SCREENING OF PIROXICAM SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS) USING FRACTIONAL FACTORIAL DESIGN

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Abstract

Piroxicam belongs to BCS class II and has low solubility. Self-nanoemulsifying drug delivery systems (SNEDDS) are considered a potential approach for increasing the solubility and release of piroxicam. This study aimed to select the components and component ratios of piroxicam SNEDDS using fractional factorial design 2^{6-2} (FFD). The variables used in the DFT development of piroxicam SNEDDS are the type and concentration of oil (triacetin and oleic acid), surfactant (kolliphor EL and Tween 60), and co-surfactants (Transcutol and PEG 400). The FFD results showed 16 runs with different proportions of the piroxicam SNEDDS components, which were then characterized by critical parameters including emulsification time, %transmittance, droplet size, and drug loading. The components and component ratios of the PKM SNEDDS were determined using single-factor plot analysis. The results showed that triacetin (oil), kolliphor EL (surfactant), Transcutol (co-surfactant) had the greatest contribution to the formation of piroxicam SNEDDS with an oil ratio range of 11.11–28.57%, surfactant 44.44–77.78%, co-surfactant 11.11–44.44 %.

***Keywords**: fractional factorial design, piroxicam, SNEDDS*

Introduction

Piroxicam belongs to a class of nonsteroidal anti-inflammatory drugs that are widely used to relieve moderate pain (Al-Timimi Z, 2021). Piroxicam is described in the VI edition of the Indonesian Pharmacopoeia as a drug that is poorly soluble in water, with a solubility of 0.023 mg/mL. The intrinsic dissolution rate of piroxicam using the disc intrinsic dissolution rate (DIDR) method at three pH values (0.1 N hydrochloric acid solution pH 1.2, acetate buffer pH 4.5, and phosphate buffer pH 6.8) below 0.1 mg/min. cm^{-2} which is the highest solubility classification limit (Shohin *et al.*, 2014; Kemenkes RI, 2020). Piroxicam with a low solubility rate will cause low drug bioavailability because most of the drug will be wasted from the site of absorption before the drug has time to be dispersed molecularly.

SNEDDS (Self-nanoemulsifying drug delivery systems) is considered a potential approach to increase drug solubility and release because it is based on lipids that are physically stable and do not require a high-energy emulsification process, which requires relatively simple production equipment and can reduce production costs. The use of SNEDDS as a drug delivery agent with low solubility can increase the rate of dissolution, making it possible to reduce the dose required to reduce side effects (Sriamornsak *et al.*, 2015). SNEDDS is an isotropic mixed system consisting of an oil phase as a drug carrier, a surfactant as

an emulsifier that reduces the interfacial tension of the oil and water phases, and a co-surfactant as an emulsifier that helps the surfactant maintain stability in the film layer between oil and water, along with the drug., which rapidly forms 20–200 nm oil-in-water (o/w) nanoemulsions when introduced into aqueous media (Morakul, 2020; Sokkula and Gande, 2020). In the conventional method, the selection of oil, surfactant, and co-surfactant components for SNEDDS was based on the ability of the components to dissolve the drug and then a pseudoternary diagram model was created to determine the ratio of each component. The drawback of this method is that it cannot describe the emulsification and mix-up correlations between each SNEDDS component, requires several steps to determine the proportion of SNEDDS, and still uses aqueous media as a nanoemulsion medium; thus, four components need to be taken into account when determining the nanoemulsion area, which causes additional trials and testing (Kuncahyo *et al.*, 2021; Cahyani *et al.*, 2020). Another method for determining the components and ratio of SNEDDS can be performed using a statistical approach with a fractional factorial design (FFD). FFD is used to determine and assess contributing factors in making SNEDDS with a few trials without losing important information, and has proven to be more efficient than the pseudoternary method (Pratiwi *et al.*, 2022; Kuncahyo *et al.*, 2019).

This study aims to select the components and component ratios of piroxicam SNEDDS using FFD 2^{6-2} using Design Expert 12 software. The variables used were triacetin and oleic acid as oil components, Kolliphor EL and Tween 60 as surfactant components, and triacetin co-surfactant as components. and PEG 400. The components and ratios of SNEDDS piroxicam were determined using a formula based on FFD 2^{6-2} and then the critical parameters, including drug loading, emulsification time, % transmittance, and droplet size. The critical parameters were analyzed using a single factor plot based on % transmittance, emulsification time, intermediate droplet size, and drug loading. Statistical parameters for the interaction between components were determined using a multiple linear regression approach.

