FORMULATION AND EVALUATION OF LIQUID SELF NANO-EMULSIFYING DRUG DELIVERY SYSTEM OF LOVASTATIN

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Abstract: This study aimed to investigate the formulation and characterization of Lovastatin in an L-SNEDDS. The selected is composed of L-SNEDDS based on a solubility study of lovastatin in many oils, surfactants, and co-surfactants. Ternary phase diagrams were constructed based on lovastatin solubility to determine lower limit and high limit of oil, surfactant, and co-surfactant selected further to optimize the system using a D-Optimal mixture design. The optimized S of lovastatin was evaluated, including size particle, polydisperse index, and emulsification time. The optimal formula of L-SNEDDS was verified and determined size particle, polydisperse index, emulsification time, drug content, and dissolution of lovastatin. The results showed that the best formula is the composition of oleic acid 5,2%; tween 80 79,5%, and PEG 400 15,8%. The particle size is below 100 nm, the polydisperse index is below 0,5, and the emulsification time is below 20 seconds. The loading of SNEDDS lovastatin is 97,01%, and the SNEDDS of lovastatin composed of oleic acid, tween 80, and PEG 400 showed increasing dissolution of lovastatin than pure lovastatin

Keywords: L-SNEDDS, lovastatin, solubility, evaluation, dissolution

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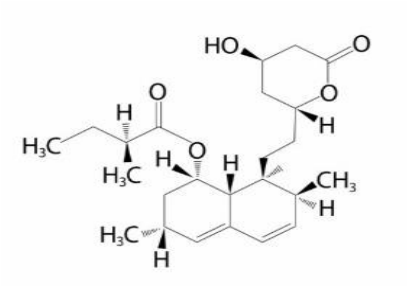
INTRODUCTION

Statins are the largest selling class of drugs currently taken by patients and are extensively effective as a cholesterol-lowering agent for the primary prevention of cardiovascular and coronary heart disease. One of the statins is lovastatin. Since the introduction of lovastatin in 1987, statins have surpassed over 100 million prescriptions a year, with an estimated 25 million patients wordlwide on the medication. It reversible competitive inhibition of 3-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme involved in cholesterol biosynthesis. Lovastatin is lipophilic drugs with log P = 4,3; molecular weight= 404,54; poorly water soluble (4 x 10-3 mg/ mL) and the categories of Biopharmaceutical Classification System class 2. Besides of that, exhibit less of bioavailability < 5% and have extensive metabolism[1]–[4].
The figure of lovastatin can see below.



Structure of Lovastatin

The characteristic of lovastatin with low solubility in water and lipophilic may cause problems in vitro and in vivo assay[5]. Therefore formulation approaches are being explored to enhance the bioavailability of poorly water-soluble drugs like lipid-based formulations. A highly effective strategy that significantly enhances dissolution and bioavailability is formulated SNEDDS(Self- Nanoemulsifying Drug Delivery System)[6].
SNEDDS is one of the lipid-based formulations and a potential formulation strategy for increasing the solubility of poorly water-soluble drugs[7]. SNEDDS are defined as a transparent system, thermodynamically stable, an isotropic mixture of oil, surfactant, and co-surfactant [7], [8]. There are many advantages of SNEDDS : rapidly form oil in water nanoemulsion and rapidly disperse to form droplets approximately nano size range when exposed to aqueous media upon gentle agitation or digestive motility in the Gastrointestinal tract. SNEDDS is a physically more stable formulation when compared to emulsions and is easier to manufacture on a large scale [7], [9]. This study aims to design and evaluate lovastatin-loaded SNEDDS to improve the dissolution of lovastatin.

MATERIAL AND METHODS

The material used in this research are lovastatin was obtained from Sanbe Pharma, oleic acid from Brataco, almond oil, corn oil, soybean oil, tween 20, cremophor RH40, tween 80, PEG 400, propyleneglycol, acetonitrile, and methanol pro HPLC using Merck product, aquabidest

The equipment used are membrane filter 0,45µm, micropipette 100-1000µL, spectrophotometry of Uv-Vis (UV Genesys), dissolution tester erweka,

