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Optimization and Characterization of Self Nano Emulsifying Drug Delivery System (SNEDDS) of Curcumin with D-Optimal Mixture Design Method

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A R T I C L E I N F O

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A B S T R A C T

Curcumin, known for its anti-inflammatory, antibacterial, anticarcinogenic, and antioxidant properties, faces challenges due to poor water solubility and low bioavailability as a BCS class II compound. The study investigates using a self-nanoemulsifying drug delivery system (SNEDDS) to enhance these properties, optimizing the formulation with the D-Optimal Mixture Design method. Sixteen formulas were prepared using oleic acid, Tween 80, and PEG 400. Each formula was characterized by particle size, % transmittance, emulsification time, and drug loading. The optimized formula, containing 10% oleic acid, 70% Tween 80, and 20% PEG 400, achieved a particle size of 80.167 nm, an emulsification time of 39.36 seconds, near 100% transmittance, and high drug loading.

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INTRODUCTION

Curcumin, a polyphenolic compound, is known to have many pharmacological effects and has been shown to exhibit high antibacterial, anticarcinogenic, anti-inflammatory, and antioxidant properties (Shan and Iskandar, 2018). The potential of curcumin is quite interesting for drug development, but curcumin has several physicochemical characteristics that make its formulation and clinical application quite difficult. According to the Biopharmaceutical Classification System (BCS), curcumin is included in BCS class II where BCS class II drugs have high permeability but low water solubility (Wan et al., 2012). Curcumin has low solubility in water (11 ng/ml, at pH 5.0) (Tonnesen et al. 2002; Kuncahyo, 2017).

Nanotechnology can be relied upon in overcoming the limitations of the active ingredient curcumin, as a poorly water-soluble drug. Self-nanoemulsifying drug delivery systems (SNEDDS) is one method that is considered to increase the solubility of poorly water-soluble drugs. SNEDDS is an isotropic mixture of oil, surfactant and cosurfactant together with the drug that will form a nanoemulsion spontaneously in aqueous media with mild stirring and has a droplet size of less than 100 nm (Azeem et al. 2008). SNEDDS has a high solubility enhancement potential for lipophilic compounds, which has been shown to significantly increase the bioavailability of curcumin in curcumin SNEDDS preparations when administered orally (Tasmina et al, 2021).

The main components in the manufacture of SNEDDS are oils, surfactants and cosurfactants. Research by Yandi, Hernawan and Istanti (2020) on the optimization of oleic acid, tween 80 and PEG 400 in mefenamic acid SNEDDS preparations showed that the optimal formula with a composition of 10% oleic acid, 80% tween 80 and 10% PEG produced SNEDDS with a transmittance value of 88.5% with a clear solution and a particle size value of 190.03 ± 1.18 nm which showed good SNEDDS. Nazari, Moezi and Heli (2017) conducted research on curcumin Self-Nanoemulsifying Drug Delivery System (SNEDDS) with oil components namely ethyl oleate, surfactant namely tween 80 and cosurfactant namely PEG 600. The optimum formula obtained in the ratio of the three components namely ethyl oleate, tween 80 and PEG 600 (50:40:10%), and carried out a characteristic test with the resulting particle size of 11.2 nm.

The choice of oil type depends on the solubility of the drug based on the ability to dissolve the drug in oil, which is the drug base in SNEDDS. The solubility test of curcumin in ethyl oleate resulted in 0.357 mg/ml. Manoj, Mangesh, Akshata and Urmila (2020) have tested the solubility of curcumin in oleic acid, with a result of 6.43 mg/ml, so in this study oleic acid was used as the oil phase. The choice of surfactant and cosurfactant type is an important component in SNEDDS formulation because it can affect the formation of the nanoemulsion phase region. Nirmalayanti (2021) conducted a surfactant screening research experiment using three types of surfactants namely tween 20, tween 60, and tween 80 which are nonionic surfactants. Screening is done in order to get a surfactant that matches the oil phase and produces more oil

volume droplets. The results obtained were that tween 80 can dissolve more oil, so it was chosen as a surfactant in the formation of nanoemulsions. In addition, tween 80 is said to be a solubilizing agent because it has lipophilic properties so that it can mix with oil and has a stable HLB 15 to form oil-in-water (M/A) type emulsions (Syaputri and Patricia, 2019).