Research Methods

Materials

Piroxicam was obtained from PT Zenith Pharmaceutical, triacetin (Loba Chemie), oleic acid (Sigma Aldrich), Kolliphor EL (Sigma Aldrich), Tween 60 (Panzeri), Transcutol (Gattefossé), PEG 400 (Korea Pla-Chem), and methanol (Smart Lab). All the materials used were of pharmaceutical or analytical grade.

Instrumentation

A UV-Vis spectrophotometer (Shimadzu 1780), magnetic stirrer (Thermo Cimarec+), particle size analyzer (Malvern 3000E), centrifuge (Biobase 80-2), dissolution tester (Biobase BK-RC6), micropipette (Dragon Lab), analytical balance (Mettler Toledo ME 304), and other supporting glasses were used.

Procedure

Experimental design for screening of SNEDDS piroxicam components and ratio

Screening of SNEDDS components used a design of experimental approach with a fractional factorial design using six factors, namely categorical factor was the type of oil, surfactant, and co-surfactant and the numerical factor was the proportion concentration of each component with two levels, namely the upper (+1) and lower (-1) levels). The experimental design for the screening of SNEDDS piroxicam using FFD (fractional factorial design) 2^{6-2} is presented in Table 1.

Table 1. Design of experimental FFD 2^{6-2}

Level	Factors					
	Categorical factors			Numerical factors		
	A	B	C	D	E	F
Lower level (-1)	Oleic acid	Tween 60	PEG 400	1	4	1
Upper level (+1)	Triacetin	Kolliphor EL	Transcutol	2	7	4

A, oil type; B, surfactan type; C, co-surfactant type; D, oil proportion; E, surfactant proportion; F, cosurfactan proportion.

The design of the fractional factorial formula 2^{6-2} was obtained using the design expert program with the factors listed in table 1. The design of fractional factorial formula 2^{6-2} and the results of the characterization of the critical parameters are presented in Table 2.

Table 2. Design of experimental FFD formula 2^{6-2} and the results of characterization of critical parameters

Run	Categorical factors			Numerical factors			Responses			
	A	B	C	D	E	F	DL (mg/mL)	ET (s)	%T (%)	DS (nm)
1	Triacetin	Tween 60	PEG 400	1	7	1	63,55±0,71	12,72±1,07	54,65±3,59	166,03± 9,89
2	Triacetin	Tween 60	Transcutol	2	4	1	60,09±0,13	10,96±0,85	78,65±1,44	835,7± 19,24
3	Triacetin	Kolliphor EL	Transcutol	1	7	1	59,10±0,04	9,84±1,24	96,65±0,63	11,96± 0,78
4	Oleic acid	Tween 60	PEG 400	1	4	1	30,71±0,09	15,80±1,92	38,54±1,31	273,63± 4,09
5	Oleic acid	Tween 60	PEG 400	2	4	4	46,20±0,15	17,34±1,96	27,90±0,3	303,53± 4,35
6	Oleic acid	Kolliphor EL	PEG 400	1	7	4	47,87±0,6	25,60±3,82	72,76±3,39	34,81± 0,62
7	Oleic acid	Kolliphor EL	Transcutol	2	4	4	51,73±0,19	29,76±2,84	60,88±1,56	261,80± 4,17
8	Triacetin	Tween 60	PEG 400	2	7	4	53,06±0,2	34,64±2,37	73,04±0,6	83,44± 5,92
9	Oleic acid	Kolliphor EL	Transcutol	1	4	1	51,94±0,15	14,85±1,28	71,07±0,35	218,73± 2,85
10	Triacetin	Kolliphor EL	PEG 400	1	4	4	61,98±0,36	10,29±1,45	96,18±0,22	13,07± 0,15
11	Triacetin	Kolliphor EL	Transcutol	2	7	4	72,13±0,69	14,43±1,54	99,08±0,21	12,88± 1,43
12	Oleic acid	Tween 60	Transcutol	1	7	4	42,87±0,47	15,70±1,46	76,28±1,66	80,04± 0,61
13	Oleic acid	Tween 60	Transcutol	2	7	1	35,43±0,97	41,82±5m96	65,65±2,17	248,90± 3,60
14	Triacetin	Kolliphor EL	PEG 400	2	4	1	58,49±0,61	14,49±1,24	63,56±0,75	233,93± 1,19
15	Oleic acid	Kolliphor EL	PEG 400	2	7	1	38,98±0,93	36,89±2,36	95,42±1,4	11,99± 0,35
16	Triacetin	Tween 60	Transcutol	1	4	4	55,96±0,19	9,62±1,15	83,56±0,59	131,63± 0,73

