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Effectiveness of SNEDDS to Increased Oral Bioavailability in Antihypertension Agents : A Review

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Abstract

Hypertension is a disease that is well known, but the drug solubility of oral Antihypertension drugs has problems with their solubility. The aim of this study was to determine the effect of the SNEDDS formulation on oral Antihypertension drugs. The research method used is a systematic literature review method with PRISMA guidelines using reputable databases namely PubMed, Scopus, and ScienceDirect. From the results of the research studies conducted, the value of the particle size in the SNEDDS preparation of oral Antihypertension drugs is in the range of 13.91–169 nm with a PDI value of ≤ 0.5, which meets the particle size requirements for SNEDDS < 200 nm, and the zeta potential indicating > ± 30 mV, an increase in AUC, Cmax, and Tmax rating in the SNEDDS preparation. This result that the application of SNEDDS to oral Antihypertension drugs is effective in increasing the bioavailability of BCS class II and IV drugs.

Keywords: *SNEDDS, Antihypertension, Bioavailability, Solubility, Permeability*

1. Introduction

Hypertension is defined as persistent systolic blood pressure (SBP) above ≥ 140 mm Hg and/or diastolic blood pressure (DBP) above ≥ 90 mm Hg after repeated examinations (Felkle et al., 2022). Antihypertension treatment is mostly commonly performed using the oral route (Buya et al., 2020). The use of oral routes became the first choice in treatment due to safety as well as convenience in drug administration to achieve the desired therapeutic effect (Desai et al., 2012).

However, oral drug delivery may inhibit drug molecules that exhibit poor aqueous solubility (Patel et al., 2011). Approximately 40% of the new chemical entities exhibit poor aqueous solubility and present major challenges to modern drug delivery systems leading to poor oral bioavailability, high intra- and intersubjective variability, and a lack of dose proportionality (Patel et al., 2011). According to the BCS classification, most class II and IV drugs have low bioavailability due to their low solubility or permeability, which greatly limits their absorption and leads to a waste of medical resources. Among them, more than 50% of the new drugs are lipophilic, with poor water solubility and low bioavailability (Zhou et al., 2018).

Antihypertension agents such as Furosemide, (Beg et al., 2012; mendes, 2017; Alhasani et al., 2019; Subramanian et al., 2016), belong to BCS class II and IV. To improve the solubility and permeability of lipophilic drugs, many formulations and delivery systems have been designed and developed, including liposomes, polymeric nanoparticles, nanoemulsions, microspheres, and inorganic nanoparticles [10]. The most accepted approach is SNEDDS (Self-Nanoemulsifying Drug Delivery System). SNEDDS is a preparation consisting of active substances, surfactants, co-surfactants, and oils. SNEDDS will form a nano-size emulsion by itself when it encounters liquid in the stomach. The application of oil SNEDDS components, surfactants and cosurfactants must be adjusted to the

compounds of the active substance, to provide a maximum effect. The determination of administration of excipients can be determined using the Smix diagram or other methods.

In the human body, the agitation required for the formation of nanoemulsions is provided by the digestive motility of the gastrointestinal tract compared to conventional lipid-based drug delivery systems, SNEDDS have shown a great improvement in the solubility and oral bioavailability of hydrophobic drugs, especially those belonging to BCS class II and IV, due to more uniform physicochemical properties and lower surface free energy (Zeng & Zhang, 2017) as well as being able to improve oral bioavailability of poorly water-soluble drugs.

Based on the above exposure, the purpose of this study is to examine the effectiveness of SNEDDS preparations against oral Antihypertension agents in increasing the bioavailability of oral Antihypertension drugs. In addition, a study of SNEDDS preparations will be carried out on their formulations and characteristics. From the results of this study, it is hoped that the positive effects of applying SNEDDS for oral delivery of active substances are difficult to dissolve lair either including antihypertension agents or other agents.

2. Materials And Methods

The research was conducted using the Systematic Literature Review (SLR) method referring to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) framework, namely identification, eligibility, screening, and included. Article searches are conducted in reputable databases, namely: PubMed, ScienceDirect, and Scopus. The results of the article search using these keywords got 33 articles from the PubMed page, 16 Articles from Scopus, and 32 articles from the old ScienceDirect. The results of the selection using inclusion and exclusion criteria obtained 19 articles for further data extraction and analysis. Article searches on the database are carried out using the search keywords: 'Antihypertension', 'SNEDDS' Antihypertension' and 'SNEDDS' Articles obtained using these keywords then enter the selection stage using inclusion and exclusion criteria. As a criterion for inclusion is a research article published in the last 10 years (2012-2022), with the theme of the article application of SNEDSS preparations on oral Antihypertension drugs. The exclusion criteria are that articles are in the form of reviews, SNEDDS formulation articles do not contain oral Antihypertension and full papers cannot be accessed. Articles selected because they meet the inclusion and exclusion criteria are then analysed and data extraction includes aspects of formulation, characterization, dissolution test results and bioavailability.

