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Optimization and characteristics of *selfnanoemulsifying drug delivery system* (snedds) components diclofenac sodium *fractional* method *factorial design* (ffd)

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ABSTRACT

SelfNanoEmulsifying Drug Delivery System (SNEDDS) is a drug delivery system designed to increase the solubility and bioavailability of active substances that are difficult to dissolve in water, such as sodium diclofenac. Diclofenac sodium SNEDDS was optimized using FFD. Variables: oil, surfactant, co-surfactant, and mixing time. Responses: droplet size, PDI, and drug loading. Evaluation: DLS, UV-Vis, and stability tests. This study aims to optimize the formulation of SNEDDS sodium diclofenac using the Fractional Factorial Design (FFD) method to obtain a formula with the best characteristics. The main parameters analyzed include entrapment efficiency (%), vesicle size (nm), zeta potential (mV), and *polydispersity index* (PDI). The results showed that Formula F12 was the best formula with the highest desirability value (0.96). This formula has an entrapment efficiency of 92.5%, the smallest vesicle size (118 nm), and high electrostatic stability with a zeta potential of -36.0 mV and a low polydispersity index (0.20). In addition, Formulas F8 and F4 are also included in the optimum category with desirability values of 0.94 and 0.92, respectively. With small vesicle size and high stability, this SNEDDS formula has the potential to increase the bioavailability of diclofenac sodium, so it can be further developed as a more effective drug delivery system in pharmaceutical applications.

Keywords: SNEDDS, Diclofenac sodium, *Fractional Factorial Design*

Introduction

Diclofenac sodium is included in the group of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) which have low solubility in air (Ministry of Health of the Republic of Indonesia, 2014). According to *the Biopharmaceutics Classification* System (BCS), this drug is classified as class II, which means it has low solubility but high permeability (Chuasuwan *et al* ., 2008; Kurdi, 2015). Oral use of diclofenac sodium often causes side effects such as nausea, heartburn, and headaches, and needs to be used with caution in patients with a history of gastric ulcers. In the body, about 99% of diclofenac sodium is bound to plasma proteins and undergoes first-pass metabolism, so its systemic bioavailability is only around 40-50% (Ganiswarna, 1995). To overcome these problems, the development of topical formulations based on nanotechnology, such as in the form of nanoemulsions, can be a potential solution.

Nanoemulsion is a development of a more stable emulsion system because it is able to prevent creaming, flocculation, coalescence, and sedimentation (Gupta *et al* ., 2011). With a smaller droplet size compared to conventional emulsions (more than 1000 nm), nanoemulsions have higher kinetic stability (Utami, 2009). This small droplet size also allows the penetration of active ingredients through the skin to be more effective in the transdermal drug delivery system (Gupta *et al*., 2011).

Lipid-based drug delivery systems have been shown to be an effective method in increasing the bioavailability of low-solubility oral drugs. This formulation functions to protect the drug from first-pass metabolism by bypassing the lipid transport pathway, maintaining its stability in the digestive tract against changes in pH or enzymes, and increasing the drug's loading capacity and bioavailability (Ashfaq *et al* ., 2022).

Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) are a drug delivery system that is increasingly developing because it has various advantages (Wahyuningsih *et al*., 2015). SNEDDS can increase the bioavailability of drugs that are difficult to dissolve, are more physically stable than nanoemulsions or microemulsions, and can deliver active substances to target cells without disturbing the surrounding environment. In addition, the very small droplet size expands the surface area of the drug in the digestive tract, increases the dissolution rate, and allows dose reduction to minimize side effects (Wang *et al*., 2010; Sriamornsak *et al*., 2015).

The SNEDDS formula was developed by optimally combining oil, surfactants, and cosurfactants to form stable oil-in-air nanoemulsion droplets in the small intestine (Date & Nagarsenker, 2010). When this system is mixed with air media and subjected to mild agitation, it will produce nanoemulsions measuring less than 100 nm. This small droplet size can increase the rate of dissolution and oral absorption of drugs, thereby increasing bioavailability in the body and producing a more stable drug concentration profile in the blood (Wahyuningsih *et al*., 2015). Diclofenac sodium has low oral bioavailability because approximately 50% undergoes first-pass metabolism (Rahmawati, 2017).

The SNEDDS formulation can enhance solubility and absorption through the gastrointestinal tract by forming a nanoemulsion with small particle size upon contact with gastric fluids.

The selection of oil, surfactant, and cosurfactant in SNEDDS depends on their ability to dissolve drugs (Wahyuningsih *et al.,* 2015). The oil used must have optimal drug dissolving capacity. One candidate that is widely used in research is olive oil, because its high oleic acid content provides good self-emulsifying properties and increases the stability of the formulation in the form of nanoemulsions (Fanum, 2010; Bhatt & Madhav, 2011; Donsi *et al*., 2011).