A, oil type; B, surfactan type; C, co-surfactant type; D, oil proportion; E, surfactant proportion
F, co-surfactant proportion; DL, drug loading; ET, emulsification time; %T, % transmittance.
DS = droplet size

Preparation of SNEDDS Piroxicam

A Combination of oil, surfactant, and co-surfactant, according to the proportions in table 2, with a total weight of 10 g, was homogenized using a magnetic stirrer at 500 rpm then added piroxicam until saturation or precipitation of piroxicam powder occurred. After saturation, the mixture was centrifuged at 10,000 rpm for 120 min and the supernatant was collected. The resulting SNEDDS were stored at room temperature until further characterization.

Characterization of SNEDDS Piroxicam

1) Drug loading

   Piroxicam (100 µL) was dissolved in methanol to a final volume of 5 mL. One milliliter of the solution was diluted to 10 mL with methanol, and the dissolved piroxicam content was analyzed using a UV spectrophotometer at a wavelength of 333 nm.

2) Emulsification time

   The emulsification time test was carried out by diluting 100 times using a type II stirrer dissolution tester by pipetting 2 mL of SNEDDS into 200 mL of aqueous solution at 37 ± 1°C and then stirring at 100 rpm. The time required to form a homogeneous nanoemulsion dispersion was also recorded.

3) %Transmittance.

   The dispersion system formed from the emulsification time test was then stirred at 500 rpm for five minutes and the %transmittance was observed using UV spectrophotometry at a wavelength of 333 nm.

4) Droplet size.

   The tests were carried out by diluted 0.1 mL) in 10 mL of distilled water and then homogenizing with a magnetic stirrer to form a nanoemulsion system. Droplet size was determined using a particle size analyzer at room temperature and a scattering angle of 173º.

Screening of SNEDDS piroxicam components and ratio

Screening for component selection and component ratios of SNEDDS piroxicam based on the contribution of each factor to critical parameters, including drug loading, emulsification time, % transmittance, and droplet size, was analyzed using a single factor plot study by examining the interactions between components using a multiple linear regression approach with the calculation in Eq. (1).

Where a is the intercept; A, B, C, D, E, F as factors; m_1, m_2, m_3, m_4, m_5, m_6 as regression coefficients with good statistical parameters with significance $p < 0.05$, R^2 is more than 0.7, adequate precision is more than 4, and the difference between adjusted R^2 and predicted R^2 is less than 0,2 (Kuncahyo *et al.*, 2021; Pratiwi *et al.*, 2022).

$$Y = a + m_1A + m_2B + m_3C + m_4D + m_5E + m_6F \quad (1)$$

Results and Discussion

Characterization of SNEDDS piroxicam

The type and proportion of oil, surfactant, and co-surfactant significantly affect the characterization of nanoemulsion. The formation of a nanoemulsion solution can be indicated by a transparent and bluish solution, whereas a clear solution indicates the formation of micelles. In runs R3, R10, R11, and R15, a clear solution was formed, which indicated the formation of micelles, while in runs R6, R8, R12, R14, and R16, a bluish transparent solution was formed, indicating the formation of a nanoemulsion (Figure 1). SNEDDS piroxicam was characterized based on critical parameters, namely drug loading, % transmittance, emulsification time, and droplet size, and the results are shown in Table 2.

Figure 1. The appearance of SNEDDS piroxicam nanoemulsion with different components and proportions of oil, surfactant, and co-surfactant.

