SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS): ANTI-AGING DRUG DELIVERY

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Abstract: Ultraviolet (UV) radiation can damage telomeres and induce free radicals, causing cellular senescence. Chronic exposure to UVB rays causes skin aging. An anti-aging drug can be formulated with a delivery system such as SNEDDS. This is an isotropic mixture consisting of oil, surfactant, and co-surfactant which rapidly forms a nanoemulsion when mixed with water. SNEDDS can be a good drug delivery system for protein drugs and drugs with low absorption rates. Topical drug delivery systems have the advantages of bypassing first-pass metabolism, avoiding discomfort risk of intravenous (IV) therapy, improving patient compliance, and increasing absorption and bioavailability because nanoemulsion-sized droplets can increase the release of poorly soluble drugs. In delivering drugs and active ingredients into the deep layers of skin, at the dermis, topical route of absorption increases the transport of hydrophobic compounds through the stratum corneum to the deeper layers of the skin and improves the skin availability. This article presents an overview of SNEDDS including its components, formulation design, characterization, potential effects for anti- aging drugs, and penetration as a topical route of delivery.

Keywords: SNEDDS, cosmetics, anti-aging, topical

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INTRODUCTION

Aging process is a progressive accumulation of various pathological changes in cells and tissues that occur over time. The process is accompanied by a gradual loss of tissue's ability to repair and maintain its normal structure and function, so that the body cannot either defend against damage or repair the damage (Rabe et al., 2006). Skin aging is characterized by the appearance of wrinkles, dermal atrophy, and elastosis associated with degradation of elastic extracellular matrix proteins, decomposition of elastin fibers, sagging skin, telangiectasias, and lentigines (Huertas et al., 2016; Lee et al., 2016).). Anti-aging drugs can be formulated with delivery systems such as liposomes (Kwona et al, 2015), solid lipid nanoparticles (Jeon et al., 2013), liquid crystalline nanostructured dispersions (Sherif et al, 2014), and self-nanoemulsifying drug delivery system (Pratiwi et al., 2017).

SNEDDS is an isotropic mixture consisting of oil, surfactant, and co-surfactant which quickly forms an emulsion when mixed with water (Nazzal and Khan, 2002). It is a lipid-based drug delivery system that is able to increase lipophilic drug bioavailability by increasing the accessibility of enzymatic reaction stimuli in the small intestine, thereby increasing absorption of oral drug administration (Kalepu et al., 2013). In addition to oral route, SNEDDS can be designed into nanoemulsions by topical route. The nanoemulsion formed in the SNEDDS has a microscopic droplet

size, which is less than 200 nm, so that the system is able to become a good drug delivery system for protein drugs and drugs with low absorption rates. Topical drug delivery systems have the main advantages of bypassing first-pass metabolism, avoiding discomfort risk of intravenous (IV) therapy, and increasing patient compliance (Rane et al., 2018). The SNEDDS formula can improve absorption and bioavailability because nanoemulsion-sized droplets can increase the release of poorly soluble drugs (Villar et al., 2012). Topical route of absorption delivers drugs and active ingredients into the deep layers of skin, particularly at the dermis(Scalia et al., 2015). Formulation of the SNEDDS using polymers can increase the transport of hydrophobic compounds through the stratum corneum to the deeper layers of the skin and improve the skin availability (Šmejkalová et al., 2017). The development of pharmaceutical and cosmetic technology is not only the discovery of new molecules but also the development of new systems to deliver active ingredients or optimize their release [Morais et al., 2008].

The SNEDDS has the main components which are oils as a drug carrier, surfactants as an emulsifier of oil in water and controller of the stability of interfacial film, and co-surfactants as the surfactants support. The type and proportion of both surfactants and co-surfactants in the formula have a major influence on the size and emulsification time of the resulted SNEDDS (Sakhti et al., 2013; Xi et al., 2009). The characteristics of SNEDDS include parameters of particle size, zeta potential, emulsification time, and morphology.