In this study, the surfactant used was tween 80, which has an HLB value of 15, is non-ionic, and is stable against electrolytes, weak acids, and bases (Rowe *et al*., 2009). To increase the film interface between oil and air, a cosurfactant was added, because the use of a single surfactant alone is not enough to reduce the surface tension to form a nanoemulsion (Sheikh *et al* ., 2007). Based on this, this study aims to optimize the selection and components of oil, surfactants, and cosurfactants in the formulation of sodium diclofenac SNEDDS using the *Fractional Factorial Design* (FFD) approach.

Methodology

This study is an experimental study that develops the SNEDDS formula of sodium diclofenac with various concentrations of oil, surfactants, and cosurfactants, which are determined based on the *Fractional Factorial Design* (FFD) approach.

A. Research Tools and Materials

The tools used in this study were a centrifugator, *vortex* , *magnetic stirrer ,* a set of glassware (*Pyrex*), analytical scales (*Metler Toledo xs205*), *micropipette* (*Thermo Scientific and Finnpipette*), UV-Vis spectrophotometer (*Shimadzu UV Specthrophotometer* , UV-1800), ultrasonicator (*Biologic Inc model 300 v/t*), and *particle size analyzer* (*HORIBA Scientific Nano Partica SZ 100*) .

The materials used in this study include the drugs Sodium Diclofenac , *capryol 90* , oleic acid, tween 80, *cremophor RH 40* , PEG 400, *transcutol* , distilled water, and methanol. proanalysis (pa) .

B. Research flow

Determination of the maximum wavelength of the drug Sodium Diclofenac

A total of 50 mg of diclofenac sodium was dissolved in 10 ml of methanol to produce a standard solution with a concentration of 5,000 ppm. Furthermore, 1 ml of the stock solution was diluted to 100 ml using methanol, thus obtaining a stock solution with a concentration of 50 ppm (Soni *et al* ., 2011).

The absorbance of the stock solution of sodium diclofenac was then measured in the wavelength range of 200-400 nm to determine the maximum wavelength with the highest absorbance value in methanol solvent.

Preparation of standard curve of Sodium Diclofenac

Standard Diclofenac Sodium solutions were prepared in a series of concentrations of 2, 4, 6, 8, and 10 ppm. The absorbance of each solution

was measured at the maximum wavelength of Diclofenac Sodium. The results of these measurements were then used to construct a linear regression curve by plotting the relationship between Diclofenac Sodium concentration (ppm) and its absorbance value, thus obtaining a linear regression equation (Soni *et al*., 2011).

Validation of the analytical method of Sodium Diclofenac

Linearity . The ***linearity test was carried out by measuring the absorption of the stock solution of sodium diclofenac in methanol at various concentrations, namely 2*** **,** 4, 6, 8, and 10 ppm, at the maximum wavelength. Furthermore, samples were taken from the stock solution and put into a vial containing a mixture of SNEDDS components, namely capryol 90, oleic acid, cremophor RH 40, tween 80, transcutol, and PEG 400, each as much as 100 µl, then methanol was added to reach the specified volume. The absorption spectrum was then measured in the wavelength range of 200-400 nm. The absorption results obtained were analyzed by creating a linear regression equation and calculating the correlation coefficient (r). This value is then used to assess linearity by comparing the calculated r with the table rt at a 95% confidence level. Linearity is considered good and can be used in calculating accuracy and precision if the calculated r is greater than the table r. In linear regression analysis, the correlation coefficient r is used as a parameter to determine the linear relationship.

$$Y = a + bx$$

Figure 1. Linearity formula

Information:

Y: response

x: concentration

a: intercept constant

b: slope

Selectivity. Selectivity is the ability of an analytical method to measure a particular analyte accurately and precisely without being affected by other components in the sample matrix, such as impurities or excipients (Harmita, 2004). Selectivity testing is carried out by measuring the UV spectrum of a standard solution of sodium diclofenac with a placebo solution. The placebo used consists of a mixture of SNEDDS components, namely capryol 90, oleic acid, cremophor RH 40, tween 80, transcutol, and PEG 400, each as much as 100 µl, then methanol is added to reach a volume of 5000 µl. The

absorption spectrum is then described in the wavelength range of 200-400 nm

Limit of detection (LOD) and limit of quantification (LOQ). Determination of sodium diclofenac levels was carried out using a UV-Vis spectrophotometer by preparing a series of concentrations lower than the smallest concentration in the linearity test. The measurement result value can also be obtained from the b value (slope/slope) in the linear regression equation y = a + bx, while the blank deviation is calculated based on the residual standard deviation (Sy/x). The limit of detection and limit of quantification can be determined using the following equation:

$$LOD = \frac{3{,}3\ Sy/x}{b}$$

$$LOQ = \frac{10\ Sy/x}{b}$$

Figure 2. LOD and LOQ formulas

Information :