Solubility Testing

For Selecting of solvent, using the solubility test. The solubility of lovastatin was determined in all components (almond oil, sunflower oil, corn oil, soybean oil, olive oil, oleic acid, tween 20, tween 80, cremophor R.H. 40, propylene glycol, and polyethylene glycol. Each component was taken at 5 ml in a vial of 10 mL and then added to a few of lovastatin until saturated. The mixtures were mixed using a magnetic stirrer for 10 minutes, then using a sonicator for 10 minutes. Put in the water bath for 15 minutes at a temperature of 40°C. The mixtures were standing for 24 hours, and the combinations were centrifugated at 6000 rpm for 10 min. Filtered the varieties using membrane filter 0.45µm, then supernatant transferred to vials. An aliquot of sample @ 2 µL added acetonitrile until 5 mL, then moved to vial 1.5 mL and injected into the HPLC system using mobile phase acetonitrile:water = 70:30 [10].

Pseudoternary Phase Diagram

Pseudo ternary phase diagrams were constructed without lovastatin to obtain appropriate concentration ranges of components and find out areas of SNEDDS. Based on the solubility study results, the phase diagram contains oleic acid as oil, tween 80 as a surfactant, and PEG 400 as a co-surfactant. Ternary mixtures were prepared with varying concentrations of oil (5-20%), surfactant (40-80%), and cosurfactant (0-45%). The proportion of oleic acid, tween 80, and PEG 400 was determined by 19 preparations. The ability to form nanoemulsion can asses from transmittance and appearance. Nineteen preparations determined the proportion of oleic acid, tween 80, and PEG 400. The ability to form nanoemulsion can asses from transmittance and appearance.

Table 1. Formula to determining Pseudoternary Diagram

No	Composition (%)		
	Oleic Acid	Tween 80	PEG 400
1	10	80	10
2	10	70	20
3	10	50	40
4	20	60	20
5	20	70	10
6	15	50	35
7	15	45	40
8	15	40	45
9	15	42.5	42.5
10	10	75	15
11	15	75	10
12	15	80	5
13	5	70	25
14	10	60	30
15	5	75	25
16	5	80	15
17	15	80	5
18	15	60	25
19	20	80	0

Optimization of lovastatin SNEDDS using D-Optimal Design

Ratio low and high-level proportion of oleic acid, tween 80 and PEG 400 based on the result of ternary phase diagram then input to D-optimal Mixture Design method software DX.7.0. Three responses to the determined optimum formula are globule size, polydisperse index, and emulsification time.

Table 2. Ratio component Lovastatin SNEDDS

Level	proportion (%)		
	Oleic acid	Tween 80	PEG 400
low	5	60	15
high	10	80	30

After determination of the concentration range of various components leading to stable SNEDDS formulation, a D-optimal design was applied to optimize the SNEDDS formula. D-optimal mixture design with three independent variables (percent content of oil, surfactant, and co-surfactant)was used for carrying out the optimization study.

The experimental matrix was constructed with 16 runs and four replicates, and the response studies were globule size, polydisperse index, and emulsification time. Design expert software was used for construction and interpretation by fitting suitable mathematical polynomial equations. The optimized formula was achieved by converting each response into an individual desirability function. The target was formulating an adequate SNEDDS to maximize stability with reduced globule, polydisperse index, and emulsification time.

Table 3. Optimization of SNEDDS lovastatin using D-Optimal Mixture Design

Run	Lovastatin (mg)	Oleic Acid	Tween 80	PEG 400
1	20.0	10.0	60.0	30.0
2	20.0	6.1	79.0	15.0
3	20.0	6.1	79.0	15.0
4	20.0	5.1	64.9	30.0
5	20.0	6.2	75.6	18.2
6	20.0	10.0	69.7	20.3
7	20.0	9.7	63.8	26.6
8	20.0	10.0	60.0	30.0
9	20.0	10.0	73.3	16.7
10	20.0	10.0	73.3	16.7
11	20.0	5.1	64.9	30.0
12	20.0	5.0	67.7	27.3
13	20.0	7.7	67.9	24.4
14	20.0	7.7	62.6	29.8
15	20.0	5.0	72.8	22.2
16	20.0	5.0	72.8	22.2