Self-Nanoemulsifying Drug Delivery System (SNEDDS)

SNEDDS is an isotropic mixture consisting of oil, surfactant, and co-surfactant which quickly forms an emulsion when mixed with water (Nazzal and Khan, 2002). It is a lipid-based

drug delivery system that is able to increase lipophilic drug bioavailability by increasing the accessibility of enzymatic reaction stimuli in the small intestine, thereby increasing absorption of oral drug administration (Pouton, 2000). The nanoemulsion formed in the SNEDDS has a microscopic droplet size, which is less than 200 nm, so that the system is able to become a good drug delivery system for protein drugs and drugs with low absorption rates.

The SNEDDS is the best way to improve the characteristics of poorly soluble drugs by increasing their bioavailability and stability (Sakhti et al., 2013). The system can reduce gravity and increase brownian motion which can prevent sedimentation or creaming, so physical stability increases (Fanun, 2010). The formulation of SNEDDS is able to increase the bioavailability of white turmeric oil with a Cmax value of 2.5 times higher than the pure oil (Zhao et al., 2009). The system has the ability to increase the solubility and stability of essential oil-based formulations (Pedro et al., 2013). The SNEDDS formulation can increase the solubility in water and the stability of Amomum compactum essential oil (Ujilestari et al., 2018). The SNEDDS can penetrate secondary metabolites of the ethyl acetate fraction of mangosteen peels into bacterial cell membranes. The system was made

using the optimal formula using a simplex lattice design method with various concentrations of oil, surfactant, and co-surfactant. SNEDDS of ethyl acetate fraction (EAF) has antibacterial activity against S. epidermidis with an inhibition zone of 11.13 mm ± 1.87 mm, greater than EAF without preparations with an inhibition zone of 9.43 mm ± 1.20 mm. (Pratiwi et al., 2021).

The SNEDDS is able to increase the efficacy of gemfibrozil citrate when used orally (Villar et al., 2012). The system is also able to increase the bioavailability of indomethacin compared to its conventional dosage form (Taha et al., 2009). The SNEDDS can regulate the rate of drug release and drugs with low solubility such as cinnarizine (Larsen et al., 2013). It can increase drug loading and drug dissolution speed (Alwadei et al, 2019). The advantage of oil-in-water nanoemulsions is its ability to carry hydrophobic drugs in the oil, so they can be emulsified in water and the drugs solubility increases when in the body (Shafiq-un-Nabi et al., 2007). The droplet structure of the O/W type nanoemulsion is composed of surfactants, co-surfactants and oil phase that carries hydrophobic drugs or active substances. The hydrophobic parts of the surfactant tail will cover the oil phase while the hydrophilic head will be outside (Figure 1).

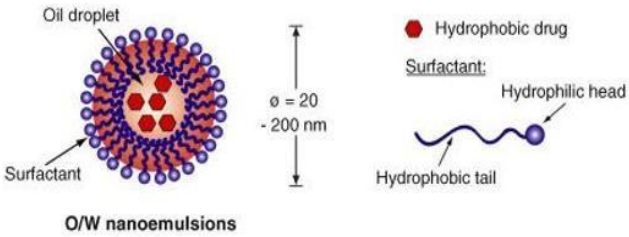

Figure 1. M/A Type Nanoemulsion Droplet Form (Chen et al., 2011)

Composition of the SNEDDS Formulation

The components of SNEDDS are oil phase, surfactant and co-surfactant. The oil phase is an important component of nanoemulsion formulations because it acts as a drug carrier for hydrophobic active substances. The drug solubility in the oil phase affects the nanoemulsion ability to keep the drug in dissolved (Pardo et al., 2015). Nanoemulsion formulations with oil phase components that are more polar can form droplet sizes that are much larger than the droplet sizes produced with non-polar oil phases (Jaworska et al., 2014). Related to polarity and solubility of oil molecules in water, the oil phase affects the stability of nanoemulsion preparations during the storage period, so it is important to know the oil phase composition that will be used in the formulation (Pardo et al., 2015). The optimal formulation of SNEDDS is influenced by physicochemical properties and concentrations of oil, surfactant, co-surfactant, ratio of each component, pH and emulsification temperature, and physicochemical properties of the drug (Date et al., 2010). SNEDDS has the main components which are oil as a drug carrier, surfactants as an emulsifier of oil in water and controller of the stability interfacial film, and co-surfactants as the surfactants assistance. The type and proportion of both surfactants and co-surfactants in the formula have a major influence on the size and emulsification time of the resulted SNEDDS (Sakhti et al., 2013; Xi et al., 2009). Surfactant characteristics such as HLB value, viscosity and affinity have a major influence on the nanoemulsification process (Sakhti et al., 2013). Excessive concentrations of surfactants and co-surfactants can cause gastrointestinal irritation (Sakhti et al., 2013; Xi et al., 2009).

