International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 15, Issue 4, 2023

Review Article

NANOTECHNOLOGY APPROACH-SELF NANOEMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS)

RAHMI ANNISA[1,2], ROIHATUL MUTIAH[2], MOCHAMMAD YUWONO[1], ESTI HENDRADI[1,3*]

[1]Department of Pharmaceutical Science, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia. [2]Department of Pharmacy, Faculty of Medicine and Health Science, Universitas Islam Negeri Maulana Malik Ibrahim, Malang, Indonesia. [3]Nanotechnology and Drug Delivery System Research Group, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia
[*]Corresponding author: Esti Hendradi; [*]Email: estihendradi@yahoo.com

Received: 21 Feb 2023, Revised and Accepted: 23 May 2023

ABSTRACT

This review article aims to develop nanotechnology in novel drug delivery systems using self-nano emulsifying drug delivery systems (SNEDDS).

This Article was selected using a database with Prism Guideline diagrams. A total of 18 articles obtained from 2010-2020 were used as the primary reference to be analyzed using a systematic review method in the form of meta-synthesis.

This review describes the mechanism of SNEDDS in increasing absorption, the components of the SNEDDS formula, the characterization of self-nano emulsifying drug delivery systems (SNEDDS), the effect of the physicochemical properties of SNEDDS on *in vivo* activity, and the basis for selecting compounds in the SNEDDS formulation. Self-Nanoemulsifying Drug Delivery System (SNEDDS) is a novel drug delivery system from nanoemulsion used to increase the solubility of lipophilic drugs. SNEDDS is an isotropic mixture consisting of oil, surfactant, and co-surfactant. SNEDDS is considered pre-concentrated nanoemulsions or anhydrous forms of nanoemulsions. In SNEDDS, the formation of nanoemulsions occurs when self-nanoemulsions come into contact with gastrointestinal fluids in the presence of light stirring in the peristaltic motion of the gastrointestinal tract. In general, SNEDDS have small particle sizes in the range of 10-200 nm. The application of the self nanoemulsion development system can be used for BCS Class II lipophilic drug compounds and BCS Class IV drugs. SNEDDS is a novel drug delivery system that can be used for oral drug delivery. In occlusion, a self-nanoemulsifying drug delivery system (SNEDDS) is a new approach for the formulation of drug molecules with poor water solubility. Self Nanoemulsifying drug delivery system (SNEDDS) is an isotropic mixture of oil, surfactant, and co-surfactant.

Keywords*:* Self-nanoemulsifying, SNEDDS, Characterization, Absorption, Mechanism

DOI: https://dx.doi.org/10.22159/ijap.2023v15i4.47644. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

In the process of discovering new pharmaceutical therapies, pharmaceutical formulation technology and drug delivery systems play an essential role [1]. Drug delivery systems are needed to facilitate the dispersion of lipophilic bioactive components in hydrophilic systems. Oil-in-water (O/W) emulsion-based carrier system is a very suitable method for the encapsulation, protection, and transport of water-insoluble bioactive components in the context of pharmaceutical applications [2]. Various techniques have been developed to increase the bioavailability of drug compounds with low solubility in water, such as liposomes, nanoemulsions, nanostructured lipid carriers (NLC), and self-nanoemulsifying drug delivery systems (SNEDDS). Self-nanoemulsifying delivery systems have been widely studied because of their simple preparation and high intestinal absorption effect, increasing the bioavailability of oral preparations of water-insoluble drug compounds.

SNEDDS is a homogeneous complex system consisting of thermodynamically stable oil, surfactant, and co-surfactant. The SNEDDS formed is oil in water (O/W), looks clear and transparent, slightly opaque, and opalescent due to the small droplet size of the dispersed phase [3]. SNEDDS, when administered orally, will rapidly disperse to form droplets in the nano (<200 nm) range. SNEDDS in various studies, has been shown to have better thermodynamic stability and short and long-term storage stability compared to other lipid systems such as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) because there is no addition of water and only oil, surfactants, co-surfactant at a balanced concentration in the formula so that the resulting droplet size is more uniform and bioavailability is higher. Studies on the ability of SNEDDS to increase the bioavailability of drugs with low solubility in the systemic circulation have been widely demonstrated. This capability applies to a variety of delivery applications: oral [4], intravenous [5], and pulmonary [6].

The composition and concentration of the formula determine the success of the formation of SNEDDS. The oil in the SNEDDS formula will affect the droplet size and stability of the nanoemulsion formed. The oil phase in SNEDDS acts as a carrier that can dissolve lipophilic active substances. The oil phase forms droplets in the gastrointestinal medium (GIT) in the presence of surfactants and co-surfactants. The oil used in this study is included in the medium-chain triglycerides (MCT), namely Miglyol 812. Miglyol 812 has a higher dissolving capacity and better stability than short-chain triglycerides (SCT) and long-chain triglycerides (LCT), such as oleic acid, olive oil, coconut oil, and virgin coconut oil [8].

Surfactants play a role in reducing interfacial tension. The choice of surfactant in SNEDDS is generally based on the safety of use and the value of hydrophilic-lipophilic balance (HLB). A high HLB value of more than ten will facilitate the decrease in the interfacial tension of the oil when the SNEDDS formula meets gastric fluid. Surfactants with low HLB values are classified as more lipophilic, and those with high HLB values are hydrophilic. Therefore, it is essential to determine surfactants with suitable HLB to form nanoemulsions when in contact with gastrointestinal media (GIT) and stabilize the formed SNEDDS [10]. Tween 80 with an HLB value of 15 was used as a surfactant because of its ability to solubilize, reduce surface tension and interfacial tension of immiscible phases [7].

The co-surfactant determines the emulsification time in the medium and the droplet size caused by the co-surfactant molecule that will place its position between the surfactants. The presence of a dense layer of surfactant and co-surfactant on the droplet surface will reduce the interfacial tension of the two liquids so that the droplet size can be maintained at the nanometer scale. Co-surfactants in SNEDDS, such as PEG 400 [11], glycerin [10] have been widely used in the formulation of SNEDDS. PEG 400 was chosen as a co-surfactant in the SNEDDS formulation of Dayak onion extract because it has a high HLB value (>10) of 11.6. It can help surfactants increase the formation of nanoemulsions spontaneously. The results of this article review are expected to be useful for knowledge, development and utilization of SNEDDS in novel drug delivery systems.