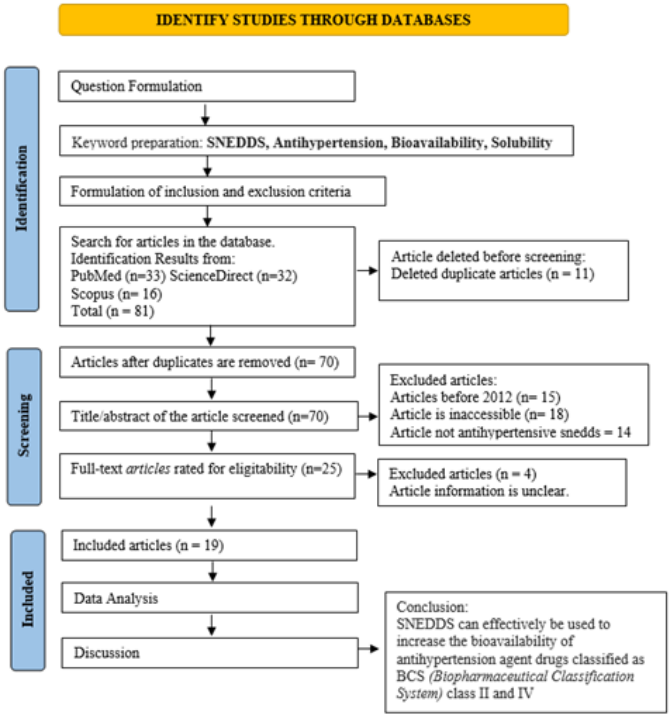


Figure 1: PRISMA of SNEDDS Data From 2012-2022

3. Results and Discussion

In the distribution of data carried out by collecting SNEDDS articles which are then stored in RIS format which is then read by VOS viewer software. In the results, there are 6 clusters. Cluster 1 is green with the topics of SNEDDS, oral drug delivery, supersaturation, sedds, absorption, drug delivery, and in vitro lipolysis. Cluster 2 is blue with the topic of solid self-nanoemulsifying drug, bioavailability. Cluster 3 is dark blue with the topics of self-nanoemulsifying drug delivery, cytotoxicity, nanoemulsion, pharmacokinetics, and self-nanoemulsifying drug deli. Cluster 4 is red with the topics of dissolution, pharmacokinetic study, solid-SNEDDS, spray drying, stability, and solid SNEDDS. Cluster 5 is yellow with the topic of oral delivery, self-nanoemulsifying drug delivery. Cluster 6 is purple with topics of self-nanoemulsifying, drug delivery, and pseudo-ternary phase diagrams. From the bibliometric map, if there is a SNEDDS study that is directed at yellow oral delivery and self-nanoemulsifying drug delivery, there is a need for preliminary research on SNEDDS in oral drugs or oral drug delivery.