Oil, Surfactants and Co-surfactants Oil

The selected oil of SNEDDS is the oil that is able to dissolve compounds or drugs with the highest concentration. The selected oil must be able to produce nanoemulsions with droplet sizes in the range of 20-200 nm (Shah et al., 2010). To select the right oil phase is very important as it affects the selection of other materials. The oil phase determines the maximum drug load in the nanoemulsion. Oil consists of triglyceride mix containing fatty acids of various chains and degrees of unsaturation (Rowe, 2009).

Table 1. Oils that can be used in the formulation of SNEDDS

Oils	Reference
Minyak zaitun	Wahyuningsih dan Latief, 2021
Minyak jinten hitam	Wahyuningsih dan Latief, 2021
Black seed oil	Alwadei dkk, 2019
VCO	Pratiwi, 2021
Sunflower oil	Pratiwi dkk, 2016
citrus essetial oil	Pratiwi dkk, 2016
kanthil essential oil	Pratiwi dkk, 2016
soy bean oil	Pratiwi dkk, 2016
corn oil	Pratiwi dkk, 2016
canola oil	Pratiwi dkk, 2016
clove oil	Farooq dkk, 2019
Castor oil	Alwadie dkk, 2019
Imwitor 988	Alwadie dkk, 2019
Labrafac PG	Kim dkk, 2018
Lauro glycol 90	Kim dkk, 2018
Myritol 318 P	Kim dkk, 2018
Labrafil M 1944 CS, M 2125 CS	Kim dkk, 2018

Surfactants

Surfactants are compounds that have hydrophilic groups on the head and hydrophobic groups on the tail. They have an important role in nanoemulsion formation by lowering the interfacial tension between oil and water phases. Addition of a surfactant causes the initial interfacial tension decrease rapidly until it reaches a certain point in which the tension stops decreasing despite continuous addition. This particular point is known as the Critical Micelle Concentration (CMC) (Shcramm et al., 2001). Based on the types of water ionization, the classification of surfactants includes anionic, cationic, amphoteric and non-ionic surfactants (Nielloud, 2000).

Surfactants are molecules/ions that are adsorbed at the interface, thus called surface- active agents that have a certain affinity for both polar and non-polar solvents. Surface-active substances that are adsorbed at the oil/water interface form a monomolecular layer and reduce interfacial tension (Sinko, 2006). The agents' characteristics, such as hydrophilic-lipophilic balance (HLB), viscosity and affinity greatly influence the nanoemulsion formation process and its droplet sizes. In some formulations, a mixture of hydrophobic and hydrophilic surfactants can be used to form nanoemulsions with the desired characteristics. Surfactants with an HLB value of less than 10 are hydrophobic like sorbitan monoester and form a water-in-oil (W/O) nanoemulsion. Meanwhile, surfactants with an HLB value of more than 10 are hydrophilic like Tween 80 and form an oil-in- water (O/W) nanoemulsion (Shah et al., 2010).

The HLB indicates the level of surfactant polarity. The higher the HLB value, the higher the polarity of the surfactant. Tween 20 (HLB 16.7) has excessive polarity while Span 20 (HLB 8.6) and Cremophore EL (HLB 15.2) are considered quite non-polar (Harry et al., 2000; Rowe, 2009). In addition to HLB, surface tension also has a considerable influence. Tween 80 has the highest surface tension (42.5 mN/m) among the others; Span 20 has surface tension of 28 Mn/M and Cremophore EL has tension value of 40.9 Mn/m (Graca et al., 2007). A large surface tension value increases the ability of ethyl acetate fraction of mangosteen peel to mix homogeneously with Tween 80.