The use of a single surfactant is not enough to reduce surface tension so that a cosurfactant is added which can increase the flexibility of the film and the function of the cosurfactant is to reduce the amount of energy needed to break the globule and produce a smaller globule size (Priya et al, 2015). Sesilia, Ilham and Resly (2021) have formulated and optimized Furosemide SNEDDS with varying concentrations of tween 80 and PEG 400 where the research shows that the interaction of tween 80 and PEG 400 components affects the decrease in emulsification time, the tween 80 component causes an increase in the percentage transmittance value while the PEG 400 component causes an increase in drug loading. With optimization results showing tween 80 of 61.4922% and PEG 400 of 18.5078% with characterization of emulsification time of 15.25 seconds, transmittance percentage of 94.20%, drug loading of 50 which is 100.2 ppm, particle size of 12.18 nm.

Based on this description, it is necessary to increase the bioavailability of curcumin with curcumin SNEDDS optimization experiments using the D-Optimal Mixture Design method which is expected to determine the right optimum formula in the preparation of curcumin SNEDDS preparations that can meet the requirements as a good SNEDDS preparation with parameters including particle size, emulsification time, % transmittance and drug loading. This study aims to determine the optimal formula and characterization of curcumin SNEDDS using the D-Optimal Mixture Design method.

THEORETICAL REVIEW

Curcumin

Curcumin is an unsaturated α-β-diketone compound with a slight electrophilic focus (Martono, 1996). Curcumin consists of two ferulic acid molecules joined at the carboxyl group carbon atom through a methylene bridge.

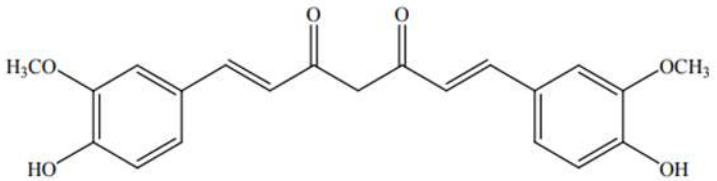


Figure 1. Structure of curcumin (Aggarwal et al., 2006))

Curcumin has a molecular weight = 368.37 g / mol (C = 68.47%; H = 5.47%; O = 26.06%), light yellow, melting point 1830 C and soluble in organic solvents (methanol, ethanol or benzene), glacial acetic acid and insoluble in water (Tonnesen and Karlsen, 1985). Curcumin crystals are rod-shaped or prism-shaped and orange-yellow. The number of carbon atoms in curcumin is less than 40, can be grouped into carotenoids (tetraterpenoid-structured pigments and are fat-soluble) by giving a yellow to red color. The stability of

curcumin is influenced by pH and light. Curcumin in water solvents will undergo a hydrolysis reaction that is highly dependent on the pH of the environment. In principle, curcumin is relatively stable at acidic pH (below pH 6.5), but will decompose rapidly at pH above neutral. Curcumin in alkaline conditions (pH 7-10) will produce ferulic acid and feruloyl methane. This is due to the presence of active methylene groups. In acidic solutions (low pH), curcumin is yellow, while in alkaline conditions curcumin produces a dark reddish brown to light yellow color. (Tonnesen and Karlsen, 1985).

Self Nano Emulsifying Delivery System (SNEDDS)

Self-Nanoemulsifying Drug Delivery System (SNEDDS) is a drug delivery system by making an isotropic mixture consisting of oil, surfactants, and cosurfactants that will form an oil-in-water nanoemulsion spontaneously in the digestive tract and produce droplets that are less than 200 nanometers in size (Salawi, 2022). SNEDDS consists of the main components, namely oil which acts as a carrier for drugs or active substances, surfactant and cosurfactant components that play a role in reducing particle size, emulsifying and maintaining active substances at the absorption site so that sedimentation does not occur in the digestive tract system. The characteristics of good SNEDDS can be determined from various parameters including particle size, percent transmittance, emulsification time, drug load, zeta potential, and in vitro dissolution tests (Kuncahyo, 2021). The advantages of SNEDDS preparations are that they can increase the bioavailability of active substances in the body through oral use, provide a large surface area with the digestive tract membrane, high stability, can reduce the dose of drug administration or frequency of use (related to increased bioavailability in the body).

Oil

The oil phase is one of the most important components in the manufacture of SNEDDS preparations because it is needed to dissolve lipophilic drugs. Drugs that have lipophilic properties should be dissolved in the O/W type nanoemulsion system while hydrophilic properties are made in the W/O type nanoemulsion system. Preformulation is an important factor in the process of developing poorly soluble nanoemulsion system drugs, or drugs with solubility depending on various formulation components. The selection of oil in the nanoemulsion formulation to maintain it in dissolved form must consider the solubility of the drug in the oil phase (Azeem et al., 2009).

