slowly through human skin when applied either in water or propylene glycol vehicles because of slow diffusion through the stratum corneum of a molecule that is very polar because of the 2 hydroxy groups. When NDELA was applied in a more lipoidal vehicle, isopropyl myristate, the rate was markedly enhanced due to a more favorable partitioning into the membrane of the stratum corneum. The partition coefficient increases proportionately in isopropyl myristate. Other lipoidal vehicles presumably would also give enhanced percutaneous absorption of NDELA (Bronaugh et al., 1981).

2.6 Stability

A stability study must be conducted on cosmetic preparation before formulation. The stability of the ingredients used in cosmetic preparations should be considered. For example, a cosmetic that contains quercetin in anionic emulsion with low lipid content and non-ionic emulsion form with high lipid content were subjected to antioxidant potential stability test. The raw ingredient (quercetin) and preparation with or without quercetin were stored at 4 °C, room temperature, and 40 °C for 180 days (6 months). For the baseline, 24 hours, 30, 60, 90 and 180 days, the samples were collected to evaluate the stability of antioxidant activity with DPPH. The result of the quercetin pre-formulation test showed a stable result in the antioxidant function aspect (Casagrande et al., 2007).

There was a pre-formulation study in the form of a stability test on liquid preparation with pH and temperature variation and biological fluid (Sassi et al., 2011). Another study tested pre-formulation using photostability and decomposition of arbutin, which is a natural skin whitening ingredient (Couteau and Coiffard, 2000). Arbutin showed good photostability, although its decomposition is 4 times higher in alkaline pH (around 9) compared to acidic pH (around 5).

To determine the optimal emulsifier concentration that can affect the stability of cosmetics with liposome-encapsulated stem cells of plants, an experiment was conducted to determine CMC and its behavior in a binary phase system. The behavior of CMC was observed to further determine the interaction between emulsifier and vesicle. The result showed that in the first binary system (BS1), anisotropic behavior was not recorded. This sample seems to contain an isotropic structure, most likely mixed surfactant micelles, which cannot be observed under a polarization microscope. This system is a 7-day isotropic solution after preparation and did not change in appearance after 30 days. However, the polarization micrograph of BS2 showed anisotropic structure-a crossing that describes lyotropic interaction dependent on the concentration of lamellar type (Couteau and Coiffard, 2000).

A pre-formulation study with accelerated stability was per-

Table 2. Examples of Stability Tests on Topical Cosmetic Preparations

No	Form of Formulation	Stability Parameter	Reference
1	Anionic emulsion with low lipid content and non-ionic emulsion with high lipid content	Antioxidant stability	(Casagrande et al., 2007)
2	Topical microbicide product	Stability in liquid with variation in pH, temperature, and biological fluid	(Sassi et al., 2011)
3	Arbutin can be used as a whitening agent in various formulas at room temperature	Photostability and decomposition of ingredients	(Couteau and Coiffard, 2000)
4	Cosmetics with liposome -encapsulated stem cells of plants	Optimal emulsifier concentration that can affect the stability	(Filipović et al., 2016)
5	Cream with fenticonazole	Rate and oxidative degradation kinetic	(Noaman et al., 2016)

formed to determine the stability of a cream preparation with Fenticonazole (FEN) that used different antioxidants to test its effect on the rate and oxidative degradation kinetics of FEN (Noaman et al., 2016). Accelerated stability can aid in identifying the possibility of products undergoing degradation and provide important information concerning stability. The most optimum formula with FEN stability in a cream preparation is the one that contains a combination of lipid-soluble antioxidants and water-soluble antioxidants, aside from its synergistic antioxidant. Several studies related to stability study on topical cosmetic preparation are presented in Table 2.

2.7 Particle Size

In cosmetic preparation, particles can affect various important physical features, the ability of the manufacturing process, and the quality of preparation. In a semi-solid preparation, particle condition affects flow property, mixing, and separation of components, and rheology characteristics. Emulsion modification also affects emulsion system particle size, such as the formation of macroemulsion, microemulsion, and nanoemulsion. Macroemulsion usually has a particle size of more than 400 nm or 0.4 µm, microemulsion between 100 and 400 nm or 0.1-0.4 µm, while nanoemulsion has less than 100 nm in size (Debnath et al., 2015). For transdermal and topical administration, particle size is an important factor for several applications. If the ingredients are distributed topically, particle size can be the main regulator of flux (Williams, 2003).

Particle size also contributes significantly to the skin penetration pathway. Particles larger than 10 mm stay on the skin surface; particles between 3-10 mm are in hair follicles; particles smaller than 3 mm can penetrate stratum corneum and follicles. For particles smaller than 3 mm, including nanoparticles, they involve percutaneous absorption, especially through the follicle pathway (Rolland, 1993). Skin penetration from polymer polystyrene nanoparticles (20 and 200 nm) reached follicle localization. However, there is no alternative non-follicular penetration pathway. A similar result was obtained in minoxidil with copolymer nanoparticles (40 nm and 130 nm). Choosing the appropriate particle size in a topical formulation can maximize local potentials within the skin area (Alvarez-Román et al., 2004).