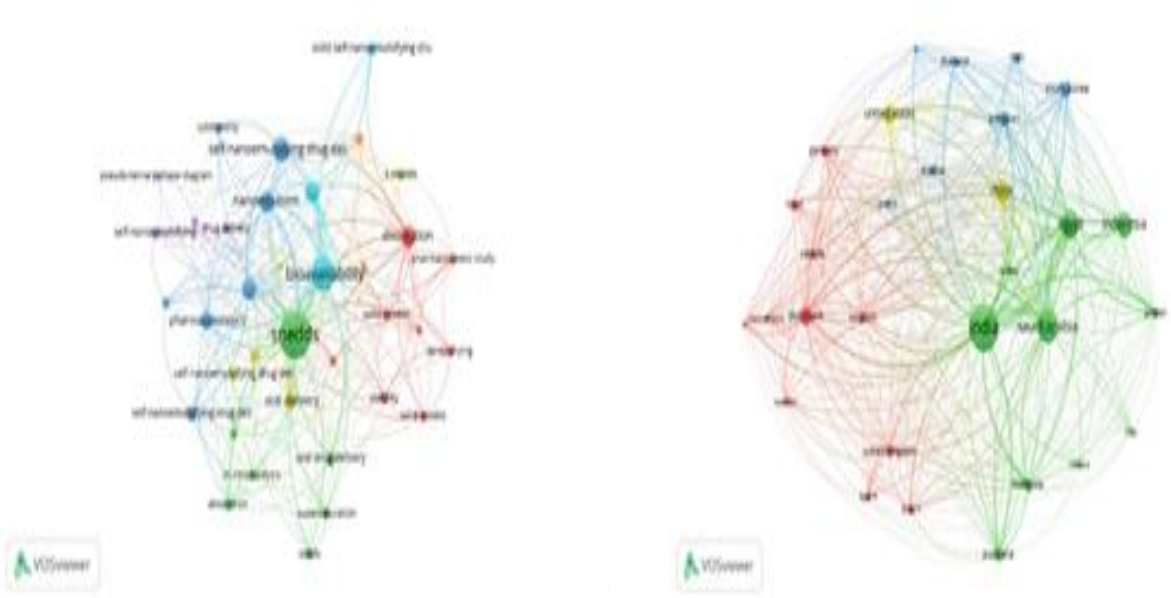


Figure 2: Bibliometric Analysis of SNEDDS Research on Antihypertension Agents

In the dissemination of data on countries that have researched SNEDDS, there are several country clusters, Cluster 1 in green, there are India, Australia, Malaysia, Taiwan, Iraq, Jordan, Saudi Arabia, Turkey, Egypt, and Indonesia. Cluster 2 is red which is Brazil, Spain, UK, Sweden, Switzerland, Denmark, Belgium, Canada, Israel, and Germany. Cluster 3 is blue there are Greece, Austria, Pakistan, Thailand, Iran, and south Korea. Cluster 4 is yellow there are China and the US. On the bibliometric map in Indonesia, there is quite a lot of research on SNEDDS, so information about SNEDDS can be developed towards further research in clinical trials to animals or humans with preliminary research by collecting data or scientific articles obtained from indexed sources.

Based on the results of studies that have been carried o- 475 -ut, it is known that quite a lot of SNEDDS systems have been developed for oral delivery of Antihypertension agents. SNEDDS are already applied to Antihypertension agents such as as Furosemide (Beg et al., 2012; Mendes, 2017; Alhasani et al., 2019; Subramanian et al., 2016). All these active substances have a low solubility in water, and this is the basis for their development in the dosage form of SNEDDS with the aim of increasing their bioavailability. The preparation is formulated using oils, surfactants and cosurfactants.

Table 1: Formulation and Characterization of SNEDDS against antihypertension agents

Name of the active substance	Formulation	Characterization Results	Reference
Lacidipine	Oil: Captex 810 D S: TPGS, Tween 60 CoS: Transcutol P, PEG 400	UG: 47 nm PDI: 0.02 WE: 1.3 second	[9]
Candesartan Cilexetil	Oil: migloil 818 S: Koliphore EL/Cremophor EL CoS: Transcutol P	UG: 13.91 nm PDI: 0.197 PZ: -0.32	[12]
Furosemide	Oil: oleic acid S: Tween 80 CoS: Propilen Glikol (PG)	UG: 89.5 nm PZ: -34.8 WE: 25.7 second	
Hydrochlorothiazide	Oil: MCT S: Cremophor EL, CoS: Transcutol P	UG: 169.6±22.8 PDI: 0.136 PZ: -31.3 WE: 18 second	[13]
Nebivolol hydrochloride	Oil: Capmul PKS EP S: Tween 60, CoS: Transcutol HP: Pasak 400	UG: 124.66±0.145 nm PDI: 0.125±0.0137 PZ: -5.74	[14]
Nifedipine	Oil: Castor Oil S: Tween 80/Span 20 CoS: PEG 400	UG: 24.05±0.02 PDI: 0.277±0.0038 WE: 14.09 second	
Valsartan	Oil: Capmul MCM S: Labrafil M 2125 CoS: Tween 80	UG: 133.7±42.8 PDI: 0.321±0.021 PZ: 24.48±4.8	[15]
	Oil: Labrafil M 1944CS, S: Cremophor RH 40, CoS: Transcutol HP	UG: 27.68 ± 0.11 PDI: 0.15 ± 0.02 PZ: −21.0 ± 0.9	[16]
Carvedilol	Oil: oleic acid S: Labrasol CoS: Transcutol HP	UG: 62.2 ± 1.1 nm PDI: 0.251±0.028	[17]
Talinolol	Oil: Capryol_PGMC S: HCO_30 CoS: Transcutol HP	UG: 26.2±1.2 nm PDI: 0.118	[18]
Ramipril	Oil: MCT S: HCO-30 CoS: TC	UG: 52.8±3.2 PZ: -19.4±5.9	[19]
	Oil: Sefsol 218 S: Acrysol EL135 CoS: Transcutol P	UG: 75.3±2.21nm PDI: 0.126±0.05 PZ: −24.4±5.78mV	[20]
Amiadarone&talinolol	Oil: Polyoxyl 40 hydrogenated castor oil S: Tween 20 CoS: Span 80	Amiadarone UG: 10±0.03 PDI: 0.48±0.001 PZ: 35±0.11 Talinolol UG: 45±0.07 PDI: 0.45±0.001 PZ: 6±0.008	[21]
Felodipine	Oil: ACC	UG: 31.11 ± 0.827	[12]