Surfactants

Surfactants are important components in the manufacture of SNEDDS with the property of being able to reduce the surface tension of a medium because surfactants have the ability to combine different phases such as oil and water (Suhendri, 2016). Other functions of surfactants are emulsification, solubilization, dispersion, and increased penetration (Alfauziah, 2018). Surfactants with an HLB value <10 are hydrophobic and can form water-in-oil (w/o) nanoemulsions. While surfactants with a value> 10 are hydrophilic and can form oil-in-water (o/w) nanoemulsions. In this study, tween 80 was used as

a surfactant. Tween 80 or polyoxyethylene-20-sorbitan monooleate (C64H124O26) has a liquid form like oil, clear, light yellow to light brown, weak distinctive aroma, bitter taste. Tween 80 is a non-ionic emulsifier that has a lipophilic and hydrophilic balance, is non-toxic, non-irritating, has a low potential to cause hypersensitivity reactions and is stable against weak acids and weak bases (Rowe et al., 2015).

Cosurfactant

Cosurfactant is a component that plays a role in helping surfactants reduce surface tension. Cosurfactants help connect surfactant molecules, which facilitates the formation of interfacial tension to become more compact. In addition, cosurfactants affect the increase in drug loading, emulsification time, and help surfactants to regulate the size of nanoparticles. Unlike surfactants, cosurfactants are unable to form micelle-like structures on their own. Cosurfactants will be tucked away and form empty spaces between the surfactants so that the structure of the surfactant becomes more swollen but has high fluidity and is able to form nanoemulsions faster (Sahumena et al., 2019).

D-Optimal Mixture DesignNano Particles

D-Optimal Mixture Design is an experimental design found in the design expert 13 software that offers experimental designs for cases where standard designs cannot do it. In this study, researchers wanted to modify the existing design and obtain a more flexible model. There are many types of statistical techniques that can be used to optimize analytical procedures, response surface methodology and Box-Behnken, but D-optimal mixture design is generally and widely used in product formulation, especially in the food, pharmaceutical and cosmetic industries. The advantage of using D-optimal mixture design is that it reduces the number of experiments needed to evaluate several variables. In addition, D-Optimal Mixture Design has the ability to identify interactions statistically, which can overcome the shortcomings of conventional formulation methods. In this D-Optimal submenu, researchers will be asked to enter the lower and upper limits for each numeric variable so that researchers can enter the lowest to largest value limits for each component value needed so that the range of variations can produce values that are in accordance with expectations. In addition, Design Expert automatically randomizes the order in which the experiment is run in order to reduce the risk of unanticipated sources of variation that affect response estimates and help to meet the assumptions of the statistical methods used in analyzing experimental data.

METHODOLOGY

Materials

The materials used in this study were 95% curcumin (PT Gansu Yasheng Hiosbon Food Group), oleic acid (Brataco, Bekasi, Indonesia), tween 80 (Brataco, Bekasi, Indonesia), standard curcumin, PEG 400 (PT Bratacho), distilled water.

Instrumentation

The tools used in this research are magnetic stirrer (Boeco German, homogenizer, analytical balance type 210-LC, Particle Size Analyzer, UV-Vis Spectrophotometer (Shimadzu, Japan), Petri dish, volumetric flask (pyrex), beaker glass, micrometer pipette, and glassware (pyrex).

Procedure

Analysis of curcumin by FTIR

Weighed 400 mg of KBr powder and 4 mg of curcumin then curcumin was crushed using KBr so that it became a solid pellet, the steps for making a standard spectrum were followed, the spectrum was read at an absorption of 500-4000 cm-1. Then read the spectrum that came out (Permatasari et al, 2022).

Determination of curcumin SNEDDS Formulation with D-Optimal Mixture Design

The SNEDDS formula design was carried out using D-Optimal Mixture Design. The mixture of components used in this study was designed based on 3 components as independent variables, namely oleic acid as the oil phase, tween 80 as a surfactant, and PEG 400 as a co-surfactant with a total concentration of the three components of 100%. The parameters used include particle size, emulsification time, % transmittance, and drug loading. The predetermined upper and lower limits were then entered into this design to serve as a reference in the manufacture of SNEDDS.