MATERIALS AND METHODS

This review was conducted as a systematic process using several databases or computer-based electronic search, including. The inclusion criteria used in compiling this Article include the year of published literature in 2005–2020, the language of published literature in English or Indonesian, and literature in research journals. Literature in the form of research related to self-nanoemulsifying, SNEDDS, characterization, absorption, mechanism. Exclusion criteria used in compiling this article, including literature in journal reviews and literary texts, cannot be accessed entirely. The literature used is in original research through the website using several databases that can be accessed easily. International databases were obtained from ScienceDirect, Springer, PubMed, Sage, and Taylor and Francis Online. The keywords used include; self-nanoemulsifying, nanoemulsion, pseudo ternary phase, characterization of SNEDDS. Data analysis in this literature study used a meta-synthesis approach (qualitative technique) because the object of the Article that represents data in the literature is heterogeneous, which is related to research variables (analyzed characteristics) that are different from each Article analyzed, so they can only be studied in descriptive form. The strategy for collecting articles is using a Prisma Guideline diagram. The total of 51 article were selected for a more detailed review. The research strategy used in the review is illustrated in fig. 1.

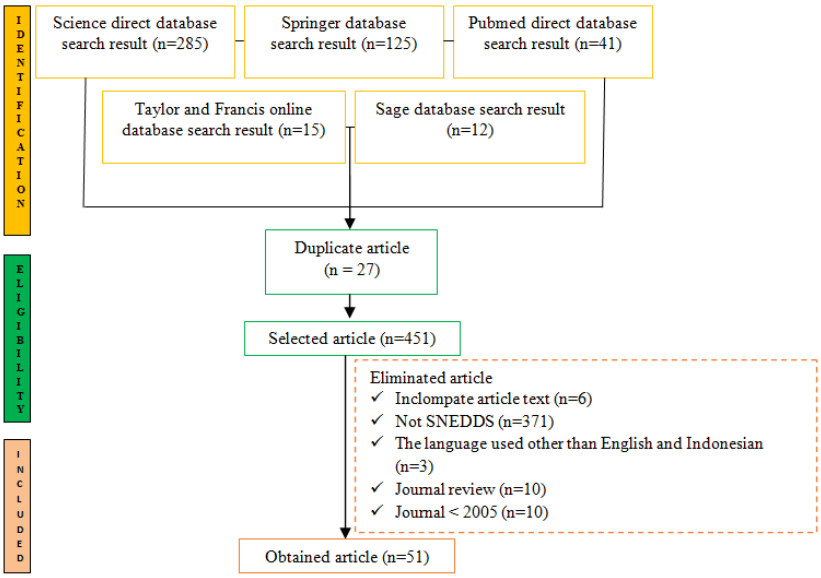

Fig. 1: Review strategy scheme

RESULTS AND DISCUSION

SNEDDS is an isotropic mixture consisting of oil, surfactant, and co-surfactant (fig. 2). The main characteristic of SNEDDS is that it can form nanoemulsions when in contact with gastrointestinal fluids in the presence of light stirring in the peristaltic motion of the gastrointestinal tract [12]. SNEDDS can produce transparent emulsions with 10-200 nm [13]. The success of the SNEDDS formula is highly dependent on the physicochemical and biological properties of its constituent components.

Despite the various advantages of SNEDDS, which can increase bioavailability, SNEDDS also have limitations. The drawbacks found in this SNEDDS are, first, there are still few *in vitro* studies on good drug formulations, then it requires a different lipid base in the formulation; the last drawback is that the drug dissolution profile still uses conventional systems with formulations that can interact before the drug arrives. in the digestive tract, which makes the drug not work optimally [8].

The effect that occurs on the SNEEDS system is based on several considerations; for example, the use of drugs with high doses is not very good because it has low solubility in water and fat; this will make drug absorption more difficult unless there is high solubility in one of them. the SNEDDS component, namely the lipophilic phase [9]. The phenomenon of the occurrence of SNEDDS is influenced by several factors, including physicochemical characteristics of the components that make up SNEDDS, component ratio, temperature and pH, physiochemical characteristics of drug substances, such as hydrophilicity/lipophilicity, pKa, and polarity [11].

Fig. 2: (A) Structure of SNEDDS (B) Process of mixing SNEDDS components [46]

SNEDDS has differences between nanoemulsions and emulsions. Emulsions and nanoemulsions are used as drug delivery systems in which two immiscible liquids are present in one preparation. Generally defined as a heterogeneous mixture consisting of a mix of oil and water components. The differences between emulsion, nanoemulsion and SNEDDS systems are presented in table 1.

Table 1: Differences in emulsion systems, nanoemulsions, SNEDDS

Characteristics	Emulsion	Nanoemulsion	SNEDDS	References
Component	Oil, surfactant, co-surfactant, and water	Oil, surfactant, co-surfactant, and water	Oil, surfactant, co-surfactant	[14-16]
Droplet size	1-10 um	10-200 nm	10-200 nm	[14-17]
Sightings	Cloudy	Transparent	Transparent	[18-20]
Stability	Kinetically stable	Thermodynamically stable	Thermodynamically stable	[21, 22]
Viscosity	Thick	dilute	Dilute	[22, 23]
Scale up	Complex	Spontaneous	Spontaneous	[23]
System establishment	In the formulation process, an emulsion is formed	In the formulation process, nanoemulsions are formed	Contact with GIT first before micelle is formed	[24]

Some of the weaknesses of drug delivery with the SNEDDS system include (1) lack of good predictive *in vitro* models for formulation assessment, (2) need for further development and validation for *in vitro* assays, (3) different lipid prototype-based formulations need to be developed and tested *in vivo* (4) the chemical instability of the drug and the high concentration of surfactant in the formulation (about 30-60%) can irritate digestion.

SNEDDS is administered in the form of soft or hard gelatin capsules and upon reaching the gastrointestinal motility of the stomach provides agitation for self-nano emulsifying into small droplets with a size of less than 200 nm to increase solubility. After oral administration, lingual and pancreatic lipases convert the oily phase of SNEDDS into an emulsion of monoglycerides, diglycerides, and fatty acids. The presence of bile acids causes the formation of micelles so that the drug will flow into the lymphatic vessels, not into the blood vessels so that it does not go through the first pass effect, as a result, oral bioavailability will increase [25-27].