Table 2. Oils that can be used in the formulation of SNEDDS

Surfactants	Reference
Cremophor RH 40	Alwadie dkk, 2019
Cremophor EL	Alwadie dkk, 2019
Tween 40	Farooq dkk, 2019
Solutol HS15	Kim dkk, 2018
Capmul MCM C8 EP	Kim dkk, 2018
Span 20	Pratiwi dkk, 2016
Tween 80	Pratiwi, 2021

Tween 20	Pratiwi dkk, 2016
Kolliphor P 407, PS 80	Kim dkk, 2018
Labrasol	Kim dkk, 2018

Co-surfactantsTo produce nanoemulsions surfactants are not sufficient to reduce the oil-water interfacial tension , thus requiring the addition of short-chain amphiphilic molecules or co-surfactants to help reduce the interfacial tension to near zero. The co-surfactants penetrate into the surfactant monolayer and provide additional fluidity, thereby disrupting the liquid crystal phase formed when the surfactant film is rigid (Rowe, 2009).
Co-surfactants optimize the decrease of interfacial tensions between the oil and water phases and assist the solubility of solutes in dispersion medium by increasing the flexibility of the layer around
droplet areas and reducing the surface free energy so that stability can be maintained. Co-surfactants can be short-chain amphiphilic molecules that can reduce the surface tension (47,48). Those with short to medium alcohol chain lengths cause the thin flexible film deform around the droplets due to interactions between surfactant molecules, and both polar head group interactions and hydrocarbon chain interactions decrease. Co-surfactants with long chains form a lamellar liquid-crystalline phase or create a high rigidity of the interfacial film (Agoes, 2012).

Table 3. Co-surfactants that can be used in the formulation of SNEDDS

Co-surfactantas	Referensi
PEG 400	Pratiwi, 2021; Wahyuningsih dan Latief, 2021
Sorbitol	Wahyuningsih dan Latief, 2021
PEG 600	Farooq dkk, 2019
dimethyl sulfoxide (DMSO)	Izham dkk, 2019
diethylene glycol mono ethylether (Transcutol)	Izham dkk, 2019
Propilenglikol	Pratiwi dkk, 2016
Transcutol P	Alwadie dkk, 2019

Construction of the Ternary Phase Diagram
D-optimal mixture Design-Expert is a software for optimizing a process or formula of a product. This program can process four different research designs, namely factorial design, combined design, mixture design, and response surface method design. The mixture design can optimize formulas using a series of component mixes. The design is divided into 2 types which are simplex lattice design for formula optimization with the same concentration interval of the used components and non simplex design for formula optimization with different concentration intervals of the used components (Nugroho, 2015).
One of the methods used to determine the optimal formula of SNEDDS is simplex lattice design (SLD) assisted by Design-Expert (DX) software. The SLD is a method used to determine the optimization of formulas for various differences in the amount of material compositions (expressed by parts), which total amount is the same or equal to one part. The response profile can be determined with an equation based on the SLD (Bolton, 1997). The design can be used to optimize a formula more easily, quickly and efficiently than the Trial method. In this design, formula optimization is carried out in various different amounts of ingredient compositions expressed in various parts, but the total amount of several formulas is constant or the same (Reddy et al., 2015; Deshmukh et al., 2016). The SLD can be used to obtain the optimum formulation of SNEDDS (liza ijap, japs).
Optimization of several responses is difficult to achieve unless the responses have a high correlation; an acceptable range can be determined for each response. The best area is the part in which the value of each response is acceptable. The formula optimization using a variation of three components is described in two dimensions which have three angles to form an equilateral triangle. The three varied components are denoted by letters A, B, and C.
Each corner of the triangle represents the pure component. Figure 2 shows an equilateral triangle depicting the variation of the three components.

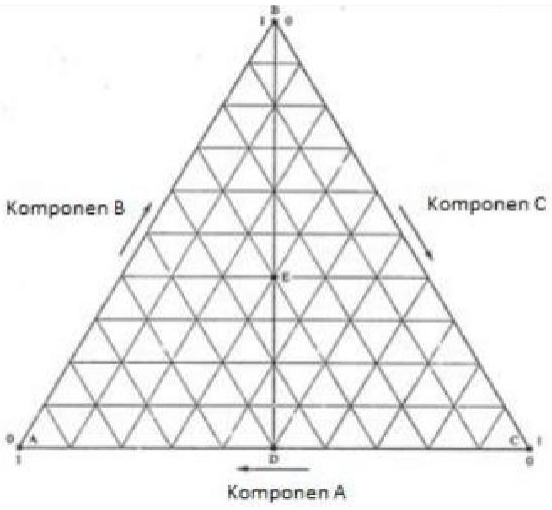

Figure 2. An Equilateral Triangle Describing Variations of Three Components (Amrutkar et al., 2014)