Preparation of curcumin SNEDDS

A nanoemulsion of curcumin was prepared by spontaneous nanoemulsification method in the oil phase of oleic acid, tween 80 and PEG 400. Then mixing was done with a magnetic stirrer for 2 minutes. After isotropic, excess curcumin powder was added little by little until a saturated (cloudy) suspension was obtained, then allowed to stand for 24 hours. If there is a precipitate it means puresaturabel. Then the suspension was put in a test tube and then centrifuged. Take the clear part then transfer it to a vial (Kuncahyo et al., 2021).

SNEDDS optimization of curcumin

The SNEDDS formula results were included in D-Optimal Mixture Design to obtain the optimal formula of curcumin SNEDDS. The optimal formula obtained is expected to achieve the parameters set consisting of particle size <200 nm, percent transmittance close to 100%, emulsification time <1 minute, high drug loading.

Characterization of Optimum Formula of curcumin SNEDDS

Particle size

SNEDDS was taken 0.1 ml then diluted in 10ml distilled water and homogenized with a magnetic stirrer until a nanoemulsion system was formed. The particle size was tested with a particle size analyzer (PSA) at room temperature and a scattering angle of 173o (Pattewar et al., 2018).

Transmitant (%)

The dispersion system resulting from the emulsification time test is then viewed for %transmitant using UV spectrophotometry at the maximum wavelength (Kuncahyo et al., 2021).

Emulsification Time

The emulsification time test was carried out by pipetting 1 ml of SNEDDS and then placing it in 100ml of distilled water, stirring at a speed of 100rpm. Record the time required to form a homogeneous dispersion system (Kuncahyo et al., 2021)..

Drug loading

SNEDDS curcumin was taken 100 µl then dissolved using methanol up to 5 ml, from the solution taken 1ml then diluted using methanol up to 10 ml then the dissolved curcumin content was analyzed using a UV spectrophotometer at the maximum wavelength (Kuncahyo et al., 2017).

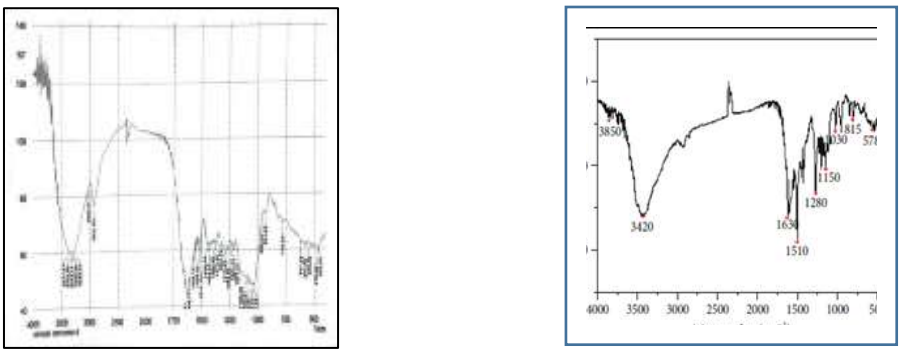
Data Analysis

The optimum formula of curcumin SNEDDS obtained from design experts was tested for characteristics including emulsification time, percent transmission, and drug loading and then tested for normality with 95% confidence level. The test has been done by comparing the results obtained from the normality test with the theoretical requirements. It will fulfill the requirement if the sig value > 0.05.

RESULTS AND DISCUSSION

Curcumin analysis by FTIR

The active ingredient curcumin has the characteristics of a yellowish-orange powder that is odorless and very difficult to dissolve in water. The level of curcumin raw materials analyzed using high-performance liquid chromatography obtained a level of 95.03% which is required in pharmacopoeia VI of more than 95% (Kemenkes RI, 2020).



(**a**) (**b**)

Figure 1. Identification spectrum of curcumin by FTIR: (a) Curcumin sample; (b) Jian et al., (2019)

The results of FTIR examination in Figure 1 showed a peak at 1625 cm-1 indicating the presence of carbonyl groups (C=O) in curcumin isolate. The characteristics of the IR spectra of curcumin are the peak at 3371 cm-1 indicating the presence of OH stretching bonds in curcumin isolate, and at 1604 cm-1 for aromatic C=C functional groups, aromatic C-H bonds at a peak of 3026 cm-1 and at a peak of 1282 cm-1 indicating the presence of C-O stretching bonds, C-O-C stretching bonds seen at a peak of 1153 cm-1 and C-OH bonds at a peak of 1234 cm-1. Identification of curcumin using FTIR with an absorption of 4000-500 cm-1 shows its typical peak in phenol hydroxyl OH stretching bend at 3,420 cm-1, C=O symmetrical stretch curcumin at 1,630 cm-1, C=O and C=C 1,510 cm-1, C=C stretching at 1,600 cm-1, and C-O aromatic stretching at 1,280 cm-1 curcumin (Jian et al., 2019) The identification results of the spectrum show that the compound used is curcumin.