Mechanism of SNEDDS in enhancing oral absorption

The bioavailability of drugs in SNEDDS can increase, with several mechanism approaches including [28]: (1) SNEDDS can cause a slowdown in gastric emptying time so that it slows down delivery to the absorption site of action; this increases in the time for the dissolution process to occur. (2) increase the solubility of the drug in the luminal. The presence of lipids in the digestive tract will increase the secretion of bile salts (BS) and endogenous bile lipids such as phospholipids (PL) and cholesterol (CH), thereby stimulating the formation of BS/PL/CH intestinal mixed micelles and increasing the solubilization capacity of the digestive tract. (3) drugs that are lipophilic, lipids can increase the amount of lymphatic transport and can increase bioavailability directly through the reduction of the first-pass metabolism. (4) the occurrence of changes in the function of the biochemical barrier in the gastrointestinal tract. Lipids and surfactants can decrease the activity of intestinal efflux transporters, as demonstrated by the p-glycoprotein efflux pump and may also reduce the amount of enterocyte-based metabolism. (5) the presence of a combination of lipids, digestion products, and surfactants can cause changes in the physical barrier function in the digestive tract. It is, therefore capable of having the effect of increasing the permeability.

The mechanism for the formation of self-nanoemulsions has not been fully elucidated. Still, it can occur when the entropy changes because the dispersion is greater than the energy required to increase the surface area [29]. The access point of conventional emulsion formulas is a direct function of the energy needed to form a novel surface between the oil and water. An overview of lymphatic transport through the intestine can be seen in fig. 3.

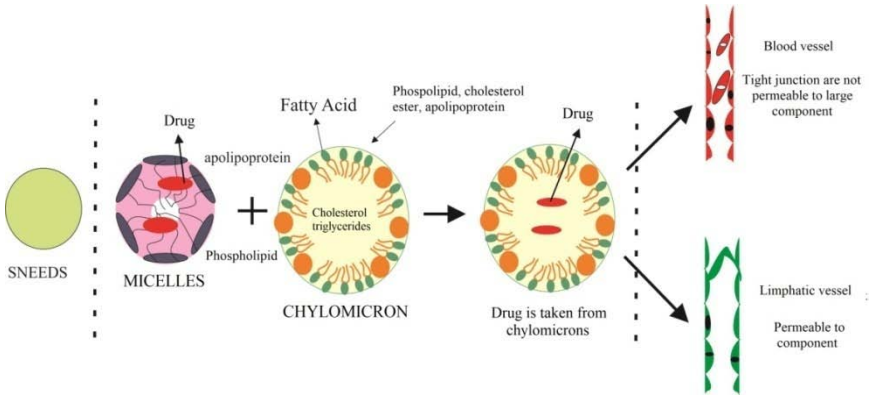

Fig. 3: Mechanism of lymphatic transport through the intestine [46]

SNEDDS formula components

Consideration of the SNEDDS component for the desired route of administration is essential at the time of formulation. The selection of constituent materials is a critical factor for the formulation. The role of the oil phase in the SNEDDS system is crucial because it affects the ability to form nanoemulsions in a fast time directly, droplet size, drug solubility, and drug fate in the body. The oil with the maximum dissolving potential for the drug model used was selected as the oily phase for the SNEDDS formulation. This is to help achieve top drug loading in SNEDDS. In the SNEDDS formulation, a mixture of oil and medium-chain triglycerides with a carbon chain length of 6-12 (C6-C12) can also be used to obtain emulsification with a high drug loading capacity. Medium-chain triglycerides have a high dissolving capacity and are resistant to oxidation so the mixture of oil and triglycerides will produce the characteristics of the oil phase needed in the self-nano emulsifying drug delivery system [30].

Oils with too long hydrocarbon chains, such as soybean oil or long-chain triglycerides (LCT) are challenging to form nanoemulsions, and the resulting droplet size is much larger than the SNEDD system using MCT. Medium-chain triglycerides and short-chain triglycerides, such

as medium-chain monoglycerides and fatty acid esters (e. g. ethyl oleate), are easier to nanoemulsify than long-chain triglycerides but exhibit no better SNEDDS stability compared with SNEDDS using medium-chain triglycerides oil. Long-chain triglycerides show a more remarkable ability to increase drug transport to intestinal lymphatics to prevent the first-pass metabolism of drugs than medium-chain tri-, di-and mono-glycerides [7]. The various components of the oil phase are listed in table 2.

Table 2: Various components of the oil phase

General class	Examples	Commercial name	Acceptability	References
Fixed oils	Soybean oil, castor oil	-	P/O/T/Oc/M	[30, 31]
MCTs	Triglycerides of capric/caprylic acids Triacetin	Miglyol 810,812, Labrafac CC Crodamol GTCC, Captex 300, 355, Captex 500	P/O/T/Oc/M	[30, 31]
Medium-chain mono-and diglycerides	Mono-and di-glycerides of capric/caprylic Acids	Capmul MCM, Imwitor 742 Akoline MCM	O/T	[32]
Long-chain mono-glycerides	Glyceryl monooleate Glyceryl monolinoleate	Peceol, Capmul-GMO Maisine-35	O/T O/T	[32-34]
PG fatty acid esters	PG monocaprylate PG monolaurate/dila urate PG dicaprylate/caprate	Capryol 90, Capmul PG-8, Sefsol 218 Lauroglycol 90, Capmul PG-12, Lauroglycol FCC Miglyol 840, Captex 200	O/T	[35, 36]
Fatty acid esters	Ethyl oleate Isopropyl myristate Isopropyl, palmitate	Crodamol EO	P/O/T/Oc/M P/T/Oc/M P/T/Oc/M	[35, 36]
Fatty acids	Oleic acid, Caprilyc acid	Crossential 094	O/T/M, O/T/M	[37]
Vitamins	Vitamin E		P/O/T/Oc/M	[38]

M; Mucosal; MCT: Medium-chain trygliceride; O: Oral; Oc: Ocular; P: Parenteral; PG: Propylene glycol; T: Topical (dermal).