	S: CR-EL CoS: LUT-E	PDI: 0.193 PZ: 7.72 – 9.63	
Lercanidipine	Oil: Cremophor EL S: Caproyl 90 CoS: Transcutol HP	UG: 20.01 nm PDI: 0.157 PZ: −11.89	[22]
	Oil: Capmul MCM L8 S: Tween 80 CoS: PEG 400	UG: 169 ± 06 nm PDI: 0.202 ± 0.024	[23]
Candesartan & HCTZ	Oil: oleic acid S: PEG 400 CoS: Tween 80	UG: 50,62 ± 0,324 PDI: 0.281 PZ: 18.1 WE: 14 second	[24]
Telmisartan	Oil: Cinnamon Oil S: Propilen Glikol CoS: PEG 400	UG: 181 nm PDI: 0.199 PZ: -0.118 mV WE: 83 s	[3]
	Oil: Acrysol EL 135 S: Tween 20 CoS: Carbitol	UG: 40 ± 4,23 nm PZ: -23,9 ± 0,42 WE: 25 second.	
Tetrandine	Oil: Oleic Acid S: SPC CoS: PEG 400	UG: 19.75±0.37 nm PZ: 1.87±0.26 mv	[25]

The Influence of Snedds on Formulations

The particle size and zeta potential of SNEDDS are important factors for determining the stability of SNEDDS. Particle size is known to affect the absorption of drugs, as studied by various researchers. In Table 2 formulations and particle size characteristics of SNEDDS preparations show a size of < 200 nm, it is in accordance with the characteristics of SNEDDS by Balakumar that the particle size of SNEDDS is an average of 20-200 nm when exposed to GI fluid under mild agitation provided by peristaltic movements, so that it will increase the effectiveness of absorption in the gastrointestinal tract (Zhou et al., 2018; Krstic et al., 2018). Potential zeta can be used to estimate the surface characteristics of nanoemulsions. Ideally, the potential value of zeta is > ±30 mV. However, it is known that the measurement of zeta potential is not very relevant to assess the stability of the SNEDDS preparation, considering that SNEDDS is a preconcentration system that will only form a nanoemulsion dispersion system in the GI tract (Krstic et al., 2018). Test Another parameter seen is the emulsification time which is useful for predicting how quickly SNEDDS preparations will form a nanoemulsion system when in contact with water. The results showed a relatively short time of 13.91-169 nm.

Oil

Natural oils and lipids have been selected to make SNEDDS for drug delivery. The selection of a particular oil for SNEDDS depends on the solubilization of the target drug and its physicochemical properties, including polarity, interfacial tension with the water phase, viscosity, density, phase behavior, and chemical stability (Rao, 2011), the oil phase affects the self-emulsifying ability of the formulation and precipitation of the drug in GIT and can assist the lymphatic transport of the drug through the GIT wall. Holm et al. used soybean oil with Maisine 35-1, polysorbate 80 (Tween 80), and Cremophor EL to spontaneously form a clear and monophasic liquid with the lipophilic drug halofantrine However, the disadvantage of this unmodified oil is the low loading capacity for lipophilic drugs. LCT helps the absorption of drugs through the intestinal lymphatic pathway. MCTs are preferred for SNEDDS due to their better solubilization properties, self-emulsification ability, and better chemical stability of the active ingredient compared to LCT (Holm et al., 2012; Zhou, 2010). In 2012, Prajapati et al. studied the effects of glycerides (mono, di, and triglycerides) on the formation of SNEDDS and showed that monoglycerides produce the formation of clear or translucent microemulsions, while additional gel phases are observed in the case of triglycerides. Research has

also shown that medium-chain blended polar glyceride oil is a better mixture for pharmaceuticals and less susceptible to oxidation. Thus, the length of the lipid chain has a great effect on the formation of the desired SNEDDS .