Characterization of drug loading resulted in variations between runs, where the use of triacetin oil resulted in drug loading according to the target (> 50 mg/mL). High drug loading can increase the loading capacity and bioavailability of drugs and has the potential to reduce drug doses and side effects. Triacetin has a higher level of lipophilicity than oleic acid because it is an ester with three alkyl groups; therefore, it has higher lipophilic properties than oleic acid, which is a monounsaturated fatty acid (Al-Timimi Z, 2021). The results of the characterization of the emulsification time showed that the majority fulfilled the SNEDDS target of being able to form nanoemulsions with mild agitation in under 30 s (Leavesextracts *et al.*, 2019). The rapid emulsification time of SNEDDS can accelerate drug absorption and increase the efficiency of drug delivery, which is influenced by several factors, such as the type and concentration of oil, surfactant, and co-surfactant (Zhao, 2015). Runs R3, R10, R11, and R15 produced good % transmittance with % transmittance > 90%, where the surfactant used was Kolliphor EL. Kolliphor EL has a branched alkyl chain structure that promotes stronger penetration into the oil than a linear alkyl chain structure, resulting in a more efficient self-nano-emulsifying formation (Bandivadekar *et al.*, 2013). The droplet sizes produced between runs also varied from 11.96 nm to 835.7 nm, in R1, R3, R6, R8, R10, R11, R12, R15, and R16 resulting in droplet sizes <200 nm which is the limit for becoming a preparation nanoemulsion (Aulia *et al*., 2021; Nandita *et al*., 2017). The majority of runs produce droplet sizes < 200 nm, which illustrates the development of SNEDDS with a fractional factorial design approach that can produce SNEDDS with the desired characteristics.

Screening of components and component ratios with fractional factorial design (FFD)

The selection components and ratios of SNEDDS piroxicam used a single plot factor study of the parameters of drug loading, % transmittance, emulsification time, and droplet size with a multiple linear regression analysis approach. A multiple linear regression analysis was used to assess the formation of a good model based on the parameters used. Parameters with a good model were characterized by a significance of $p < 0.05$, $R^2 > 0.7$, adequate precision > 4, and the difference between the adjusted R^2 and predicted R^2 was less than 0.2. The statistical parameters for drug loading, emulsification time, %transmittance, and droplet size are listed in Table 2.

Table 2. Statistical parameters of drug loading, emulsification time, % transmittance, and droplet size

Parameter	Drug loading	Emulsification time (inverse)	% Transmittance (inverse sqrt)	Droplet size (square root)
p-value model	0,0014	0,003	0,0002	0,0016
R^2	0,907	0,739	0,945	0,771
Adjusted R^2	0,872	0,644	0,896	0,688
Predicted R^2	0,630	0,449	0,778	0,516
Adequate precision	10,422	7,948	16,322	10,52

The increase in drug loading parameters is influenced by the type of oil and surfactant. Oil type was the most influential factor in increasing the drug loading. The oil phase is the most important component for dissolving lipophilic drugs in the SNEDDS system to obtain maximum drug loading (Morakul, 2020). The selection of the oil type factor between oleic acid and triacetin is shown in figure 2a, which shows the line plot of drug loading increasing towards triacetin, indicating that triacetin oil type can increase drug loading compared to oleic acid. In another study, triacetin showed a dominant ability compared to other types of oil to dissolve piroxicam (Al-Timimi Z, 2021). Triacetin is a medium-chain triglyceride (MCT) that can increase solubility compared with the use of vegetable oils, such as oleic acid (Buya *et al.*, 2020). The choice of surfactant type between Kolliphor EL and Tween 60 is shown in Figure 2b. The plot line of drug loading increased towards kolliphor EL, indicating that kolliphor EL as a surfactant can increase drug solubility in the SNEDDS system. In another study, the results were the same, where kolliphor EL dissolved hydrophobic drugs better than Tween 60 (Al-Timimi Z, 2021; Abushal *et al.*, 2022).