Previous research on the development of SNEDDS of Dayak onion ethanol extract used vegetable oil as the oil phase, including olive oil, coconut oil, oleic acid and VCO. VCO is one type of oil with a medium-chain fatty acid. The results of this study show that vegetable oil is not much better than medium-chain triglycerides such as Miglyol 812 [8]. The use of medium-chain triglycerides can stabilize preparations better than oils with longer chains. That is why the oil used in the SNEDDS research this time is Miglyol 812, which consists of a mixture of saturated fatty acid triglycerides, especially those derived from caprylic acid and capric acid. Miglyol 812 is a slightly yellowish liquid oil, practically odorless, tasteless, and solidifies at about 0oC. Miglyol 812 itself is one of the oils that has been used in various formulations such as oral, parenteral and topical preparations. For use in oral formulations, Miglyol 812 is used as a basis for making oral emulsions, microemulsions, self-nano emulsifying systems, solutions, or drug suspensions that are unstable or insoluble in aqueous media, so that preparations are expected to be more stable [39].

Miglyol 812 consists of a mixture of medium-chain unsaturated fatty acid triglycerides, mainly of caprylic acid and capric acid. Miglyol 812 contains not less than 90 % saturated fatty acids. Miglyol 812 oil has a yellowish color, is practically odorless and tasteless, and solidifies at about 0 °C ([40]. Surfactants also have an essential role in SNEDDS to reduce droplet size. They can stabilize the active substance for a long storage period at the absorption site to prevent precipitation in the gastrointestinal tract. The basis for selecting SNEDDS can be seen from the HLB value, viscosity, and affinity in the oil phase, which have a significant influence on the nanoemulsion process and the resulting droplet particle size [41]. Surfactants should be selected according to the route of administration to be used and must be safe and non-toxic for use. The surfactant is harmful, has no beneficial biological effect, or does not depend on the chemical properties and concentration of the surfactant. Selection of the right surfactant concentration is critical, as the use of too much surfactant that can irritate the digestive tract. Water-soluble surfactants such as tween 80 and tween 20 are often used in the SNEDDS formula. It is safe, biocompatible, and relatively stable because it is not affected by changes in pH. The type of surfactant used in the SNEDDS formula is a surfactant with an HLB value of more than ten, and this is because an HLB>10 will be able to form an oil-in-water (W/W) nanoemulsion. In some formulations, a mixture of hydrophobic and hydrophilic surfactants can be used to form nanoemulsions with the desired characteristics [42]. Some general considerations that can aid in the selection of surfactants in the SNEDDS system are: (1) exhibit good surface activity and lower surface tension (2) form an interfacial film, either singly or conjugated with other molecules that are also adsorbed (3) can be dispersed at the interface quickly to ensure that the interfacial tension is sufficiently lowered and the nanoemulsion is formed immediately (4) the mixture of the water-soluble oil component with the water-soluble component is more stable than the single component (5) the nonpolar component is the oil phase, the more hydrophilic is the surfactant. If the oil to be emulsified is less polar, then the surfactant must be lipophilic.

Co-surfactants aim to assist the work of surfactants in lowering the surface tension of water and oil and increasing the dissolution of the active substance. Examples of co-surfactants are glycerol, ethanol, transcutol, and propylene glycol. The co-surfactant in the SNEDDS formulation also serves to increase the drug loading capacity in the SNEDDS system. Co-surfactants affect the emulsification time and nanoemulsion droplet size. The chosen co-surfactant is short-chain alcohol because it can reduce interfacial tension, increase interfacial fluidity, and increase the mixing of water and oil because of its partition between the two phases [43-45].

Characterization of self-nanoemulsifying drug delivery systems (SNEDDS)

Percent (%) transmittance

In testing a sample, the transmittance is defined as the light intensity in percent (%). The interpretation of the transmittance test results can be observed physically by looking at the clarity of a preparation. The clearer a formulation that is formulated, it will produce a high % transmittance with a value of 80-100%. The transmittance value in the SNEDDS test explains that the SNEDDS formula has been homogeneously mixed with droplet sizes ranging from nanometers to<200 nm with a clear and transparent appearance.

This test is one of the critical factors in looking at the physical properties of the nanoemulsion system that has been formed, which is included in the quality parameters for the characterization of SNEDDS preparations. This increases the surface area so that the release and absorption of drugs in the gastrointestinal tract can occur more quickly. The excellent transmittance value for SNEDDS is more than 80%. The percent transmittance was measured using a UV-Vis spectrophotometer at a wavelength of 650 nm. If the percent transmittance of the sample has a result that is close to the percent

transmittance of distilled water, which is 100%, then the selection is declared to have a level of clarity similar to that of water [46].

Emulsification time

Emulsification time is a test carried out to measure the speed of SNEDDS forming nanoemulsions after contact with intestinal fluids in the stomach. The main requirement of SNEDDS is said to meet the needs it can form nanoemulsions directly with light stirring. The selection of oil, surfactant and co-surfactant in the SNEDDS formula is critical to emulsification in the gastrointestinal tract. The faster the emulsification time, the higher the absorption of the drug. The interpretation of a good emulsification time test results is if, within 1-2 min, it can form a nanoemulsion by producing a clear and transparent liquid.

Viscosity

Viscosity testing aims to determine the amount of resistance of the flow given by a liquid. Viscosity is related to the relative motion between parts of the fluid, so this quantity measures the difficulty level of fluid flow. The greater the viscosity of a fluid, the more difficult it is for the liquid to flow.

Droplet size

Pharmaceutical preparations that use SNEDDS will, of course, have a particle size below 200 nm so that SNEDDS can become a drug delivery system that has high clarity and stability. The small particle size in the SNEDD system results in an apparent preparation when testing the percent transmittance. The presence of small particle size can prevent sedimentation from increased stability. This test uses a particle size analyzer (PSA) instrument.

Emulsification time

This test was conducted to determine the stability of nanoparticles' bonding in digestive juices and the extent to which SNEDDS can interact with gastric acid to form a self-emulsification system. Performed to mimic the physiological dilution process after oral administration, the selected formula was diluted with water, AGF (Artificial Gastric Fluid) and AIF (Artificial Intestinal Fluid) without enzymes.