Characterization of the SNEDDS Droplet size

Droplet size determines the rate and extent of drug release and drug absorption. The smaller the particle size, the larger the interfacial surface area which can lead to faster absorption and increased bioavailability. The SNEDDS with an average droplet size below 200 nm shows excellent bioavailability. Particle size of emulsion is an important factor in self-emulsification performance as it determines the rate and extent of drug release and absorption. In this study, the particle size of the optimal SNEDDS formulation was 81.7 nm, and the average particle size was 504.4 nm, thus indicating that all particles were in the nanometer range (Farooq et al., 2019). In the SNEDDS study of mangosteen peel, the droplet size was at 77.3 nm ± 0.232 nm (Pratiwi, 2021). The droplet size decreases due to the increase of surfactant concentrations (Kassem et al., 2016). The higher the ratio of surfactants compared to co-surfactants, the smaller the size of the obtained nanoemulsion (Xi et al., 2009). Surfactants can cause a decrease in the interfacial film and stabilize it, thus resulting in a smaller droplet diameter, while the addition of co-surfactants can cause a wider interfacial film (Fahmy et al., 2015, Hosny et al., 2013). The relative proportion of surfactant and co-surfactant makes variation of droplet sizes (Singh et al., 2010).

The particle size of the nanoemulsion is also influenced by the composition of oil (Fernandez et al., 2004). Oil is able to increase the ability of SNEDDS to carry drugs, but it makes the nanoemulsion size larger, so that the ratio of oil used is always smaller than that of surfactants (Larsen et al., 2013). The nanoemulsion droplet size can regulate the effective drug release (Parmar et al., 2011; Badran et al., 2014; Singh et al., 2010). In another study, the average droplet size of five formulations was found in the range of 26.45-85.94 nm. This is related to the relative increase of the surfactant proportion in oil droplet stabilization as a result of the localization of surfactant molecules at the oil- water interface (Parmar et al., 2011; Dixit et al., 2010). The small droplet size of the SNEDDS formula is due to the reduced surface tension led by the presence of surfactants and co-surfactants (Yoo et al., 2010). Polydispersity index (PDI) value indicates the homogeneity of nanoemulsion particles. The PDI value varies from 0.0 to 1.0, and the closer to 0 the particle is, the more homogeneous it become (Patel et al., 2010). A PDI of less than 0.5 indicates a uniform globule size distribution (Balakumar et al., 2013; Shakeel et al., 2014).

Potensial Zeta

Zeta potential is responsible for the degree of repulsion between adjacent, similarly charged, scattered droplets. The zeta potential value of ±30 mV is sufficient for microemulsion stability. The zeta potential of the optimized SNEDDS formulation (A20) was 16.7 mV which satisfies stability requirement (Farooq et al., 2019), Porter et al, 2001, Sek et al, 2001). In the SNEDDS study of mangosteen peel, the zeta potential value was 8.29 ± 0.04 mV (Pratiwi, 2021). The value in the range of ± 30 mV is the limit to be able to maintain emulsion stability as it is close to neutral thus reducing the possibility of particles to form aggregates (Honary and Zahir, 2013). At the zeta potential, the droplet surface charge affects the stability of SNEDDS formulation due to the electrostatic repulsion among droplets preventing nanoemulsion incorporation. The negative value obtained in the study was led by the presence of surfactants and co-surfactants in the emulsion (Yoo et al., 2010). The study of Kaseem et al. (2016) showed that the optimized formulations were negatively charged, with values ranging from -15.3 to -23.9 mV, indicating a stable system and well separated emulsion bubbles (Agrawal et al., 2015). The presence of electrostatic repulsion among negatively charged droplets avoids the coalescence formation in the nanoemulsion (Badran et al., 2014). Non-ionic surfactants produce a negatively charged interface at neutral pH due to the differential adsorption of hydroxyl ions (OH~) and hydrated oxonium ions (H3O+) (Choi et al., 2014).