Formulation and Evaluation of Lovastatin L-SNEDDS

Self nano-emulsifying liquid system was prepared by dissolving lovastatin 10 mg in an accurately weighed mixture

of oil, surfactant, and co-surfactant in a stoppered glass vial and mixed with a stirrer for 15 minutes to ensure uniform drug distribution. After mixing, then the formula SNEDDS of lovastatin sonication for 15 minutes. Further, the formula of SNEDDS lovastatin was characterized and evaluated.
Characterization and evaluation included: Robustness to dilution, Determination of globule size, polydisperse index and time of emulsification, and in vitro drug release.
SNEDDS of lovastatin was diluted 100 times with 0,1 N HCl and then observed for phase separation or drug precipitation through 24 hour storage period. The formula of SNEDDS lovastatin, which showed no phase separation or precipitation through the specified time, was considered robust to dilution. This was a good indication of the stability of SNEDDS lovastatin at infinite dilution [11].
Globule size and polydisperse index were determined at 25 oC by dynamic light scattering analysis using Zetasizer 3000HS (Malvern Instruments). Globule size is an important indicator of the physical stability of a nanoemulsion. 10 µL of lovastatin SNEDDS diluted using
10 mL of water and analyzed using Malvern Instruments. The globule size was expressed as the average globule size of a droplet in the system and polydispersity index, which indicates the width of size distribution [11].
Self-emulsification time is required by the preconcentrate to form a homogeneous mixture upon dilution. One mL lovastatin SNEDDS dissolved in 250 mL water at 37±0,5 °C and agitation using a paddle rotating at 50 rpm. The time taken for emulsification was noted [12], [13].

Drug content of lovastatin
An amount of 10 µL lovastatin SNEDDS has filled to a volumetric flask of 10 mL and added with methanol to 10 mL. Then sonicated for 15 minutes and filtered. The solution was assayed using spectrophotometric UV-Vis at 238 nm [14], [15].

Dissolution of Lovastatin L-SNEDDS
An amount of SNEDDS lovastatin equivalent to 20 mg lovastatin, filled into hard capsules (capsule size 000). The capsule was filled with SNEDDS lovastatin equivalent to 20 mg lovastatin. The dissolution medium uses 500 mL of buffer phosphate pH 6.8 at 37±0.5 °C using a speed of 100 rpm and apparatus II. Five mL of sample was periodically withdrawn at time intervals of 5,10,20,30,40,50, and 60 min and replaced instantly by an equal amount of buffer phosphate at pH 6,8 to maintain the same volume. The concentration of lovastatin was determined using a UV spectrophotometer of 238 nm[16].

RESULTS AND DISCUSSION

Solubility test: Screening of oils, surfactants, and co-surfactant with solubility testing. The solubility of poorly water-soluble lovastatin in various oil, surfactant, and co-surfactant was analyzed to screen the components of SNEDDS. The result of the screening of solvent can see below in figure-1.

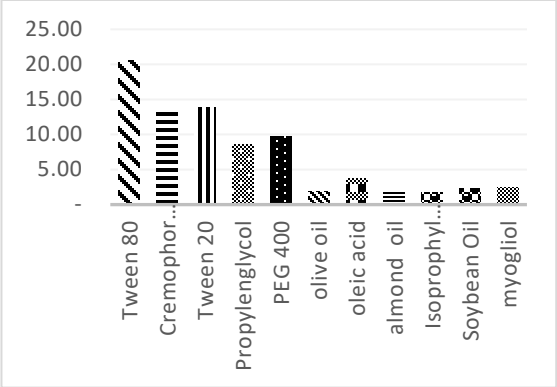


Figure 1. Solubility of lovastatin in tween 80, Cremhopor RH 40, Tween 20, Propylenglicol, PEG 400, olive oil, oleic acid, almond oil, isopropyl myristate, soybean oil, and miglyol

The solubility of lovastatin is more soluble in oleic acid than in other oils because the component of oleic acid in other oils is lower. Besides that, in many oils like almond oil, olive oil, and soybean oil, there are many components of unsaturated fatty acid[17]. This solubility of lovastatin in surfactant tween 80 higher than other surfactants. Besides that, tween 80 can enhance absorption capabilities and activity, including the inhibitory effect on P-gp, mediated efflux, and CYP450 enzymes [16]. The solubility of lovastatin in co-surfactant showed that PEG 400 was higher than propylene glycol. Based on this data, oleic acid, tween 80, and PEG 400 selected solvents to form SNEDDS lovastatin[10].