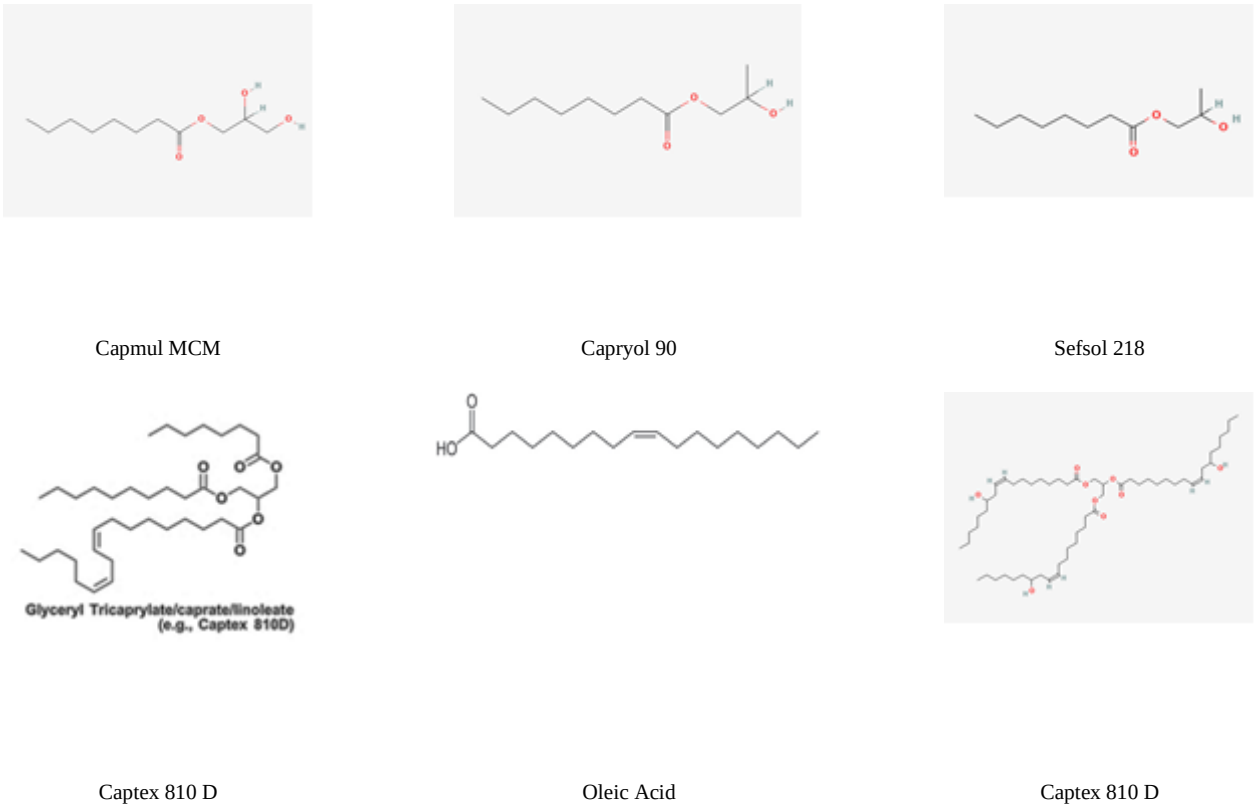


Figure 3: Medium Chain Triglyceride and Long Chain Triglyceride and (PubChem)

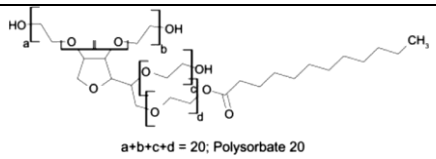
Surfactants

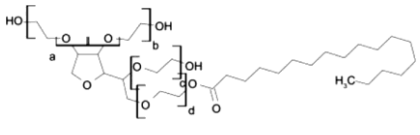
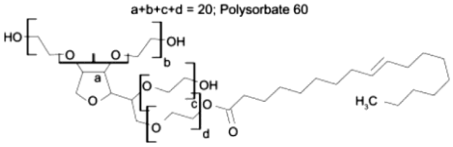
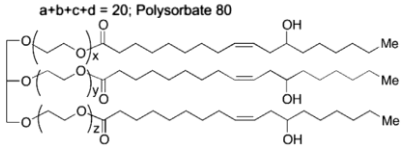
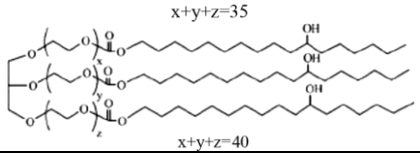
Surfactants play a key role in setting up stable SNEDDS. Surfactants usually consist of nonpolar lipophilic hydrocarbon chains (hydrophobic) and polar hydrophilic (oleophobic) groups, and thus surfactant molecules are amphiphilic molecules that have lipophilic and hydrophilic properties. The addition of surfactants serves to help the globule layer in SNEDDS preparations. In immiscible oil-water systems, surfactants are located at the oil and water interfaces, stabilizing oil droplets in SNEDDS by lowering the interface-free energy and surface tension.