Thermodynamic stability test

Assessment of the stability of the nanoemulsion system can be done by testing the thermodynamic equilibrium. The types of thermodynamic stability are the heating-cooling cycle and the freeze-thaw cycle. Interpretation of this stability test results by observing the absence of phase separation after being treated according to the storage temperature for a certain time.

Effect of physicochemical properties of SNEDDS on *in vivo* activity

Particle size

In the oral route of drug administration, the particle size of SNEDDS is critical because it can directly influence *in vitro* assays (e. g., stability and release kinetics) and *in vivo* activity. It has been reported that the small droplet size of SNEDDS has a beneficial effect on the bioavailability of administered drugs. One study of the SNEDDS formulation with the same components but using different methods explained the bioavailability of cyclosporine A (CSA) in rats by administering the drug in nanoemulsion-formed particles of various sizes. With the decrease in droplet size, there was an increase in the oral absorption of CsA. The SNEDDS CsA test was carried out on healthy volunteers with the results of particle size characteristics testing of 25-400 nm. This study demonstrated an inverse correlation between the particle size of the studied SNEDDS and the oral bioavailability of CsA. Based on these results, it can be concluded that particle size distribution is critical because it affects the availability of drugs in the body after the oral administration of medicines [47].

Zeta potential

A high zeta potential value (±30 mV) indicates an electrostatic solid repulsive force, thus indicating the possibility of no flocculation, which suggests the formation of the formulated SNEDDS. However, because SNEDDS is used in the form of a pre-concentrated formulation, it can be included in a soft capsule. The formation of nano-dispersions only occurs when SNEDDS is in contact with gastrointestinal fluids. The charge of the particles formed can influence the bioavailability of orally administered SNEDDS. The charge interactions that appear depend on human intestinal cells in terms of drug absorption [48].

Another study in the formulation of SNEDDS progesterone by conducting a potential zeta test showed that the formulated SNEDDS progesterone could form positively charged particles after dilution with the aqueous phase. Therefore, it is known that positively charged particles can interact with negatively charged mucosal surfaces of the GI tract and enhance cellular absorption of orally administered drugs. Oral administration of the drug in this formulation resulted in increased progesterone bioavailability in female rats. Thus it can be concluded that the droplet size and the charge of the particles formed after SNEDDS contact with the GI liquid or aqueous phase can affect stability, release kinetics, and most importantly affect, drug absorption.

Drug solubility

BCS class II drug compounds have low solubility in water. Lipid-based drug formulations can increase drug solubility by using maximal doses. Lipid-based formulations, including SNEDDS can induce changes in lipid composition in the GI tract. Thus, the dissolved phase is not obtained directly from the given lipid-based formulation but is most likely from intra-luminal processing. The lipids are in contact before the absorption process. Therefore, a review of the physiology of lipid absorption in the GI is key to understanding the role of lipids and the mechanism by which lipid-based formulations can increase drug solubility. The delivery system with lipid-based materials in the duodenum can stimulate the secretion of endogenous-derived bile solubilizing components such as bile salts and bile lipids (cholesterol and phospholipids). Bile increases the solubility of lipid products (e. g. 2-monoglycerides and fatty acids) in the intestinal lumen to form micelles. The formation of mixed-phase micelles significantly expands the drug-dissolving capacity of the small intestine. When a water-soluble drug is administered with the lipid present in the formulation, then the drug can be distributed among the colloidal fluids formed. This process prevents the precipitation of the drug and causes an increase in solubility in gastrointestinal fluids. In addition, the utilization of SNEDDS can generate a large interfacial area for partitioning lipophilic drugs between the oil and gastrointestinal (GI) fluids. Some studies have reported that SNEDDS can increase the solubility of drug compounds that have poor solubility in water [49-51].

Membrane permeability

The increase in transcellular permeability may be due to the increased bioavailability of drugs administered in the form of SNEDDS. One of the mechanisms behind this phenomenon is associated with the SNEDDS component of the enterocyte membrane, causing an increase in fluidity and thereby increasing passive permeability. Other studies have shown that changes in membrane fluidity by SNEDDS components can change the conformation of membrane-bound transporters to inhibit membrane-bound efflux transporters. Drug permeability can be increased by using SNEDDS as SOP through a combination of mechanisms, namely passive transcellular enhancement and efflux transporters. Certain nonionic surfactants used in SNEDDS components may reduce drug efflux pump activity. Efflux transporters that have a function in terms of drug absorption are the product of the MDR 1 P-glycoprotein (P-gp) gene. These plasma membrane-bound proteins are distributed in the drug elimination organs. In the apical membrane of intestinal epithelial cells its role is to secrete compounds back into the intestinal lumen. Therefore, the mixture may act as a barrier to the oral absorption of P-gp substrates. Tween, Spans, Cremophors (EL and RH40) and vitamin E TPGS are examples of nonionic surfactants that have been reported to inhibit P-gp efflux activity. Increases in maximal plasma drug concentration (Cmax) and area under the curve (AUC) of the well-known P-gp digoxin substrate when orally administered with Tween 80 to mice.

Effects of SNEDDS on the first-pass metabolism

In general, the liver plays a role in the process of first-pass metabolism, where the intestinal wall serves as a barrier to drug permeability. The conventional point of view is based on the observation that enzymes that metabolize enzymes in the liver are lower than they should be. Nonetheless, the enzyme of sub-CYP3A is expressed in villous end enterocytes of the small intestine. The CYP3A enzyme subgroup is thought to have a significant role in stage I metabolism in humans. CYP3A plays a role in oxidative metabolism in ~50% of currently marketed drugs. This suggests that CYP3A enzymes constitute >70% of small intestinal CYP P450s, whereas CYP3A constitutes only 30% of human liver CYPs. Thus, the perception that the liver is the only major organ responsible for the effect of the first-pass metabolism is replaced by the intestinal wall can also significantly contribute to the drug metabolism process. Clinical pharmacokinetic studies on phase I metabolism demonstrated a substantial role of metabolism on the oral bioavailability of CsA in healthy volunteers. The results revealed that 14% of orally administered CsA was not maximally absorbed due to irreversible efflux by P-gp or GI degradation, 51% (of the absorbed dose) was metabolized in enterocytes, and only 8% was lost due to metabolism. First, pass in the heart. In addition, intestinal phase I first-pass metabolism is clinically relevant for several other drugs: midazolam, tacrolimus, nifedipine, felodipine, and verapamil. Thus, the observations of this study demonstrate the superiority of intestinal enzymes in first-pass metabolism. Therefore, the influence of the gut on phase I first-pass metabolism on oral drug bioavailability cannot be ignored. Intestinal first-pass metabolism and hepatic first-pass metabolism are two different processes; therefore, some drugs metabolized in the liver become the main barrier in the absorption process, while other medications metabolized in the intestinal first-pass may predominate [24].