Characterization of curcumin SNEDDS

The preparation of curcumin SNEDDS is done by mixing the oil phase, surfactant and cosurfactant with a magnetic stirrer then adding curcumin until saturated or until the curcumin powder precipitates, resulting in a yellow color of curcumin SNEDDS

Figure 2. SNEDDS of curcumin with combined concentrations of oleic acid, tween 80 and PEG 400.

Characterization of curcumin SNEDDS aims to determine that the preparation is qualified and stable, then testing is carried out based on critical parameters, namely particle size, emulsification time, % transmittance, and drug loading. SNEDDS particle size is one of the most important parameters in the development of SNEDDS because the resulting particle size will affect the adsorption of drugs in the body. Increasing the amount of oleic acid as oil in the formulation will increase the particle size, whereas increasing the amount of surfactant and cosurfactant usage can decrease the particle size due to the increase of emulsifier around the droplet interface and the decrease of interfacial tension in the system. The % transmittance obtained affects the clarity of the SNEDDS produced. The higher the % transmittance value will produce a clear and transparent solution. Determination of loading drug is done to determine the ability of SNEDDS in dissolving curcumin to saturation and determine the content of curcumin in the SNEDDS formula. The loading drug results are used to determine how much volume of SNEDDS is needed in one use by comparing the dose used with the curcumin dissolved in the SNEDDS system (Kuncahyo et al., 2021)

The SNEDDS formula design obtained from D-Optimal Mixture Design and characterization results with critical parameters can be seen in (Table 1).

Table 1. SNEDDS curcumin formula design from D-Optimal Mixture Design and critical parameter characterization results

Formula	Composition (%)			Test Parameters			
	A	B	C	PS (nm)	%T (%)	ET(dtk)	DL (mg/ml)
1	24,75	60,8	14,45	186,9	40,1	91,3	3,9
2	24,87	55,13	20	247,8	35,5	93,3	2,7
3	20,42	60,96	18,62	218.2	52,0	106,0	3,4
4	29,73	55,39	14,89	283.2	29,5	104,7	3,0
5	28,43	61,57	10	247.7	58,0	79,0	3,8
6	10	70	20	56.47	95,4	41,7	3,5
7	23,59	66,41	10	198.3	71,9	97,0	3,9
8	14,89	65,11	20	108.1	86,4	57,0	3,4
9	20,42	60,96	18,62	213.5	60,9	116,3	2,8
10	20,11	65,21	14,68	191.3	65,8	133,0	3,1
11	16,86	70	13,14	157.7	80,5	53,0	3,5
12	29,73	55,39	14,88	225.3	50,2	101,0	2,7
13	28,42	61,57	10	244.1	41,8	69,3	2,7
14	30	50	20	252.6	21,6	214,3	2,8
15	16,86	70	13,14	108.7	87,1	58,0	2,4
16	24,75	60,8	14,45	175.8	66,6	96,7	3,9

PS, particle size; ET, emulsification time; %T, % transmitant; DL, drug loading.

Based on Table 2, it can be seen that particle size, emulsification time, % transmittance and drug loading have significant values with p values <0.05 (significant). This means that the value of the four parameters is influenced by the formula components in the D-Optimal design. The lack of fit value can be seen in table 2 aims to determine whether the model listed has a mismatch with the response data. The lack of fit value on the four parameters obtained a value> 0.05 (insignificant) explains that there is a fit between the response data and the Linear Mixture model.

Table 2. Statistical results of the parameters particle size, % transmittance, emulsification time and drug loading

ANOVA Parameters	Particle sizel	% Transmitant	Emulsification time	Drug loading
Model (p<0,05)	< 0,0001	< 0,0001	< 0,0001	0,0194
Lack of fit (p>0,05)	0,3208	0,9796	0,3251	0,4961
R- squared	0,8174	0,8623	0,9930	0,4547
Adj Rsquared	0,7893	0,8411	0,9825	0,3708
Coefficient				
A	350,58	9,19	10,68	3,43
B	61,71	117,52	-365,59	4,17
C	118,88	48,12	-122299,86	1,94
AB			1090,68	
AC			22824,25	
BC			22741,81	
ABC			-24517,43	
Mixture Model	*Linear*	*Linear*	*Cubic*	*Linear*