Morphology

SNEDDS morphology testing can be done with scanning electron microscopy (SEM) and transmission electron microscopy (TEM). SEM studies were carried out for particle shapes and morphological analysis of solid formulations only, whereas TEM experiments involved all formulated SNEDDS. Microscopic observation of S-SNEDDS under the SEM instrument revealedthe presence of agglomerates of particles with rough surface morphology. This microstructure corresponds to a large matrix in which multiple channels are formed in aqueous medium (Rani et al., 2017), facilitating water infiltration and spontaneous dispersion of nanodroplets upon hydration. Furthermore, the TEM experiments made it possible to confirm the presence of SNEDDS in all aqueous formulations. The TEM analysis revealed the presence of individually dispersed particles in the nanometric range (approximately 10 nm), confirming the nanoparticle properties of the prepared formulations, however, the observed particle sizes did not match the data from the DLS experiment, in which the mean size was found to be larger than 50 nm (Mukubwa et al, 2020). Previous studies reporting SNEDDS with similar DLS sizes (e.g. around 100 nm) (Khoo et al., 1998; Kassem et al., 2016; Dou et al., 2018) showed that the difference between TEM and DLS particle sizes can be due to particle solvation resulting in a large hydrodynamic diameter (Eaton et al., 2017; Eltobshi et al., 2018). Nevertheless, the overall results from the microscopic analysis confirmed the good self- emulsification efficiency of lipid-based formulation, which would lead to increased bioavailability and increased therapeutic efficacy of the encapsulated active ingredients (Tang et al., 2013; Memvanga et al., 2013a).

Emulsification time

A short emulsification time is mediated by the action of surfactants and co-surfactants which are able to immediately form an oil interface layer. Co-surfactants have more role in emulsification time and not in droplet size reduction. The compounds will slip and form empty spaces among surfactants and increase fluidity, so they can form nanoemulsions faster (Parmar et al., 2011). Oil component can increase the emulsification time of nanoemulsions; the addition of ethyl oleate to SNEDDS can increase the emulsification time despite the smaller particle size with increasing surfactant concentration (Zhao et al., 2010). Increasing the oil concentration can decelerate the emulsification time because the surfactant and co-surfactant concentrations become smaller, so they cannot form emulsions in a short time (Beg et al., 2013; Eid et al., 2012). The short emulsification time is influenced by the small oil concentrations and high co-surfactant concentrations, thereby making the viscosity smaller (Basalious et al., 2010). The lower the emulsification time value, the better and faster the nanoemulsion formation in distilled water (Pratiwi, 2021).

Skin Aging

Aging process is a progressive accumulation of various pathological changes in cells and tissues that occur over time. The process accompanied by a gradual loss of tissue's ability to repair and maintain its normal structure and function, so that the body cannot either defend against damage or repair the damage (Rabe et al., 2006). Skin aging is characterized by the appearance of wrinkles, dermal atrophy, and elastosis associated with degradation of elastic extracellular matrix proteins,

decomposition of elastin fibers, sagging skin, telangiectasias, and lentigines (Huertas et al., 2016; Lee et al., 2016).). Major damage causes aging characterized by increased MMP and loss of collagen. MMP-1 is responsible as an initiator of collagenase that affects fragmentation (Zheng et al., 2014; Puhirot et al., 2016, Xia et al., 2015). MMP-2 and MMP-9 are responsible for collagen degradation (Zheng et al., 2014; Xia et al., 2015). TGF-β causes collagen synthesis reduction and collagen loss (Zheng et al., 2014; Puhirot et al., 2016, Xia et al., 2015). Photoaging is a skin disorder and damage caused by a chronic exposure to UV rays on skin that is experiencing intrinsic aging. Many skin functions decline with age, but photoaging occurs more rapidly. In photoaging, there are changes in macroscopic, microscopic and functional conditions of skin due to chronic and repeated exposure, mainly led by radiation of solar ultraviolet or artificial light sources (Kim et al., 2012a).