Pseudoternary diagram phase
Pseudo ternary phase diagram of selected oil, surfactant, and co-surfactant was plotted for optimization of the concentration of oil, surfactant, and cosurfactant. The ability to form nanoemulsion can asses from transmittance and appearance. The system that is clear or translucent was identified from the ternary phase diagram. The analysis of phase behavior allowed classifying two different regions based on visual observation: appearance and transmittance. The system with translucent produced clear (with % transmittance more than or equal to 95%) or translucent (with % transmittance more than or equal to 90%) dispersion were considered to optimize SNEDDS using a D-optimal mixture design.

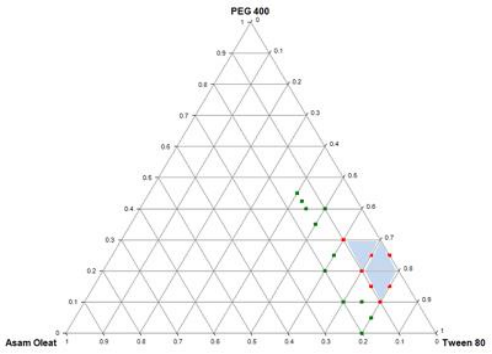


Figure 2. Pseudo Ternary Phase Diagram

Table 4. Identified Ternary Phase Diagram

No.	% transmittance	Appearance
1	94.3	clear
2	89.9	translucent
3	59.5	turbid
4	56.5	turbid
5	45.3	turbid
6	64.1	turbid
7	65.2	turbid
8	64.2	turbid
9	65.2	turbid
10	94.6	clear
11	64.8	turbid
12	60.9	turbid
13	96.1	clear
14	89.7	clear
15	99.4	clear
16	99.3	clear
17	60.2	turbid
18	61.5	turbid
19	51	turbid

Based on the Pseudo ternary diagram, the region of nanoemulsion identified with appearance and transmittance from the 19 formula has seven formula with transmittance ≥90% and appearance translucent/clear. The percentage of transmittance is an important parameter to determine the isotropic nature of the system. A percentage of transmittance closer to 100% indicates the self-nanoemulsion was clear, transparent, and globule size in the nanometric range, then the system has a large surface for drug release, high capacity for enhanced absorption, and increased oral bioavailability[18]. Then, we conclude that to determine the proportion of region of nanoemulsion to oleic acid, tween 80 and PEG 400 in the range 5-10%; 60-80%; and 15-30%.

D-Optimal Mixture Design

The experimental matrix was constructed with 16 runs and four replicates, and the response studies were globule size, polydisperse index, and emulsification time. The result of determination optimization of lovastatin SNEDDS using a D-optimal Mixture design can see below in **Table 5**.

Table 5. The response studies using D-optimal Mixture Design

Run	Globule size	PDI	Emulsification time
1	90,51	0,667	14,44
2	18,5	0,398	8,56
3	13,74	0,162	10,02
4	14,91	0,195	13,12
5	13,08	0,208	12,03
6	148,9	0,534	11,76
7	198,4	0,424	15,05
8	105,1	0,425	16,38
9	115,5	0,484	17,12
10	120,2	0,41	17,06
11	15,27	0,263	10,24
12	18,17	0,373	12,36
13	120,7	0,48	10,18
14	67,73	0,546	11,02
15	13,55	0,443	9,36
16	13,74	0,452	10,01

Table 6. Desirability of SNEDDS lovastatin

Formula	Oleic Acid	Tween 80	PEG 400	Desirability
1	5,2	78,95	15,82	0,888

Table 7. Verification of SNEDDS lovastatin

Formula	Measurement			Mean ±SD
	1	2	3	
Globule size (nm)	43,05	46,7	48,58	46,11±2,30
Polydisperse Index	0,27	0,15	0,31	0,24±0,07
Emulsification time (second)	10,12	9,65	11,5	10,42±0,79

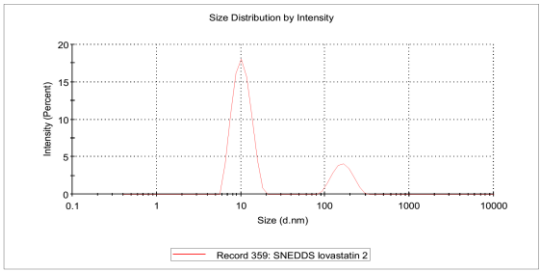


Figure 3. Determination of Globule Size using Malvern PSA

Robustness to dilution means the ability of SNEDDS to be diluted without separation or precipitation of the drug. When SNEDDS dilution, resulting nanoemulsion that is clear and transparent with no phase separation during 24 hours, we conclude that the formula is stable at infinite aqueous dilution[18].