Surfactants can be classified as ionic surfactants (including anionic, cationic, and zwitterionic) and nonionic surfactants. According to the value of the lipophilic hydrophilic equilibrium (HLB), they can also be categorized as lipophilic (HLB < 10) or hydrophilic (HLB > 10) surfactants. Generally, nonionic surfactants are used to make SNEDDS because they are lower in toxicity compared to anionic and cationic ones.

In addition, nonionic surfactants have shown strong emulsion stabilization over a wider range of ionic strength and pH. The most widely used surfactants in the studies that have been studied are Tween 60, Cremophor EL, Tween 80, Cremophor RH 40 tan Tween 20, and Labrasol. All of them are a type of nonionic surfactant that is widely used for the formulation of SNEDDS due to its lower toxicity compared to cationic and anionic surfactants.

Table 2: Molecular Structure of Surfactant (Verma et al., 2016)

Name	Molecular structure	HLB
Tween 20 Polyoxyethylene (20) monolaurate sorbitan		16.7

Tween 60 Polyoxyethylene (20) monostearate sorbitan	 a+b+c+d = 20; Polysorbate 60	14.9
Tween 80 Polyoxyethylene (20) monooleate sorbitan	 a+b+c+d = 20; Polysorbate 80	15.0
Cremophor EL	 x+y+z=35	13.0
Cremophor RH40	 x+y+z=40	15.0

The selection of surfactants in SNEDDS largely depends on the HLB value of the surfactant. Several studies have shown that nonionic surfactants with HLB >12 can spontaneously form SNEDDS with droplet sizes below 100 nm after dilution with digestive juices in GIT. The concentration of surfactants has been shown to affect the droplet size of the emulsion. An increase in the concentration of surfactants leads to a decrease in droplet size due to reduced surface tension at the oil-water interface. However, in some cases, higher concentrations of surfactants lead to an increase in droplet size, associated with interfacial interference by more penetration of water into oil droplets. A mixture of different types of surfactants often shows synergism in its effect on the properties of the system. This synergism can be attributed to the non-dual-mixing effect in the aggregate, resulting in a concentration of critical micelles and interfacial tension that is substantially lower than expected based on the properties of the unmixed surfactant. Weerapol et al. investigated the impact of HLB and the molecular structure of surfactants on the formation of SNEDDS (Weerapol et al., 2014).

After filtering out various oils and surfactants, they developed liquid SNEDDS containing nifedipine using surfactant blends, including Tween/Span or Cremophor/Span, showing that droplet size mainly depends on the molecular structure of the surfactant On HLB 10, a mixture of Cremophor and lipophilic surfactants with longer CH chain lengths (C18, Span 80) causes nano-sized emulsions, while shorter CH chain lengths (C12, Span 20) gives only micrometer-sized emulsions. In addition, the droplet size of SNEDDS is reduced when the HLB of the surfactant mixture (Cremophor/Span) is >9. The decrease in the droplet size of SNEDDS with high HLB surfactants may be due to their higher hydrophilicity, which facilitates the reduction of interface curvature, leading to smaller droplet sizes.

CO-Surfactants

Co-surfactants in SNEDDS are used to cooperate with surfactants to improve the solubility of drugs and improve the dispersibility of hydrophilic surfactants in the oil phase, thereby promoting homogeneity and stability of formulations (Verma et al., 2016). Furthermore, cosurfactants increase interfacial fluidity by penetrating the surfactant film, creating a space between the surfactant molecules. Surfactants and cosurfactants are specifically absorbed in the interface area, thereby reducing interfacial energy, and providing a mechanical barrier to coalescence and improving the thermodynamic stability of nanoemulsion formulations. Common cosurfactants used in this study were Transcutol P, PEG 400, corbitol and poly (ethylene glycol) (PEG). Although cosurfactants can increase the solubility of drugs in SNEDDS, their concentration in SNEDDS should be minimized due to their high polarity. They tend to migrate towards the aqueous phase after dispersion into an aqueous medium, possibly causing drug precipitation. In addition, alcohol and other volatile cosurfactants can evaporate into the shell of soft or hard gelatin capsules, thereby also causing drug precipitation.