A factor that affects skin aging is intrinsic aging. This is also known as natural aging process, which is an ongoing process usually starting at the age of 20; it is caused by various factors, namely the body's own physiological factors such as genetic, hormonal and racial factors (Chung et al., 2003; Yaar and Gilchrest, 2008), as well as pathological factors such as disease and malnutrition. The intrinsic aging can occur due to the accumulation of endogenous damage caused by the formation of reactive oxygen compounds during cellular oxidation metabolism. In addition to a decrease in growth factors and hormones, telomere shortening in cell division is one of the causes of intrinsic skin aging. Extrinsic aging occurs as a result of cumulative damage from UV radiation. Sun exposure can induce premature skin aging and is often referred to premature skin aging (Glogau, 2004). UV radiation with a wavelength of 200 - 400 nm constitutes 5% of the entire range of solar radiation. In general, UV light is divided into three, namely UVA (320 – 400 nm), UVB (290 – 320 nm), and UVC (200 – 290 nm). The third UV type can be absorbed directly by the ozone layer in the atmosphere. UV radiation triggers the formation of reactive oxygen species (ROS) which can damage DNA and inhibit the work of the tyrosine phosphatase enzyme. UV can also reduce retinoic acid receptors (RARs), trigger an increase in nuclear factor-kB (NFk), and result in decreased collagen productionas well as collagen breakdown due to matrix metalloproteinase (MMP) activity (Afaq and Mukhtar, 2006).

Potential effects of the SNEDDS for anti-aging drugs

Nanoemulsions can be found in a wide variety of cosmetic products such as bath oils, body creams, anti-wrinkle and anti-aging preparations. Due to their small and uniform droplet size, nanoemulsions are transparent, liquid and pleasant to the touch (Sarker et al., 2005; Guglielmini et al., 2008). Compared with traditional emulsions, nanoemulsions have better dispersion properties on the skin, and their unique texture and rheological

properties make them very valuable in cosmetic technology. Formulations containing nanoemulsions range from water-like liquids to semi-solid gels. Many patents reflect the active development of nanoemulsion formulations. Nanoemulsions containing liquid, non-ionic, amphiphilic lipids, such as diglyceryl isostearate, sorbitan oleate, and -
butylglucoside caprate, are stable at storage between 0°C and 45°C (Ribier et al., 1988), and they can be formulated with fragrances and have an active penetration into the skin surface layer. Nanoemulsions prepared with anionic, amphiphilic lipids from phosphoric acid fatty esters and oxyethylene derivatives also retain good transparency and cosmetic properties despite the addition of large amounts of oil to the formulation (Simonnet et al., 2001). Other O/W nanoemulsions based on one or more non-ionic and/or anionic amphiphilic lipids and one or more water-soluble neutral polymers (eg oxides), polyvinyl alcohol; polyvinylcaprolactam), allow the composition viscosity increase without affecting transparency or improving the oil phase level (L'alloret et al., 2006). Stable and translucent cosmetic nanoemulsions consisting of a ternary surfactant system of polymeric ethoxylated fatty esters, fatty acid esters of sorbitan and alkali metal salts of cetyl phosphate or palmitoyl sarcosinate do not require gelling agents for stabilization (Quemin et al., 2005), thus making it suitable for use on sensitive skin. Several other nanoemulsion technologies have been developed for diverse properties, including sun protection, anti-wrinkle, anti-aging skin and other cosmetic targets (Haake et al., 2007; Calderilla et al., 2006; Yilmaz et al., 2006; Yoo et al., 2006; Huglin et al., 2005).

In this study, mangosteen peels containing xanthones as an anti-aging active compound experienced solubility problems, so they were formulated with SNEDDS, and in the penetration test using snake skin peels a significant difference was obtained between the mangosteen peel fraction in the SNEDDS preparation and the mangosteen peel fraction without SNEDDS; it was characterized by an increase in penetration of α-mangostin via the stratum corneum (Pratiwi et al., 2017). The SNEDDS can form nanoemulsions with the water addition (Pratiwi et al., 2021).