Globule size is a critical characteristic for self emulsification. The polydisperse index indicates how the globules are dispersed in the continuous phase. The polydisperse index is defined as the ratio of the standard deviation to the average droplet size. Low PDI indicates monodisperse emulsion with high stability, while high PDI indicates polydisperse emulsion and broad size distribution with low stability[19].

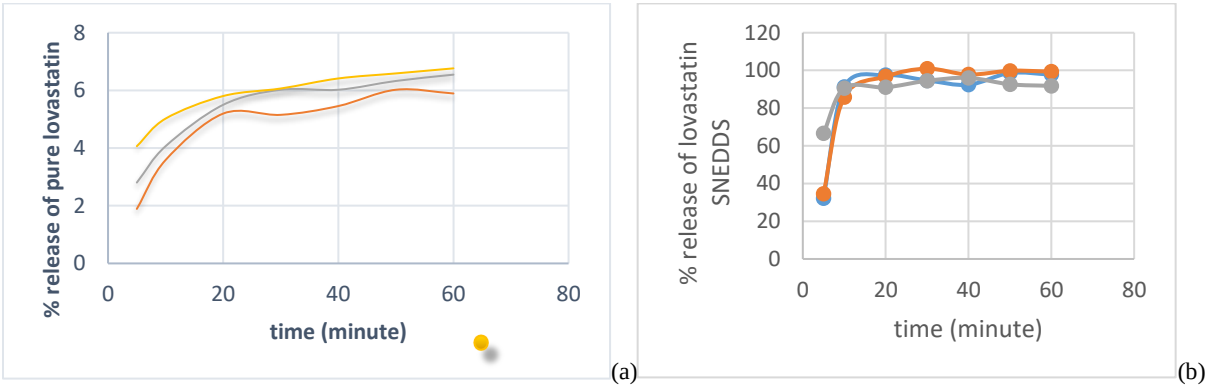
The self-emulsification time is an important index for the assessment efficiency of emulsification. The SNEDDS is thermodynamically spontaneous if free energy is required to nanoemulsion lower means it disperses completely and quickly when subject to contact with aqueous dilution under mild agitation. The result showed that self-emulsification time is lower when surfactant concentration increases[18], [20].

The drug content of lovastatin in SNEDDS

The drug content aims to evaluate the formulation for drug loading efficiency. The result showed that the percentage of drug content was 97,01%. It is indicated that 1 mL of SNEDDS contains 9,7 mg of lovastatin[21].

The dissolution of Lovastatin SNEDDS

The in vitro drug release was evaluated using apparatus II, medium phosphate buffer at pH 6,8. The dissolution rate of lovastatin SNEDDS compared with pure lovastatin. The result showed that lovastatin SNEDDS had a higher rate of dissolution than pure lovastatin.
It can see in figure 4.



(a) (b)

Figure 4. The dissolution profile of pure lovastatin (a) and lovastatin SNEDDS (b)

The dissolution profile of lovastatin SNEDDS is more significant than pure lovastatin. The dissolution lovastatin SNEDDS achieve 96%, but pure lovastatin 8%. The fast dissolution rate of SNEDDS depends on the composition of surfactant in the formula. The surfactant used in the formulation is responsible for the conversion oil phase into a small particle by reducing the surface tension at the oil and water interface[21].

CONCLUSION

The results showed that lovastatin SNEDDS with a composition of oleic acid, tween, and PEG 400 have a particle size average of 46.11, polydispersity index of 0.24, and emulsification time 10.42, lovastatin content in SNEDDS 97.01% and have an excellent dissolution rate compared to pure lovastatin.

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Ethical Approval: This study did not use experimental animals so it does not require approval from the ethics committee.

Conflict Of Interest: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Informed Consent: The research focused on the formulation and evaluation of Self Nano-Emulsifying Drug Delivery System of Lovastatin

Authorship

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