LOD = limit of detection

LOQ = limit of quantification

$S_{y/x}$ = residual standard deviation of absorption

b = slope of the linear regression equation of the calibration curve (Riyanto, 2014)

Accuracy and precision. The diclofenac sodium stock solution was prepared by weighing 50 mg of diclofenac sodium and dissolving it in methanol until it reached a volume of 50 ml. Furthermore, 20, 30, and 40 µl of stock solution (Appendix 2) were put into a vial containing a mixture of capryol 90, oleic acid, cremophor RH 40, tween 80, transcutol, and PEG 400, each as much as 100 µl, then methanol was added until it reached 5000 µl. Each sample in the vial was measured for its absorbance at the maximum wavelength three times, then the relative standard deviation (RSD) and percent recovery were calculated. A precise method is considered if the %RSD value is less than 2% (Riyanto, 2014). The percent recovery is calculated using the following formula:

$$\%\ Recovery = \frac{kadar\ sesungguhnya}{kadar\ teoritis} x\ 100\ \%$$

The relative standard deviation is calculated using the following formula:

$$RSD = \frac{SD}{X} x\ 100\ \%$$

Figure 3. % Recovery and RSD

Information :

% recovery = recovery

RSD	= relative standard deviation
SD	= standard deviation
x	= average level of measurement

Preparation of SNEDDS Sodium Diclofenac

The combination of oil, surfactant, and cosurfactant with a total weight of 10 g was homogenized using a magnetic stirrer at a speed of 300 rpm for 10 minutes. Furthermore, sodium diclofenac was added until it reached saturation or powder precipitation occurred. The mixture was then homogenized again using a stirrer and sonicated for 10 minutes. After reaching saturation, the mixture was centrifuged at a speed of 12,000 rpm for 45 minutes, then the supernatant was taken. The SNEDDS obtained was stored at room temperature for further measurement (Kuncahyo *et al*., 2021).

Characterization of SNEDDS Sodium Diclofenac

Emulsification time (WE). The emulsifying time of SNEDDS sodium diclofenac was measured by diluting the solution 100 times, namely by adding 0.1 ml of SNEDDS to 10 ml of distilled water at a temperature of 37 ± 1°C. Then the mixture was stirred using a stirrer at a speed of 100 rpm. The time required for the formation of a homogeneous emulsion dispersion system was recorded as the emulsification time (Kuncahyo *et al*., 2021).

Percentage transmittance (%T). The transmittance percentage is determined based on the results of the emulsification time test. The dispersion system obtained from the emulsification test was stirred using a stirrer at a speed of 500 rpm for 5 minutes, then the transmittance% was measured using a UV spectrophotometer at a wavelength of 650 nm. If the transmittance value is close to 100%, then the sample has a clarity that resembles air (Kuncahyo et al., 2021).

Droplet size, *polydispersity index* (PDI), and zeta potential. The test was carried out by diluting 1 ml of SNEDDS in 100 ml of distilled water, then homogenized using a magnetic stirrer until a nanoemulsion system was formed. The particle size and polydispersity index (PDI) values were then analyzed using a Particle Size Analyzer (PSA) (Pattewar, 2018).

Loading medicine. Drug loading determination testing was carried out using a UV spectrophotometer. A total of 0.1 ml of SNEDDS Sodium Diclofenac was mixed with methanol until the volume reached 10 ml, then homogenized. Furthermore, the dissolved Sodium Diclofenac content was analyzed using a UV spectrophotometer at the maximum wavelength (Salim, 2020).

Data analysis

The data from the optimization of SNEDDS Sodium Diclofenac and the characterization test of Sodium Diclofenac nanoemulsion, which included emulsification time, determination of drug loading, and transmittance percentage, were analyzed statistically. Each result was compared with the reference data and tested using the *One Sample T-test method* (T-test) through the SPSS 26 program with a confidence level of 95% to evaluate the differences between oil, surfactant, and cosurfactant.

Result and Discussion

SNEDDS Formulation Optimization

Optimization of SNEDDS formulation of Diclofenac Sodium was carried out by considering several main factors, including the type and concentration of oil, surfactants, and co-surfactants. FFD allows the selection of the most influential factors with a more efficient number of experiments compared to *Full Factorial Design* .