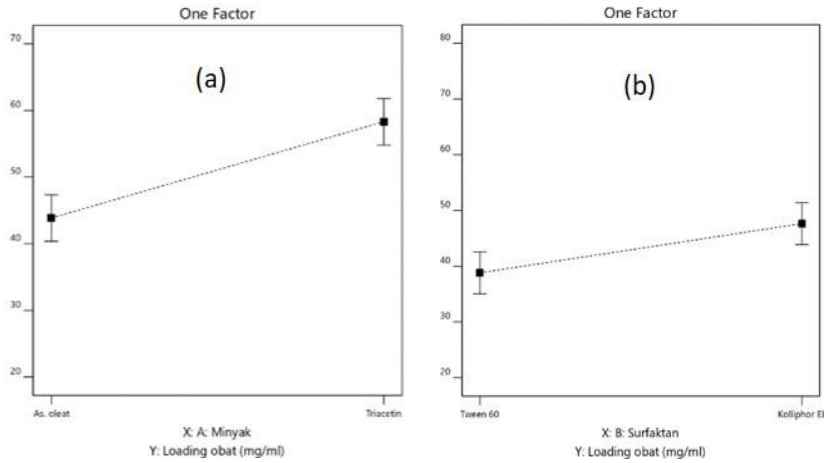

Figure 2. Single plot factor for drug loading, (a) oil type, (b) surfactant type

The %transmittance parameter describes the ability of surfactants and co-surfactants to form nano-emulsions when SNEDDS preparations are dispersed in a liquid medium. Nanoemulsion systems with small globules tend to transmit light so that the appearance of the solution appears transparent and the resulting transmittance is greater. The clearer or The transmittance is closer to the transmittance of distilled water (100%), it is estimated that the emulsion droplets

have reached nanometer size (Cahyani *et al*., 2020; Sahumena *et al*., 2019).

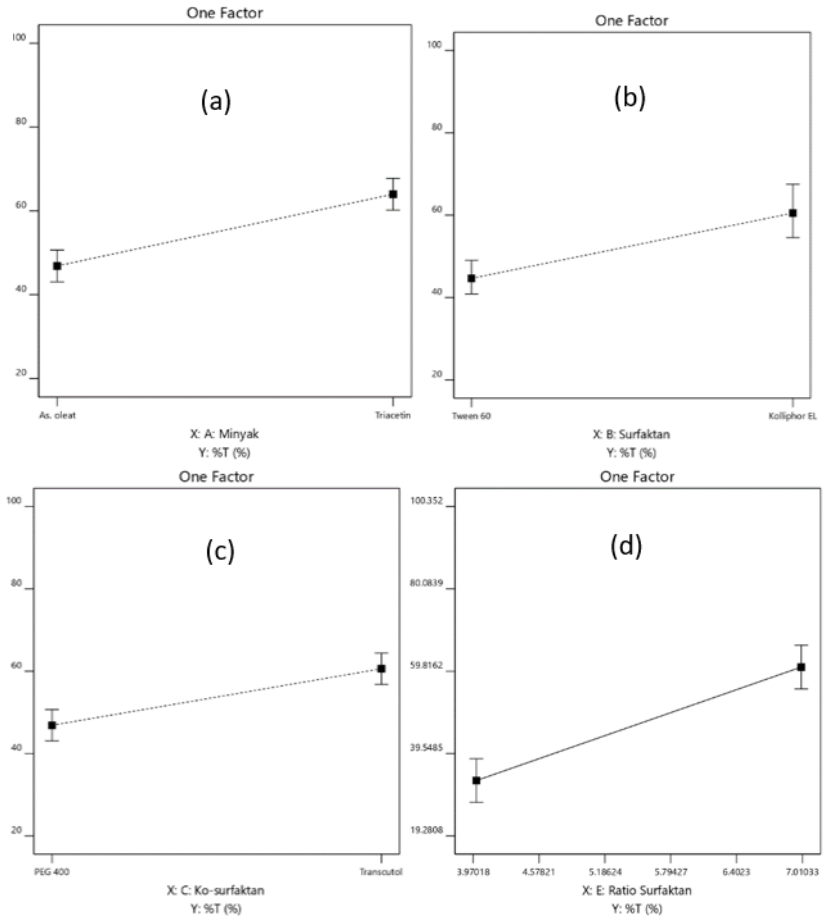

Figure 3. Single plot factor for % transmittance, (a) oil type, (b) surfactant type (c) co-surfactant type, and (d) surfactant ratio

Triacetin significantly increased the % transmittance compared to oleic acid oil, where the line plot increased in the direction of triacetin (figure 3a). In Figure 3b, kolliphor EL as a surfactant significantly increased the % transmittance compared to Tween 60, with the line plot increasing towards the EL kolliphor. As shown in figure 3c, the Transcutol surfactant type with a high ratio also increases the %transmittance. In figure 3d, the line plot increases as the use of surfactant increases, illustrating that greater use of surfactant increases the % transmittance. Kolliphor EL has a higher nano-emulsifying capacity than Tween 60 because it has a branched alkyl structure that can encourage stronger penetration into the oil to form nano emulsion droplets that increase %transmittance (Bandivadekar *et al.*, 2013; Nurismawati and Priani, 2021).