From the results of the characterization of the preparation, it is known that the resulting SNEDDS preparation has good characteristics and can spontaneously form nanoemulsions when dispersed in water. The particle diameter value is in the range of 13.91-169 nm with a PDI value of ≤0.5, which meets the particle requirements for SNEDDS, which is <200 nm. Some journals also conduct zeta potential analysis for SNEDDS preparations, to predict stability. Ideally, the potential value of zeta is >±30 mV. However, the measurement of zeta potential is not very relevant to assess the stability of the SNEDDS preparation, since SNEDDS is a new preconcentration system that will form a nanoemulsion dispersion system in the GI tract (Krstic et al., 2018). Emulsification time testing is the next test that is useful for predicting how quickly SNEDDS preparations form a nanoemulsion system in contact with water momentarily. The results show a relatively short time in the range of 18-26 seconds.

The Effect of Snedds Formulations on The Dissolution of Active Substances

In Figure 3, data on the dissolution/release of the active substance in the dosage form SNEDDS, compared to its pure active is displayed. Dissolution is the process of dissolving the active substance in the carrier medium. The dissolution profile of the SNEDDS formula was tested in vitro using the appropriate apparatus and dissolution media, from the data in the table it can be concluded that the formulation of SNEDDS can significantly improve the dissolution of active substances that have natural characteristics of being difficult to dissolve in water, seen in an increase in the percentage of dissolution of SNEDDS which increases compared to the dissolution of its pure substance. Effect of SNEDDS Formulation on dissolution of active substances. As previously explained, these compounds generally fall into the category of BCS class 2 and 4, so they have low solubility and permeability in water. This can be seen from the dissolution data for its relatively low pure active substance.

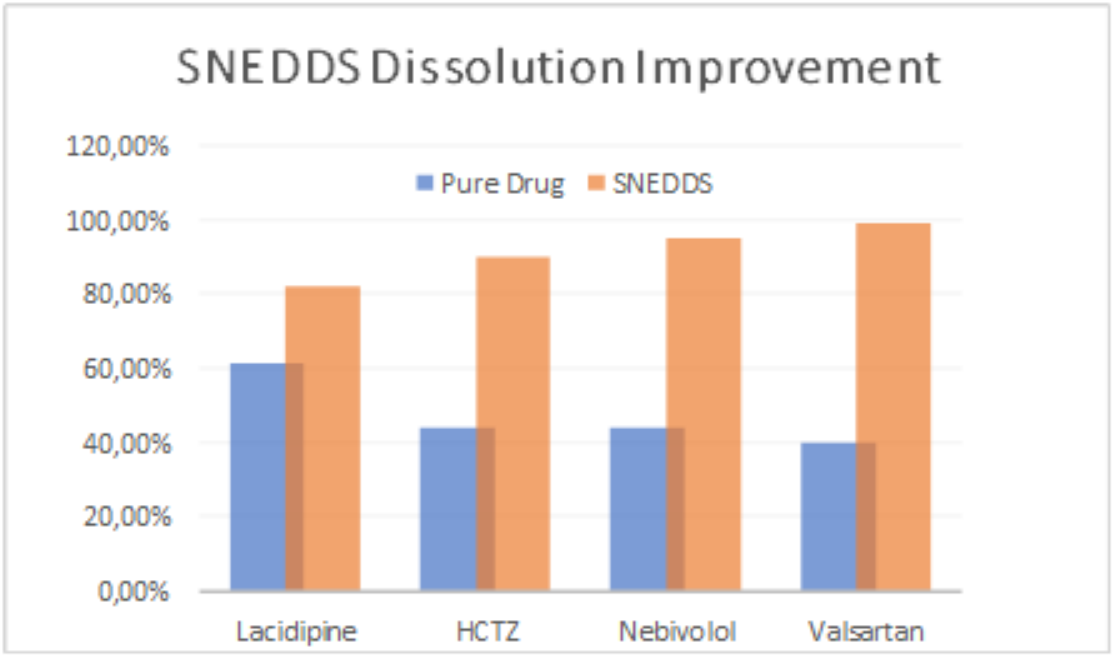


Figure 4: SNEDDS Dissolution Improvement Lacidipine, HCTZ, Nebivolol, Valsartan

In general, the formulation of SNEDDS leads to an increase in dissolution to 80%. An increase in the percent dissolution of active substances through the SNEDDS delivery system can occur because the active substance is dissolved in a nano-sized oil globule wrapped by a layer of surfactants and cosurfactants that allow it to be dispersed easily in water, making it easier to disperse.