Analysis of particle size aims to provide quantitative data on particle size distribution (PSD), mean size, and form of a substance used in the formulation of cosmetics. Particle size analysis is also needed to ensure the quality of the final preparation form. One of the parameters used to asses emulsion stability is using determination of changes in the average of particle size. The determination of emulsion particle size can be conducted using some method such as an optical microscopy, sedimentation, coulter counter and laser scattering-based particle characterization. Optical microscopy is the one of most common used technique in particle size analysis. It is suitable for particle that having range between 0.2-100 µm. The sedimentation test using Andreasen pipette can be used for the analysis of light powders in coarse dispersions such as emulsions. Coulter counter is also known as conducting method. The particle size analysis is measured by the electrical resistance (Hussein et al., 2021). Laser scattering-based particle characterization techniques can also be used for sizing particles. These techniques can be divided into two groups based on the operating principles : Static Light Scattering (SLS) and Dynamic Light Scattering (DLS). The average particle size of emulsion can be identified by DLS (Figueiredo et al., 2021). Various examples of studies concerning particle size in cosmetic preparations are presented in Table 3.

2.8 Wettability

Wettability is a key factor related to function in the biological system, including the wetting behavior of liquid on the surface of cosmetic ingredients. Wettability in emulsion acts on a complex fluidic system that involves polar and nonpolar fluids (Li et al., 2019). Surface tension directly affects the duration of wettability and contact angle. In normal conditions, the lower the oil surface tension, the better the wettability (Chunyan

et al., 2014). The smaller the contact angle of the emulsion, the better the wettability.

Emulsion dispersion significantly affects contact angle. Emulsion dispersion reduces tension on the emulsion surface, increasing the wettability of emulsion and reducing contact angle. However, in a concentration under critical micelle concentration, the surface tension of emulsion increases, causing a decrease in emulsion wettability comparable to an increase of emulsion concentration (Liu et al., 2018).

The emulsifier can reduce surface tension between liquid substances within a component. Low surface tension facilitates the dispersibility of emulsion in the skin. A single emulsifier is specific, tends to be lipophilic or hydrophilic. The use of a single emulsifier can reduce surface tension, albeit with weak stability. Therefore, a combination of different emulsifiers, hydrophilic and lipophilic, is needed to balance the components (Shangguan et al., 2011). Hopefully, this will improve the stability of the emulsion. Characteristic differences of emulsifiers can also cause different HLB values. The higher the HLB value, the larger the contact angle, thus reducing wettability (Liu et al., 2018). Several studies related to wettability on cosmetic ingredients are presented in Table 4.

2.9 Hygroscopicity

Several cosmetic ingredients, especially in water-soluble salt form have the ability to absorb moisture. Adsorption and moisture in the system can be dependable on atmosphere moisture, temperature, surface area, exposure, and mechanism of absorption (Van Campen et al., 1983). Hygroscopic ingredients absorb water because of hydrate formation or absorption in several locations. This can affect several parameters, such as chemical stability, the ability to flow, and compatibility (Ainurofiq et al., 2020).

Hygroscopicity test is performed by placing samples in an open thin powder bed to maximized air exposure. These samples are stored in a controlled environment with relative humidity prepared with a saturated diluted salt solution (Weast, 1974). Moisture absorption is observed in various intervals of the testing period (0 to 24 hours) and storing duration (0 to 12 weeks). The analysis method to observe humidity includes gas chromatography, Karl Fischer titration, gravimetry, or TGA. The choice of method depends on the targeted precision and the amount of moisture adsorbed to the sample (Verma and Mishra, 2016).

Hygroscopicity can be measured in emulsion preparations containing sugar. Sugars with low molecular weight, such as lactose glucose, and fructose in an amorphous state have high solubility and hygroscopicity. Crystal sugar may contain an amorphous fraction due to the particle size reduction and milling process (Jayasundera et al., 2009). A surface covering with hygroscopic ingredients (such as lactose) produces good wettability due to the small contact angle (Faldt and Bergenstahl, 1996; Kim et al., 2002). Microcapsule hygroscopicity is calculated based on the difference of weight measured based on the amount of water absorbed (Tontul and Topuz, 2014).

2.10 Type of Preparation

The emulsion-based formulation has better compatibility chemically, physically, and biologically with skin compared to other transdermal and topical cosmetic preparations, such as solution, ointment, and patch. The outermost layer of the skin, known as the stratum corneum, is composed of 10-20% of lipid and 70-80% of protein according to its dry weight. In a normal skin condition, the stratum corneum contains 15-20% of water. However, in saturated hydrated skin, it can contain up to 300% of water. The skin surface, especially around the face and scalp, is usually covered by a lipophilic sebum layer composed of wax, wax ester, fatty acid, triglycerides, and a small amount of water produced from normal sweat. During topical applications, emulsion, which consists of oil and water phase, can be dispersed well and similar to the condition on the skin surface, which has the highest compatibility with skin. Compared to ointment, the emulsion does not hinder normal moisture evaporation, thus reducing skin discomfort (Lu and Gao, 2010).