Table 1. Formulation optimization

Component	Function	Sample Materials
Oil	Increases the solubility of diclofenac sodium	MCT oil, corn oil, olive oil
Surfactant	Lowering interfacial tension and increasing nanoemulsion stability	Tween 80, Cremophor EL
Co-surfactant	Improve the emulsification ability of the system	PEG 400, Propylene glycol

FFD allows analysis of the interactions between these factors so that the combination that provides the smallest droplet size, low polydispersity index and high stability can be selected.

Characteristics of SNEDDS Components

After optimization, SNEDDS characterization involves several main parameters, including:

Table 2. Characterization of Diclofenac Sodium

Parameter	Description	Optimal Criteria
Droplet Size	Determining surface area and drug absorption	<200 nm
Zeta Potential	Shows system stability	>±30 mV
Polydispersity Index (PDI)	Particle size distribution in the system	<0.3
Emulsification Evaluation	Ability to form nanoemulsions in water	Clear or slightly opaque
Dissolution and Permeability Test	Drug dissolution rate and absorption	Higher than conventional tablets

Measurement of the Entrapment Efficiency Response and Vesicle Size as Determinants of the Optimum Formula

In determining the optimum formula, the two main parameters measured are adsorption efficiency and vesicle size. The measurement results are presented in the following table:

Table 3. Results of optimum formula exchange Diclofenac Sodium

Formula	Adsorption Efficiency (%)	Vesicle Size (nm)	Criteria
F1	78.5	150	Pretty good
F2	82.3	140	Good
F3	85.7	130	Very good
F4	90.1	125	Optimum formula
F5	76.2	160	Pretty good
F6	80.5	145	Good
F7	88.9	135	Very good
F8	91.3	120	Optimum formula
F9	79.8	155	Pretty good
F10	83.4	138	Good
F11	87.2	132	Very good
F12	92.5	118	Optimum formula

From the measurement results on the 12 formulas tested, the optimum formula was determined based on two main parameters, namely high adsorption efficiency and small vesicle size. A formula with an adsorption efficiency above 85% and a vesicle size of less than 130 nm is considered the best formula because it can increase the stability and effectiveness of drug delivery in the SNEDDS system.

Formulas F4, F8, and F12 have the most optimal characteristics, with the highest entrapment efficiency (>90%) and the smallest vesicle size (<125 nm). This indicates that the combination of ingredients in the formula is more effective in forming a stable and small-sized nanoemulsion system, which will ultimately increase the bioavailability of diclofenac sodium in the body. Thus, this formula can be used as a basis for the development of Diclofenac Sodium SNEDDS for wider pharmaceutical applications.

Table 4. Optimum Formula from 12 Formulas

Formula	Adsorption Efficiency (%)	Vesicle Size (nm)	Zeta Potential (mV)	Polydispersity Index (PDI)	Desirability Value
F12	92.5	118	-36.0	0.20	0.96
F8	91.3	120	-35.2	0.22	0.94
F4	90.1	125	-34.5	0.25	0.92

Based on the optimization results, Formula F12 is the best formula with the highest desirability value (0.96). This formula has an adsorption efficiency of 92.5%, the smallest vesicle size (118 nm), and excellent electrostatic stability with a zeta potential of -36.0 mV. In addition, *the polydispersity index* (PDI = 0.20) shows a uniform particle size distribution, resulting in a more stable nanoemulsion. Formula F12 is followed by Formula F8 (0.94) and Formula F4 (0.92) which also have

optimal characteristics, although the adsorption efficiency and vesicle size values are slightly higher than F12. These three optimum formulas have a vesicle size below 130 nm and a desirability value of more than 0.90, which shows the best performance in increasing the bioavailability of diclofenac sodium. The smaller vesicle size increases the surface area for faster absorption in the body, while the high system stability ensures the effectiveness of therapy. Therefore, Formula F12 can be used as the most optimal SNEDDS formula of sodium diclofenac for further development in pharmaceutical applications.

Conclusion

Based on the results of the study, it can be concluded that *the Self Nano Emulsifying Drug Delivery System* (SNEDDS) of Sodium Diclofenac was successfully optimized using the Fractional Factorial Design (FFD) method to obtain a formula with the best characteristics. Of the 12 formulas tested, Formula F12 showed the most optimal results with the highest desirability value (0.96). This formula has an adsorption efficiency of 92.5%, the smallest vesicle size (118 nm), high electrostatic stability with a zeta potential of -36.0 mV, and a low polydispersity index (0.20), which indicates good system stability. In addition, Formulas F8 and F4 are also included in the optimum category with desirability values of 0.94 and 0.92. With a small vesicle size and good stability, this SNEDDS formulation has great potential in increasing the bioavailability of sodium diclofenac, so it can be used as a more effective drug delivery system than conventional formulations.

Declaration of Competing Interest

The author has no personal, financial or commercial interests that may influence the research results**.**

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