The emulsification time provides an overview of SNEDDS preparations, which can easily form emulsions in the body due to peristaltic movements in the digestive tract. The emulsification time has the potential for faster drug absorption and can accelerate drug effects (Erliyana *et al.*, 2022). The oil phase is an important component in SNEDDS preparation for the spontaneous formation of nanoemulsions (Date *et al.*, 2010).

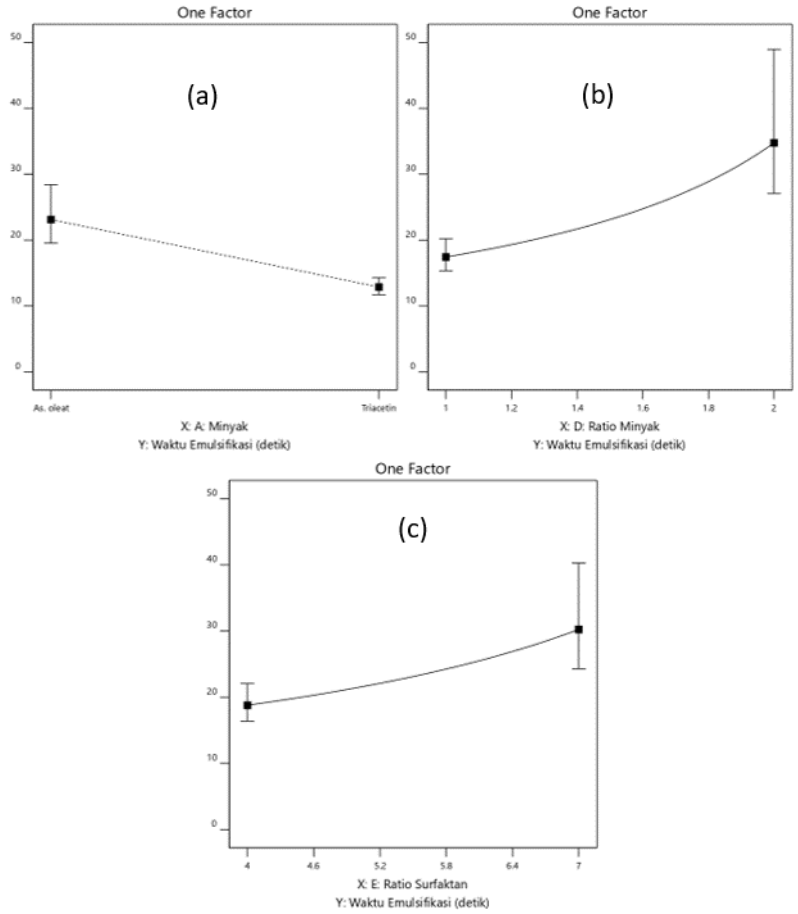

Figure 4. Single plot factor for emulsification time, (a) oil type, (b) oil ratio, (c) co-surfactant ratio

Figure 4a triacetin has a significant effect on the speed of emulsification compared to oleic acid, however increasing oil phase in the formulation will decrease the emulsification time (Figure 4b). The use of the triacetin oil phase can increase the emulsification time compared to the use of vegetable oil phases such as oleic acid (Buya *et al.*, 2020). Triacetin oil type can increase the speed of dispersion so that it speeds up the emulsification time but the higher the usage can reduce the speed of dispersion and increase the size of the droplet (Baloch *et al.*, 2019). The ratio of surfactant use also affects the speed of emulsification. It can be seen from the single plot factor graph in Figure 4c that an increase in the ratio of use of co-surfactant can reduce the speed of emulsification. Increasing the proportion of co-surfactants will directly reduce the proportion of surfactants in the formula where surfactants play a very important role in reducing the interfacial tension between the water and oil phases.(Zafar *et al.*, 2022; Nasr *et al.*, 2016).

Emulsion droplet size is the most important parameter in the development of SNEDDS because droplet size or emulsion droplets directly affect not only in vitro characteristics such as dissolution but also in vivo characteristics such as absorption. A smaller droplet size can be interpreted as a larger interface area, which increases the solubility and permeability of the drug (Buya *et al.*, 2020).