Particle size in SNEDDS preparations is an important factor in the ability of self-emulsification because particle size determines the rate of drug release which can affect the absorption process. Particle size assessment resulting from the D-Optimal Mixture Design method resulted in varying particle sizes ranging from 56.47 nm to 283.2nm. Formulas 1, 6, 7, 8, 10, and 11 produce particle sizes < 200 nm which is the size limit to become SNEDDS (Kuncahyo, 2021). SNEDDS with the smallest particle size in this study was produced by F6 with a result of 56.47nm. Evaluation of the contribution of the components oleic acid, tween 80 and PEG 400 with different compositions, and variables on the particle size response has the final equation :

$$Y= +350,58(A)+ 61,71(B)+118,88 (C) \quad (1)$$

Keterangan:
Y1 = Particle size (nm)
A = Oleaic Acid
B = Tween 80
C = PEG 400

Based on the results of the regression equation for particle size, it was found that the concentration of oleic acid (+350.58) was most influential in increasing particle size compared to tween 80 and PEG 400. Particle size has a significant value with a p value <0.05, which means that particle size is influenced by the formula components in the D-Optimal design, the lack of fit value obtained is 0.3208>0.05, which means there is no significant error between the linear mixture model and the response data. The R-squared value obtained is 0.8174, where the R-squared value which is closer to 1 indicates that the response data follows the D-Optimal mixture design model suggesting a Linear model for particle size with a value of F = 29.1 which means this model is significant. The Adjusted R2 value is 0.8174 and predicted R2 with a value of 0.7323 which shows that the difference between the two values is < 2 so it is said that this model is appropriate and can be used. For the Adeq precision value obtained of 15.7303, it is said to be appropriate because this value> 4.

Figure 3 shows that there is a significant relationship between the particle size response and the percentage of oil components, namely oleic acid, Tween 80 as a surfactant, and PEG 400 as a cosurfactant. It can be seen that the contour plot of Figure 2 at a point that is closer to the red color shows a larger particle size accompanied by a higher presentation of oleic acid concentration (A), at a point that is closer to the blue area shows a smaller particle size value along with the greater concentration of Tween 80 (B) and PEG (C) used in curcumin SNEDDS. This is because surfactants and cosurfactants are not able to reduce the interfacial tension of oils with high amounts. Based on the results of the particle size parameter testing, the use of high amounts of oil can significantly increase the particle size. While increasing the concentration of surfactants and cosurfactants used in curcumin SNEEDS significantly decreased the particle size. Because surfactants and cosurfactants can affect particle size through surface tension, the surface tension of an emulsion that is lowered by surfactants causes the particle size to be small because of the energy that can

break and reduce the particle size in the emulsion (Buya etal, 2020; Zeng et al, 2017).

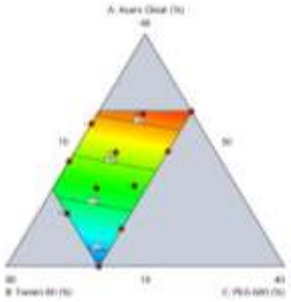


Figure 3. Contour plot of particle size of curcumin SNEDDS

% Transmittance is done to determine the SNEDDS curcumin dissolved in a clear nanoemulsion with a consistency close to 100%, The results of % transmittance in this study have a value range of 29.5% to 95.4%, The % transmittance value that is close to 100% indicates that the SNEDDS made is clear and transparent, In addition, the clarity of SNEDDS also indicates that the particle size in the SNEDDS formula is nanometer-sized. (Cahyani et al., 2020; Sahumena et al., 2019). The results of the ANOVA test % transmittance obtained p value <0.05 indicates that there is a significant influence by the components in the D-Optimal design. The obtained R-squared value of 0.8623 indicates a good fit produced for the response data because the R-squared value is close to the value of 1. Design experts suggest a Linear model for % transmittance with a value of F = 40.71 meaning this model is significant. The Adjusted R-squared value is 0.8411 and predicted R-squared with a value of 0.8105, which shows that the difference between the two values is < 2 so it is said that this model is suitable and can be used. For the Adeq precision value obtained of 19.0956, it is said to be appropriate because this value is> 4. Evaluation of the contribution of oleic acid components, tween 80 and PEG 400 with different compositions, and variables on the % transmittance response has a final equation:

Y2 = +19,19 (A) + 117,52 (B) + 48,12 (C) (2)
Keterangan:
Y2 = % transmitant
A = Oleic Acid
B = Tween 80
C = PEG 400