Effect of Snedds Formulations on Bioavailability

The next effect of SNEDDS after dissolution is on the bioavailability value or bioavailability of oral drug antihypertension. The parameters studied are the value of Tmax (*maximum time*), AUC (*area under cover*) and Cmax value *(maximum plasma concentration).* Bioavailability or bioavailability

indicates the fraction of drugs that successfully enter the systemic circulation after administration of drugs in certain dosage forms. Bioavailability or bioavailability indicates the fraction of drugs that successfully enter the systemic circulation after the administration of drugs in certain dosage forms. The number of drugs that reach the blood can be seen from the parameters of the maximum concentration Cmax value) and AUC (area under curve) based on in vivo testing (Zhou, 2010).

Based on the data shown in Table 4. The formulation of SNEDDS is able to increase the bioavailability of antihypertension agents characterized by an increase in Cmax and AUC values compared to pure substances/suspensions. While the increase in maximum time in SNEDDS is higher than before the application of SNEDDS, the increase in emulsification time indicates how quickly drugs with SNEDDS formulations can work in the GIT or *gastrointestinal area*, this indicates that the application of SNEDDS shows a better impact than pure preparations in how the drug works in the stomach.

Table 3: Effect of SNEDDS Formulation on Bioavailability

Active Substance Name	Bioavailability		Reference
	Marketed Product	SNEDDS	
Lacidipine	T_{max} = 2.0 C_{max} = 0,127± 0,01* Auc = 2.68±1.06*	T_{max} = 1.5 C_{max} = 0,286± 0,02* Auc = 6.78±1.12*	[9]
Candesartan Cilexetil	T_{max} = 4 C_{max} = 1.37±0.35 Auc = 1	T_{max} = 3 C_{max} = 2.4±0.29 Auc = 1.69	[12]
Nifedipine	-	T_{max} = 14.09 Auc = 9.857	
Valsartan	T_{max} = 1.02±0.61 C_{max} = 1687.98±193.07 Auc = 673.51±21.78	T_{max} = 0.75±0.31 C_{max} = 1812.62±72.15 Auc = 655.24±29.15	[15]
Carvedilol	T_{max} = 1.501±0.101 C_{max} = 0.740±0.007 Auc = 2.821±0.232	T_{max} = 0.754±0.111 C_{max} = 1.925±0.192 Auc = 7.174±0.542	[17]

Increased bioavailability suggests that the process of absorption of the active substance in the GI tract occurs better, which causes the active substance to successfully pass from the gastrointestinal tract to the systemic circulation more. This process of increasing absorption can occur due to two factors, the first is due to the better solubility of the active substance, which can facilitate the absorption process, the second is because the active substance dissolved in the oil globule node allows for absorption through transcellular/paracellular mechanisms or lymphatic pathways (Subramanian et al., 2016). In the bioavailability of the drug lacidipine there was an increase in the oral bioavailability of SNEDDS formulations compared to the LD tablet formulations marketed and the results obtained are shown in Table 4. Cmax, T max and AUC of LD SNEDDS formulation showed an increase in AUC, C max (p/0.05) and a decrease in T max when compared to LD tablets marketed.

A 2.5-fold increase in oral bioavailability of LD from SNEDDS than tablets marketed has demonstrated the efficacy of solution of the form of SNEDDS in an increase in oral bioavailability of LD. Bioavailability study results suggest that the increased LD bioavailability of SNEDDS formulations may be due to better solubilization with rapid and efficient drug dispersion n in the GI tract and pre-ventilation of LD precipitation for a period suitable for absorption (Zhou,2010). The increase in drug bioavailability occurs not only in the drug lacidipine but also in candesartan, nifedipine, valsartan and carvediol. This suggests that the application of SNEDDS to oral antihypertension agents can be a solution to poor solubility in oral antihypertension drugs.

4. Conclusion

The limitations of oral drugs are in their solubility and need solutions to increasing the bioavailability of BCS class II and IV drugs that have poor solubility and permeability. The solution used is

SNEDDS which is a method that uses a mixture of oil, surfactant and cosurfactant to increase the solubility of the drug. In studies that have been carried out in other countries, it was found that the application of SNEDDS to antihypertension agent drugs classified as BCS *(Biopharmaceutical Classification System)* class II and IV that SNEDDS is effective in increasing the bioavailability of the drug. Therefore, SNEDDS is a solution to improving the oral bioavailability of drugs for the better.

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