In drug delivery systems to avoid the first-pass metabolism in the liver. It can be assumed that some lipophilic drugs can associate with TG from chylomicrons in enterocytes and enter the systemic circulation via the lymphatics. Lipid-based delivery systems such as SNEDDS can be used to enhance lymphatic drug transport. The oil phase used in the SNEDDS formulation is a critical component. Not only can the oil phase facilitate the dissolution of lipophilic compounds, but it can also affect the absorption of the inserted drug. Several investigators reported that the biologic taxonomy of these drugs is strongly influenced by long-chain triglycerides (LCTs), suggesting that lipid-based delivery systems containing LCTs, such as SNEDDS, can explain lymphatic transport of lipophilic drugs by bypassing the hepatic portal vein pathway and increasing their bioavailability. Orally. It has been recently reported that not only SNEDDS oil components can play a role in lymphatic transport, but certain surfactants can also produce the same effect. As surfactant concentrations in SNEDDS formulations are high and can reach up to 60%, their contribution to lymphatic transport needs to be explored further [7, 8].

Effects of SNEDDS on drug bioavailability by oral administration

The previous section of this review focused on the different barriers in the absorption process of most BCS class II compounds. Many studies have explained that SNEDDS has the advantage of increasing the bioavailability of *in vivo* characteristics. Scientists as a suitable formulation, have widely studied SNEDDS to increase the bioavailability of oral preparations, especially for drug compounds included in BCS class II. To date,>30% of drugs marketed in the US and 70% of all new drug candidates are lipophilic and consequently have poor water solubility. In general, the bioavailability of class II compounds is deficient. The use of lipid-based SOPs such as SNEDDS can increase the bioavailability of class II drugs. Utilization of lipid-based drug delivery systems in general and SNEDDS, in particular, shows great potential in increasing solubility, increasing bioavailability, and reducing inter-subject variability. The ability of SNEDDS to increase the bioavailability of orally administered drugs from water-insoluble drugs. The data summarized in the current review suggest that SNEDDS can increase oral bioavailability through several mechanisms, such as reduced intra-enterocyte metabolism by CYP P450 enzymes, reduced P-gp efflux activity, and bypassing hepatic first-pass metabolism via lymphatic uptake [27].

CONCLUSION

Self Nanoemulsifying drug delivery system (SNEDDS) is a new approach for the formulation of drug molecules with poor water solubility. Self Nanoemulsifying drug delivery system (SNEDDS) is an isotropic mixture of oil, surfactant, and co-surfactant. When introduced into the aqueous phase, it emulsifies spontaneously to produce a fine nanoemulsion with gentle agitation. SNEDDS is a good alternative for drug formulations that are difficult to dissolve in water. SNEDDS increases the dissolution of the drug due to the increase in the surface area of the dispersion and the rate of absorption of drug molecules. Oral delivery of lipophilic drugs can be made possible by SNEDDS, essential for increasing oral bioavailability. According to this approach, it is possible to prolong the drug release by incorporating the polymer in the composition. SNEDDS appears to be emerging as a unique and industrially enduring approach with future developments.

ACKNOWLEDGMENT

This review article is part of the Doctoral Program of Pharmaceutical Science, Faculty of Pharmacy, Universitas Airlangga. Do not forget to convey to Kementrian Agama Republik Indonesia, which has provided scholarship funds for the 5000 doctoral programs.

AUTHORS CONTRIBUTIONS

Conceptualization: Annisa, R. Data curation: Annisa, R., Mutiah, R. Supervision: Hendradi, E., Yuwono, M. Writing–original draft: Annisa, R. Writing–review and editing: Hendradi, E., Yuwono, M.

CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest.

REFERENCES

1. Martien R, Adhyatmika IDK, Irianto, Verda F, Dian PS. Perkembangan teknologi nanopartikel sebagai Penghantaran obat. Majalah Farmaseutik. 2012;8(1):133-44.
2. Huang QR, Yu HL, Ru QM. Bioavailability and delivery of nutraceuticals using nanotechnology. J Food Sci. 2010;75(1):R50-7. doi: 10.1111/j.1750-3841.2009.01457.x, PMID 20492195.
3. Sakloetsakun D, Dunnhaupt S, Barthelmes J, Perera G, Bernkop Schnurch A. Combining two technologies: multifunctional polymers and self-nanoemulsifying drug delivery system (SNEDDS) for oral insulin administration. Int J Biol Macromol. 2013;61:363-72. doi: 10.1016/j.ijbiomac.2013.08.002, PMID 23933302.
4. Nasr A, Gardouh A, Ghorab M. Novel solid self-nano emulsifying drug delivery system (S-SNEDDS) for oral delivery of olmesartan medoxomil: design, formulation, pharmacokinetic and bioavailability evaluation. Pharmaceutics. 2016;8(3):1-29. doi: 10.3390/pharmaceutics8030020, PMID 27355963.
5. Li P, Nielsen HM, Mullertz A. Impact of lipid-based drug delivery system on the transport and uptake of insulin delivery: *in vitro* and *in vivo* evaluations of enteric coating and drug loading. Int J Pharm. 2016;477:390-8.
6. Tonnis WF, Kersten GF, Frijlink HW, Hinrichs WL, de Boer AH, Amorij JP. Pulmonary vaccine delivery: a realistic approach? J Aerosol Med Pulm Drug Deliv. 2012;25(5):249-60. doi: 10.1089/jamp.2011.0931, PMID 22856876.
7. Yuwono M, Hendradi E, Annisa R. Design and optimization of eleutherine palmifolia extract-loaded SNEDDS using HLB approach. JRP. 2020;24(6):943-51. doi: 10.35333/JRP.2020.254.
8. Annisa R, Hendradi E, Yuwono M. Effect of vegetable oil on self-nanoemulsifying drug delivery system of Dayak onion [*Eleutherine palmifolia* (L.) merr.] extract using hydrophilic-lipophilic balance approach: formulation, characterization. Int J Drug Deliv Technol. 2020;10(2):230-15.
9. Avachat AM, Patel VG. Self-nanoemulsifying drug delivery system of stabilized ellagic acid-phospholipid complex with improved dissolution and permeability. Saudi Pharm J. 2015;23(3):276-89. doi: 10.1016/j.jsps.2014.11.001, PMID 26106276.
10. Winarti L, Suwaldi MR, Hakim L. Formulation of self-nano emulsifying drug delivery system of bovine serum albumin