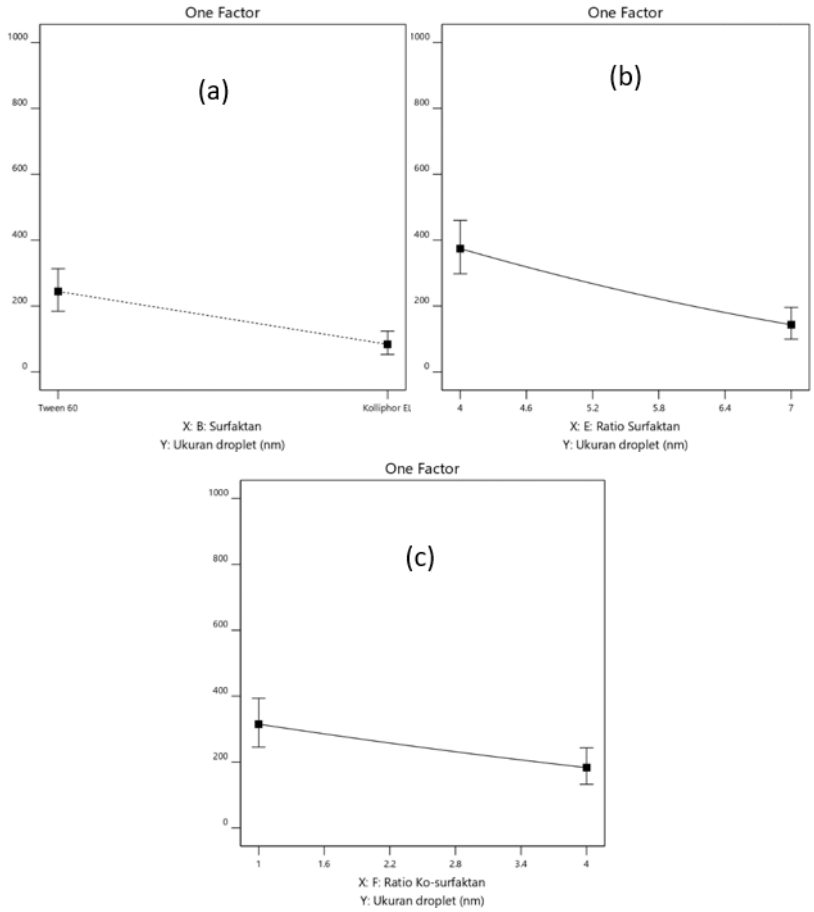

Figure 5. Single plot factor for droplet size, (a) surfactant type, (b) surfactant ratio, and (c) co-surfactant ratio

The main influences on the droplet size parameters were the surfactant type and ratio. Kolliphor EL as a surfactant gives a smaller emulsion droplet size compared to Tween 60, and a high surfactant ratio can reduce the emulsion droplet size, as shown in figure 5a, where the line plot decreases towards the kolliphor EL. Kolliphor EL has a lower ethoxylation level and a branched alkyl chain structure, which allows stronger penetration into the oil than surfactants with a linear alkyl chain structure, such as Tween 60, resulting in smaller droplet sizes (Bandivadekar *et al.*, 2013; Zeng *et al.*, 2017). Increasing the amount of surfactant can reduce the size of the emulsion droplet, as shown by the single plot factor in Figure 5b, where the line plot decreases as the proportion of surfactant increases. The property of reducing the surface tension of surfactants at the oil-water interface reduces the free energy for emulsification, so that smaller droplet sizes can be formed (Date *et al.*, 2010). The nanometer droplet size in SNEDDS can increase drug release and bioavailability because smaller particles have a larger surface area, and the oil base is more easily absorbed by tissues by diffusing through the gastric mucosal tissue (Poovi and Damodharan, 2018). SNEDDS can also directly facilitate drug delivery to the active site, thereby reducing drug interactions with the liver or reducing the first-pass effect (Zhao, 2015)

Conclusions

A single plot factor assessment of critical point parameters including drug loading, emulsification time, % transmittance, and droplet size in the SNEDDS piroxicam fractional factorial

design resulted in the selected category factors, namely triacetin as oil type, kolliphor EL as a surfactant, and transcutol as co-surfactant. Numerical factors were determined based on the ratio at the initial screening stage, namely oil ratio 11.11 - 28.57 %, surfactant ratio 44.44 - 77.78 %, and co-surfactant ratio 11.11 - 44.44 %. The results of this study make it easier to determine the proportions of the ingredients in SNEDDS piroxicam. In the future, it will be necessary to optimize the formula to determine the optimal proportion of each ingredient, SNEDDS piroxicam.

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Conflict of Interest

All authors declare there was no conflict of interest.

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