Based on the regression coefficient value for % transmittance, it is found that the concentration of tween 80 has a synergistic effect as increasing the concentration of tween 80 will increase the % transmittance value and shows that tween 80 (+117.52) is most influential in increasing % transmittance compared to oleic acid and PEG 400. The % transmittance test in Figure 4 shows that the red color area shows the area with the highest value, while the dark blue color is the area with a low value, at a higher % transmittance value, the

movement of the contour plot is getting closer to the red color, namely at a high concentration of tween 80, and vice versa. This is because the use of tween 80 as a surfactant can form an o/w nanoemulsion system when dispersed in Artificial Gastric Fluid (AGF) media, thus increasing the physical clarity of the nanoemulsion (Huda and Wahyuningsih, 2016).

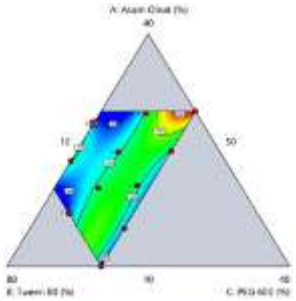


Figure 4. Contour plot of % transmitan of curcumin SNEDD

The emulsification time is carried out to determine the time required by SNEDDS curcumin to form a nanoemulsion with the right proportion when interacting with the gastrointestinal tract in the body (Kuncahyo, 2021). It can be said that a good emulsion when emulsification occurs in less than 1 minute with a clear or transparent visual. Data in table 1, it can be seen that the emulsification time obtained in the range of 41.67 - 214.333 seconds with a p value <0.05 of <0.0001 which follows the cubic formula model shows that the emulsification time is influenced by the components in the D-Optimal design. The lack of fit value obtained is 0, >0.05 which means there is no significant error between the cubic model and the response data, the R-Squared value obtained is 0.9865 which indicates that a good fit is produced for the response data because the R-Squared value is close to the value of 1. Design experts suggest a Linear model for moisture with an F value = 94.41 meaning this model is significant. The Adjusted-Squared value is 0.9825 and the predicted-Squared value is -0.1121, which shows the negative result of the predicted-Squared representing that there is a possibility that another model is better than this model. In some cases higher models can also predict better. For the Adeq precision value obtained of 41.8592, it is said to be appropriate because this value is> 4. Evaluation of the contribution of the components oleic acid, tween 80 and PEG 400 with different compositions, and the variable on emulsification time response has the final equation

Y3 =+10,68 (A) - 365,59 (B) -122299,86 (C) + 1090,68 (AB) + 22824,25 (AC) + 22741,81 (BC) -24517,43 (ABC) (3)

Keterangan:
Y3 = Emulsification Time
A = Oleic Acid
B = Tween 80
C = PEG 400

Based on the results of the regression equation for emulsification time, it was found that the concentration of oleic acid (+10.68) had an effect in increasing particle size compared to tween 80 and PEG 400. The concentration

of tween 80 (-365.59) in the regression equation obtained negative results which presented that the addition of tween 80 concentration decreased the value of emulsification time.

Figure 5 shows that the smaller the concentration of tween 80 (B) used in SNEDDS, the longer the emulsification time can be seen at the point in the red area, this is because the smaller the concentration of surfactants in SNEDDS will affect the ability to form a clear emulsion to be longer so that the emulsification time increases.

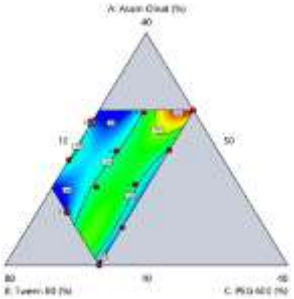


Figure 5. Contour plot of emulsification time of curcumin SNEDS.

Determination of drug loading is carried out to determine the ability of SNEDDS to dissolve drugs until they are sufficiently saturated and determine the drug content in the SNEDDS formula (Kuncahyo, 2021). The ANOVA test results of drug loading with a p value <0.05 of 0.0194 indicate that there is a significant influence by the formula components in the D-Optimal design. The R-Squared value obtained is 0.9865, indicating a good fit between the model and the response data where the R-Squared value obtained is close to 1. In the Fit Statistic results, an R-Squared value of 0.4547 is obtained, indicating a good fit produced for the response data because the R2 value is close to 1. Design experts suggest a Linear model for drug loading with an F value = 5.42, meaning this model is significant. The Adjusted R-Squared value is 0.542 and predicted R-Squared with a value of 0.2577, which shows that the difference between the two values is < 2 so it is said that this model is suitable and can be used. For the Adeq precision value obtained of 6.7039, it is said to be appropriate because this value is> 4.