Compared to a solution, the viscosity in an emulsion can be easily adjusted to prevent evaporation during and after application and to control the surface condition. Other than that, an emulsion is elegant cosmetically and more attractive to consumers. As a delivery system for pharmaceutical ingredients and cosmetics, an emulsion is compatible with substances soluble in water and not soluble in water, causing a simpler molecular dispersion. Suspension or emulsion matrix has the ability to cover dispersed particles by maintaining the consistency and integrity of formulation (Lu and Gao, 2010).

To improve compatibility, a polymeric emulsifier such as dimethicones (polysiloxane), poly (acrylamidosulfonate) acid, and poly (acrylate) can be used, which are modified hydrophobically with the C12 sidechain used to substitute general surfactant. This polymeric emulsifier shows simple production procedures, high oil compatibility, high skin compatibility even in sensitive skin, and good stability (Kettler et al., 2008). Moreover, a biocompatible organic particle can be used to obtain a skin-compatible emulsion. Emulsion stabilized by Quercus Suber-Based has the characteristics needed to be an appropriate delivery system for topical preparations, producing pH compatible for human skin, i.e. pH 5.42 ± 0.01 (Carriço et al., 2019).

2.11 pH

pH is an important physicochemical factor, which acts in various molecular metabolism and cell regulation process. The pH of skin epithelium, especially stratum corneum is important as a physical, chemical, and microbiological barrier (Pulit Prociak et al., 2019). Topical cosmetic preparations should be within skin pH, i.e. 4.5-6.5. The pH value should not be too acidic because it can irritate the skin, and should not be too alkaline because it can cause scaly skin due to damage to the stratum corneum coat (Schreml et al., 2010). Measurement of pH (acidity) is performed electrochemically using a pH-meter at room temperature (Akhtar et al., 2011). The potential dif-

Table 3. Several Studies Related to Particle Size in Cosmetic Preparations

No	Effect of Particle Size	Reference
1	Cosmetic pre-formulation with 5-6 µm particle size has a good delivery	(Gamoudi and Srasra, 2017)
2	In 100 µm particle size, preservative delivery can be optimized	(Yorgancioglu and Bayramoglu, 2013)
3	Emulsion stability can be improved by reducing the size of the emulsion particle An increase in stability can be obtained in narrow particle distribution	(Cui et al., 2010; Zhu et al., 2015)
4	Particle size is kept small to maintain interfacial tension and keep the emulsion texture in cosmetic formulation	(Menon and Wasan, 1988)

Table 4. Studies on Wettability in Cosmetic Ingredients

No	Study on Wettability	References
1	Particle wettability can be achieved by modifying its surface with surfactant, oil molecule, acid, or polymer	(Xiao et al., 2018)
2	Increasing contact angle will reduce viscosity in O/W emulsion stabilized with solid particle/Pickering emulsion	(Pal, 2018)
3	Particles easily wetted in the oil phase have a contact angle of > 90° which requires W/O type emulsifier. Particles easily wetted in the water phase have a contact angle of < 90° which requires O/W type of emulsifier.	(Binks and Fletcher, 2001; Binks, 2002; Pickering, 1907)
4	Modification of the gold nanoparticles with polyethylene glycol (PEG) ended with thiol and alkana-thiol molecule shows stabilization effective for emulsion because of strong adsorption in the interface between oil/water	(Larson-Smith and Pozzo, 2012)
5	Colloidal silica particles modified with hydrophobic organosilane and hydrophilic PEG silane containing methyl and propyl group for Pickering emulsion	(Björkegren et al., 2017)

ference from reference electrodes can produce a voltage that represents a linear pH value that can be calculated with the Nernst equation (Wohlrab and Gebert, 2018).

3. CONCLUSIONS

The pre-formulation study can involve organoleptic evaluation, formula compatibility, sensitivity and irritability, thermal effect, partition coefficient, stability, particle size, wettability, hygroscopicity, preparation type, and pH recommended to be performed during the information searching step related to the physicochemical properties of ingredients used for cosmetic preparations. Pre-formulation of cosmetic preparation is beneficial to determine the quality of the ingredients within the preparation before formulation. If the pre-formulation test is good, then the formulation process and final evaluation of cosmetic preparation can be continued. If the physicochemical property is not good, then evaluation and development of other ingredients can be conducted to obtain a good pre-formulation. With a pre-formulation study, the production of cosmetic preparation can be more effective because it directs the choice of ingredients and optimum ingredient composition.

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