using HLB (hydrophilic-lipophilic balance) approach. Indo J Pharm. 2016;27:117-2.

11. Nazari Vanani RN, Azarpira N, Heli H. Development of self-nanoemulsifying drug delivery systems for oil extracts of Citrus *Aurantium l.* blossoms and *Rose damascena* and evaluation of anticancer properties. J Drug Deliv Sci Technol. 2018;47:330-6. doi: 10.1016/j.jddst.2018.08.003.
12. Mathew R, Varkey J. Formulation and *in vitro* evaluation of self nano emulsifying drug delivery system of quercetin for enhancement of oral bioavailability. Int J Curr Pharm Sci 2022;14(1):60-9. doi: 10.22159/ijcpr.2022v14i1.44113.
13. Cirri M, Bragagni M, Mennini N, Mura P. Development of a new delivery system consisting in "drug–in cyclodextrin–in nanostructured lipid carriers" for ketoprofen topical delivery. Eur J Pharm Biopharm. 2012;80(1):46-53. doi: 10.1016/j.ejpb.2011.07.015. PMID 21839833.
14. Aldawsari HM, Elfaky MA, Fahmy UA, Aljaeid BM, Alshareef OA, El-Say KM. Development of a fluvastatin-loaded self-nanoemulsifying system to maximize therapeutic efficacy in human colorectal carcinoma cells. J Drug Deliv Sci Technol. 2018;46:7-13. doi: 10.1016/j.jddst.2018.04.015.
15. Balakaumar K, Raghavan CV, Selvan NT, Prasad RH, Abdu S. Self-nano emulsifying drug delivery system (SNEDDS) of rosuvastatin calcium: design, formulation, bioavailability and pharmacokinetic evaluation. Colloids Surf Biointer. 2013;112:337-43.
16. Date AA, Nagarsenker MS. Design and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) for cefpodoxime proxetil. Int J Pharm. 2007;329(1-2):166-72. doi: 10.1016/j.ijpharm.2006.08.038, PMID 17010543.
17. Desmukh A, Kulkarni S. Solid self micro emulsifying drug delivery system of ritonavir. Drug Deliv Indian pharma. 2014;40:477-87.
18. Garg V, Kaur P, Singh SK, Kumar B, Bawa P, Gulati M. Solid self-nanoemulsifying drug delivery systems for oral delivery of polypeptide-k: formulation, optimization, *in vitro* and *in vivo* antidiabetic evaluation. Eur J Pharm Sci. 2017;109:297-315. doi: 10.1016/j.ejps.2017.08.022, PMID 28842349.
19. Patel J, Patel A, Raval M, Sheth N. Formulation and development of a self-nanoemulsifying drug delivery system of irbesartan. J Adv Pharm Technol Res. 2011;2(1):9-16. doi: 10.4103/2231-4040.79799, PMID 22171286.
20. Pouton CW. Self-emulsifying drug delivery systems: assessment of the efficiency of emulsification. International Journal of Pharmaceutics. 1985;27(2-3):335-48. doi: 10.1016/0378-5173(85)90081-X.
21. Pratiwi L, Fudholi A, Martien R, Pramono S. Self-nanoemulsifying drug delivery system (SNEDDS) for topical delivery of mangosteen peels (Garcinia mangostana L.,): formulation design and *in vitro* studies. JYP. 2017;9(3):341-6. doi: 10.5530/jyp.2017.9.68.
22. Priani SE, Nurrayyan N, Darusman F. Formulation self nano emulsifying drug delivery system glimepiride using oleic acid as oil phase. Pharmaciana. 2017;7(2):67-276. doi: 10.12928/pharmaciana.v7i2.7387.
23. Erawati T, Hendradi E, Soeratri W. Praformulation study of p-methoxy cinnamic acid (APMS) nanoemulsion using vegetable oils (soybean oil, corn oil, VCO). Int J Pharm Pharm Sci. 2014;6(2):99-101.
24. Nazzal SA, Gardouh A, Ghorah M. Novel solid self nanoemulsifying drug delivery system (S-SNEDDS) for oral delivery of olmesartan medoxomil: design, formulation, pharmacokinetics, and bioavailability evaluation. Pharmaceutics. 2016;8(20):1-29.
25. Pujara ND. Self-nanoemulsifying drug delivery systems: a novel approach. Int J Curr Pharm Res. 2012;4:18-23.
26. Komura H, Iwaki M. *In vitro* and *in vivo* small intestinal metabolism of CYP3A and UGT substrates in preclinical animals species and humans: species differences. Drug Metab Rev. 2011;43(4):476-98. doi: 10.3109/03602532.2011.597401, PMID 21859377.
27. Makadia HA, Bhatt AY, Parmar RB, Paun JS, Tank HM. Self-nanoemulsifying drug delivery systems (SNEDDS): future aspects. Asian J Pharm Res. 2013;3:21-7.
28. Gottemukkula LD, Sampathi S. SNEDDS as lipid-based nanocarrier systems: concepts and formulation insights. Int J App Pharm. 2022;14(2):1-9. doi: 10.22159/ijap.2022v14i2.42930.
29. Yadav. Novel approach: herbal remedies and natural products in pharmaceutical science as Nano drug delivery systems. Int J Pharm Technol. 2011;3(3):3092-116.
30. Syukri Y, Nugroho BH, Istanti I. Penggunaan d-optimal mixture design untuk optimasi dan formulasi self-nano emulsifying drug delivery system (SNEEDS) asam mefenamat. J Sains Farm Klin. 2020;7(3):25-31. doi: 10.25077/jsfk.7.3.180-187.2020.
31. Jain S, Kambam S, Thanki K, Jain AK. Cyclosporine a loaded self-nanoemulsifying drug delivery system (SNEDDS): implication of a functional excipient based co-encapsulation strategy on oral bioavailability and nephrotoxicity. RSC Adv. 2015;5(61):49633-42. doi: 10.1039/C5RA04762E.
32. Reddy S, Sowjanya N. Formulation and *in vitro* characterization of solid self nanoemulsifying drug delivery system (s-SNEDDS) of simvastatin. J Pharm Sci Res. 2015;7:40-8.
33. Kaur G, Harikumar SL. Formulation development of self nanoemulsifying drug delivery systems (SNEDDS) of celecoxib for improvement of oral bioavailability. Pharmacophore. 2013;4:120-30.
34. Sakhti U, Lobo JR, Uppuluri KB. Self-nano emulsifying drug delivery system (SNEDDS) for delivery of hydrophobic drugs. Biomed Pharmacol J. 2013;4:335-6.
35. Rao SVR, Shao J. Self-nanoemulsifying drug delivery systems (SNEDDS) for oral delivery of protein drug: formulation development. Int J Pharm. 2008;362(2-3):7-8.
36. Gursoy N, Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharma. 2008;58(3):173-82.
37. Kommuru TR, Gurley B, Khan MA, Reddy IK. Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: formulation development and bioavailability assessment. Int J Pharm. 2001;212(2):233-46. doi: 10.1016/s0378-5173(00)00614-1, PMID 11165081.
38. Kazi M, Mohammed A, Ajaz A, Mohammad R, Fars K, Alanazi MM Badri, Azmat Ali Khan, Amer M Alanazi, Muhammad Delwar Hussain. Evaluation of self-nanoemulsifying drug delivery system (SNEDDS) for poorly water-soluble talinolol: preparation, *in vivo* and *in vitro* assessment. J Front Pharm. 2019;2:205-301.
39. Khan AW, Kotta S, Ansari SH, Sharma RK, Ali J. Self-nanoemulsifying drug delivery system (SNEDDS) of the poorly water-soluble grapefruit flavonoid Naringenin: design, characterization, *in vitro* and *in vivo* evaluation. Drug Deliv. 2015;22(4):552-61. doi: 10.3109/10717544.2013.878003, PMID 24512268.
40. Marasini N, Yan YD, Poudel BK, Choi HG, Yong CS, Kim JO. Development and optimization of self-nanoemulsifying drug delivery system with enhanced bioavailability by box-behnken design and desirability function. J Pharm Sci. 2012;101(12):4584-96. doi: 10.1002/jps.23333. PMID 23023800.
41. Sangar, Priyanka, Baghdar S, Shelake S, Patil P, Baghwat D. Design, development, and evaluation of self nanoemulsifying drug delivery system of garlic oil using capryol PGMC. Indian J Pharm Educ Res. 2019;53:4-9.
42. Ujhelyi Z, Vecsernyes M, Feher P, Kosa D, Arany P, Nemes D. Physico-chemical characterization of self-emulsifying drug delivery systems. Drug Discov Today Technol. 2018;27:81-6. doi: 10.1016/j.ddtec.2018.06.005, PMID 30103867.
43. Villar AMS, Naveros BC, Campmany ACC, Trenchs MA, Rocabert CB, Bellowa LH. Design and optimization of self-nanoemulsifying drug delivery systems (SNEDDS) for enhanced dissolution of gemfibrozil. Int J Pharm. 2012;431(1-2):161-75. doi: 10.1016/j.ijpharm.2012.04.001, PMID 22498011.
44. Wahhab AA. Optimization of self-nanoemulsifying formulations for weakly basic lipophilic drugs: role of acidification and experimental design. Brazil J Pharm Sci. 2016;52(4):231-20.
45. Wang L, Dong J, Chen J, Eastoe J, Li X. Design and optimization of a new self-nanoemulsifying drug delivery system (SNEDDS). J Colloid Interface Sci. 2009;330(2):443-8. doi: 10.1016/j.jcis.2008.10.077, PMID 19038395.