Topical delivery of SNEDDS through skin barrier

Topical drug delivery systems have the advantages of bypassing first-pass metabolism and avoiding the discomfort risk of intravenous (IV) therapy. Topical formulations improve patient compliance. The systems include two basic types of products: external topicals that are applied to the skin tissue or sprayed (gels, emulgels, lotions, etc.) and internal topicals which are applied to the mucous membranes orally, vaginally or for rectal use (solutions, drops, etc.) (Rane et al., 2018). Currently, the development of pharmaceutical and cosmetic technology is not only the discovery of new molecules but also the development of new systems to deliver active ingredients or optimize their release (Morais et al., 2008). Studies involving nanotechnology seek to apply new technological approaches to extend the benefits provided by drug delivery systems, i.e., effective, safe and reliable, which demonstrate good bioavailability and pharmacodynamics and reduces side effects (Bonif´acio et al., 2014, Chorilli et al., 2009). The SNEDDS formulation provides excellent physical characteristics for skin applications. The SNEDDS-L1 formulation exhibited small droplet size on
the order of 18 nm, negative zeta potential (12.40±0.20 mV), and viscosity (0.19±0.01 Pas) which provided good dispersion and retention on the skin surface (Ponto et al., 2021).

In vitro drug release method for topical preparations is based on the principle of a diffusion system using the Franz cell system. Drug absorption through the skin is influenced by several factors, such as formulation, skin type and condition, temperature and humidity. The preparation being tested is placed on top membrane of the diffusion cell donor compartment, and sampling is done by taking the fluid in the receptor compartment. Drug transfer from the preparation through the membrane is calculated based on the drug concentration of the receptor fluid. In transdermal preparations, the drug must be transported from its formulation in the donor compartment across the skin barrier membrane to the receptor compartment. Drugs can penetrate the skin through transappendageal route as well as penetrating route. In the transapendageal pathway, the drugs penetrate the skin via sweat glands and hair follicles. In the penetration pathway which is the main route, the drugs penetrate the stratum corneum both intercellularly and intracellularly. The transport route for lipophilic compounds is intercellular (composed of lipid lamellae), while the one for hydrophilic compounds is transcellular (composed of a protein matrix) (Benson and Watkinson, 2012).

Based on the research, the amount of transported α-mangostin of the mangosteen peel SNEDDS for 8 hours is greater than the ethyl acetate fraction nanoemulsions. The mangosteen peel fractions without preparation have the smallest amount. This shows that the ethyl acetate fractions of mangosteen peels formulated with SNEDDS and nanoemulsions can increase the penetration of α- mangostin through the stratum corneum (lz jyp). The SNEDDS formula can improve absorption and bioavailability as nanoemulsion-sized droplets can increase the release of poorly soluble drugs (Villar et al., 2012). Topical route of absorption delivers drugs and active ingredients into the deep layers of skin, particularly at the dermis (Scalia et al., 2015). Formulations using polymers can increase the transport of hydrophobic compounds through the stratum corneum to the deeper layers of the skin and improve the skin availability (Šmejkalová et al., 2017). Drugs must have a sufficiently high lipid solubility to increase their partitioning on lipid membranes (Alvi et al., 2011). The main challenge in the formulation is the transport barrier through the skin (Prasanthi and Lakshmi, 2012). Cosmetic and dermatological preparations require a higher increase in the effectiveness of drugs on the skin to penetrate into the receptor compartment, compared to conventional preparations (Rahimpour et al., 2012). These preparations increase the drug penetration into the skin, and due to its lipid properties, the drug penetrates the skin layer and remains for a long period, thus allowing it to be targeted on the skin. The carrier material can affect the increase of penetration (Sasivimolphan et al., 2012). In the SNEDDS study with CoQ10, an active substance, there is an increase of 33% in an

hour, and it improves to97% within six hours (Nepal et al., 2010).

A membrane that can be used in the diffusion test is shed snake skin. It was chosen as shed snake skin has a stratum corneum with structure, thickness and lipid composition that resembles the stratum corneum of human skin and a permeability coefficient value that is similar to that of humans (Sasivimolphan et al., 2012). Several studies reported that some compounds penetrate through shed snake skin and human stratum corneum at similar rates (Itoh et al., 1997; Rigg et al., 1990).

CONCLUSION

SNEDDS can be designed into nanoemulsions, and the nanoemulsions formed can be used as a delivery system for anti-aging drug. The SNEDDS is formulated using a combination of oils, surfactants, and co-surfactants. The choice of components that make up SNEDDS affects characteristics and skin penetration ability.

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Author Contributions

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The authors report no conflicts of interest in this work.

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