Evaluate the contribution of the components oleic acid, tween 80 and PEG 400 with different compositions, and the variables on the Drug loading response have a final equation.

Y4 = +3,43 (A) + 4,17 (B) + 1,94 (C) (4)
Keterangan:
Y4 = Drug loading
A = Oleic Acid
B = Tween 80
C = PEG 400

Based on the regression coefficient value for drug loading, it is found that the concentration of tween 80 (+4.17) has the most influence in increasing drug loading compared to oleic acid and PEG 400. Figure 6 shows the relationship between the components of the SDNEDDS formula, namely oleic

acid, tween 80 and PEG 400 with the formation of color gradations, where the red area is the limit of the highest value while the blue area is the limit of the lowest value. Based on the contour plot generated from the determination of drug loading, it can be seen that the tween concentration affects the drug loading value which is marked by a red contour plot, namely in tween 80. The drug loading produced in this test is in the range of 2.77mg/ml to 3.9287mg/ml. The results of determining drug loading in this study obtained the highest results, namely in formula 7 of 3.92872. This is because in formula 7 there is a fairly high concentration of tween 80, this is because tween 80 as a surfactant is able to help the oil component dissolve the drug so that a high drug loading is obtained (Kuncahyo., 2021).

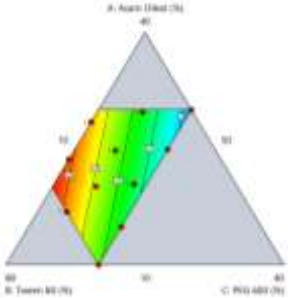


Figure 6. Contour plot of drug loading curcumin SNEDDS

The determination of the optimum formula of curcumin SNEDDS was carried out using Design Expert 13 software with a numerical approach. The parameters used in this study to determine the optimum formula were particle size, % transmittance, emulsification time and drug loading by entering the upper and lower limit values of the concentration of oleic acid, tween 80, and PEG 400. After entering the expected response value criteria, D-Optimal Mixture Design recommended the optimal formula for curcumin SNEDDS.

Prediction of the optimum formula with D-Optimal Mixture Design was obtained for each component with a concentration of oleic acid of 10%, tween 80 of 70%, PEG 400 of 20%, 3 replications of the optimum formula were carried out which were then tested with the parameters of particle size, emulsification time, % transmittance and drug loading, then verified by comparing the value of each parameter with the predicted value obtained.

The optimal formula that has been made in three replications and tested for response based on each parameter produces data as shown in table 3.

Table 3. Comparison of predicted value with test value of optimum formula

Parameters	Predicted Value	Result Value	Value *Sig.*	Description
Particle size (nm)	80,769	80,167 ± 0.286	0,97	Not Different
Emulsification Time	39,556	39,357 ± 0.161	0,223	Not Different
% Transmitant	94,388	94,1± 0.081	0,38	Not Different
Loading Drug (mg/ml)	3,423	3,466 ± 0.030	0,179	Not Different

The predicted value derived from D-Optimal Mixture Design is compared with the test value using SPSS 25 with the One Sample T-test test at the 95% confidence level to test the significance of the average difference between the predicted value generated by D Optimal mixture design and the test value, The response in each parameter obtained sig value> 0.05 which indicates that between the predicted value and the test value there is no significant difference.

CONCLUSIONS AND RECOMMENDATIONS

Variations in the concentration of oleic acid, tween 80 and PEG 400 with D-Optimal Mixture Design influenced curcumin SNEDDS with a particle size < 200nm, gave an emulsification time of less than 1 minute, gave a % transmittance value close to 100%, and gave a high drug loading. The proportion of oleic acid 10%, tween 80 by 70% and PEG 400 by 20% which can produce the optimum formula of curcumin SNEDDS with D-Optimal Mixture Design on critical parameters of particle size of 80.167nm, emulsification time of 39.36 seconds, transmittance value of 94.1%, and drug loading of 3.466 mg/ml.

FURTHER STUDY

After conducting research on the optimization and characterization of curcumin Self Nano Emulsifying Drug Deliver System (SNEDDS) components using the D-Optimal Mixture Design method, it can be suggested that further studies need to be carried out regarding the stability of curcumin SNEDDS and further development to make curcumin SNEDDS solids which can later be made into tablet dosage forms

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