46. Zhao TJ, Maniglio D, Chen J, Chen B, Motta A, Migliaresi C. Design and optimization of self-nanoemulsifying formulations for lipophilic drugs. Nanotechnology. 2015;26(12):125102. doi: 10.1088/0957-4484/26/12/125102, PMID 25744555.
47. Wu Y, Yang W, Wang C, Hu J, Fu S. Chitosan nanoparticles as a novel delivery system for ammonium glycyrrhizinate. Int J Pharm. 2005;295(1-2):235-45. doi: 10.1016/j.ijpharm.2005.01.042, PMID 15848008.
48. Ye J, Wu H, Huang C, Lin W, Zhang C, Huang B. Comparisons of *in vitro* Fick's first law, lipolysis, and *in vivo* rat models for oral absorption on BCS II drugs in SNEDDS. Int J Nanomedicine. 2019;14:5623-36. doi: 10.2147/IJN.S203911. PMID 31440045.
49. Yin L, Qin C, Chen K, Zhu C, Cao H, Zhou J. Gastro-floating tablets of cephalexin: preparation and *in vitro*/*in vivo* evaluation. Int J Pharm. 2013;452(1-2):241-8. doi: 10.1016/j.ijpharm.2013.05.011, PMID 23680730.
50. Sintov AC, Shapiro L. New microemulsion vehicle facilitates percutaneous penetration *in vitro* and cutaneous drug bioavailability *in vivo*. J Control Release. 2004;95(2):173-83. doi: 10.1016/j.jconrel.2003.11.004, PMID 14980766.
51. Shafiq-un-Nabi S, Shakeel F, Talegaonkar S, Ali J, Baboota S, Ahuja A. Formulation development and optimization using nanoemulsion technique: a technical note. AAPS PharmSciTech. 2007;8(2):28. doi: 10.1208/pt0802028. PMID 17622106.