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RESEARCH ARTICLE

Effect ratio of stearic acid and oleic acid on characteristics of diclofenac sodium nanostructured lipid carrier

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Abstract

Background: Osteoarthritis treatment generally involves using a Non-steroidal Anti-Inflammatory Drug (NSAID), and the most common is Diclofenac sodium. The oral use of diclofenac sodium presents some adverse effects on the gastrointestinal tract. Transdermal diclofenac sodium's biological efficacy can be affected by factors including its log P value of 1.13. Nanostructured Lipid Carrier (NLC) may solve these concerns. **Objective:** This study examined how stearic and oleic acid concentrations customise diclofenac sodium NLC's physicochemical properties. **Method:** High shear homogenisation was used to compare stearic acid and oleic acid at 6:4, 7:3, and 8:2. Furthermore, the physicochemical properties of diclofenac sodium NLC were assessed, such as organoleptic, particle size and poly-dispersity index, pH, viscosity, zeta potential, entrapment efficiency, profiles of FTIR and DSC. **Result:** This study found that particle size ranged from 333.60 ± 144.29 to 791.77 ± 85.57, and entrapment efficiency was 89.38 ± 3.69 to 76.96 ± 3.29. Increasing the content of oleic acid as a liquid lipid reduces particle size and improves diclofenac sodium NLC entrapment. According to One-Way ANOVA, the dependent variable was not significantly affected by any independent variables (p-value > 0.05) except for particle size and entrapment efficiency. **Conclusion:** Stearic acid-oleic acid concentration ratios affect diclofenac sodium NLC's physicochemical properties.

Introduction

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) and has demonstrated efficacy in managing acute pain and various inflammatory conditions, such as osteoarthritis (Nguyen *et al.,* 2017). On average, diclofenac sodium is administered orally at a daily dosage of 25 mg (Dietrich *et al.,* 2014). However, its oral administration is associated with adverse effects on the gastrointestinal tract (Nguyen *et al.*, 2017). The solubility of diclofenac sodium is 0.8 ± 0.2 µg/mL (Avdeef *et al.,* 2000), with a log P value of 1.13. This log P value indicates that only a small quantity of drugs can penetrate the skin (Annisa *et al.,* 2016). The utilisation of nanostructured lipid carrier (NLC) is being explored to enhance sodium diclofenac's log P value.

NLC represent the next evolutionary stage of solid lipid nanoparticles (SLN), serving as a carrier system with several benefits for drug delivery, including enhanced penetration by its small particle size and occlusive (Hendradi *et al.,* 2021). Besides, its larger surface area results in a longer residence time on the skin surface, resulting in a longer skin contact time of the drug, enabling sustained release (Bawazeer *et al.,* 2020). Previous studies showed that meloxicam is an NSAID-loaded NLC that can increase penetration into the skin (Annisa *et al.,* 2016). In this research, diclofenac sodium NLC was made by applying a high shear

homogenisation method with components consisting of different solid and liquid lipid concentrations, which will affect particle size and entrapment efficiency.

According to sources, utilising a blend of stearic acid and oleic acid in ratios of 6:4 creates diethyl ammonium diclofenac particle size is 300 nm and achieves an entrapment efficiency above 70% (Hendradi *et al.,* 2017), utilising of monostearin and miglyol 808 in ratios of 7:4 creates meloxicam particle size is 400 nm and achieves an entrapment efficiency above 90% (Annisa *et al.,* 2016), and utilising of compritol 888 ATO and miglyol in ratios of 8:2 creates aceclofenac particle sizes is 350 nm and achieves an entrapment efficiency above 90% (Phatak & Chaundhari, 2013). The entrapment efficiency of meloxicam in the NLC system is enhanced by increasing the concentration of liquid lipids (Anggraeni & Hendradi, 2017). This study employed three ratios of stearic acid and oleic acid, which were 6:4, 7:3, and 8:2, with diclofenac sodium as the active ingredient.

Stearic acid exhibits biodegradability, low toxicity, and affordability, so it was chosen as a solid lipid in this study. Stearic acid is a saturated fatty acid known for its lipophilic properties (Dantas *et al.,* 2018). Stearic acid, a type of long-chain fatty acid with 18-carbon, has been found to enhance the flexibility of the lipid structure. This allows for incorporating significant quantities of active substances (Souto *et al.,* 2022). The selection of oleic acid as a liquid lipid is based on its ability to form a less structured crystal lattice. This property allows for a greater number of drugs to be accommodated, leading to improved stability and better capacity for drug loading (Dantas *et al.,* 2018).

Based on the description above, this research aimed to determine the effects of stearic and oleic acid concentrations on the physicochemical properties of diclofenac sodium NLC. The novelty of this research is the use of diclofenac sodium as a model and lipids with different concentrations.

Methods

Materials

Diclofenac sodium (Manufactured by PT. Dexa Medica, Indonesia); other materials used were stearic acid (Avantor Performance Materials Taiwan Co., Ltd, Hsinchu), oleic acid (Marks & Nos Inc), and Tween 80 (PT. Kao, Indonesia).

Preparation of diclofenac sodium NLC

Before proceeding to the experiment, the quantities of the ingredients were measured. Subsequently, the stearic acid, oleic acid (6:4, 7:3, 8:2) and 1.16g diclofenac sodium were mixed in a glass beaker and applied heat using a hot plate set to 75°C. The mixture was stirred rapidly using an Ultra-turrax homogeniser (Ika T-25) operating at 3800 rpm for 5 min. Conversely, the aqueous phase consisting of 5 g Tween 80 and phosphate buffer with a pH of 6.0 ± 0.05 ad 100 g was prepared and heated to a temperature of 75°C. The next step was to distribute the aqueous phase into the combination of lipids and active ingredients by employing a homogeniser set at 13000 rpm for 5 min, which was done. This process was repeated twice. During the cooling stage, the mixture was agitated at 50 revolutions per minute (rpm) using a hotplate stirrer until it reached a temperature of 25°C, forming NLC. The completed NLC is measured to ascertain its ultimate weight.

Organoleptic test

Each formulation of NLC was visually described based on organoleptic properties, including consistency, colour, and odour.

Particle size and polydispersity index (PDI) test

The Delsa nano-analyser (Beckman Coulter) was used to quantify particle size and PDI. 50 mg of NLC was measured and combined with 50 ml of distilled water. The mixture was then stirred at 500 rpm per minute for 10 minutes. Subsequently, 2 mL of the solution was extracted and combined with 8 mL of distilled water. The mixture was then agitated at a rate of 100 rpm per minute for 10 minutes before half of it was transferred into the cuvette. The device was turned on, and the menu for selecting particle size was accessed.

pH test

The pH was determined using a pH meter manufactured by Eutech Instrument. 1 gram of NLC was measured and mixed with 9 mL of CO_2-free distilled water, stirring until the mixture became uniform. Subsequently, the electrode was immersed in the resulting solution.

Viscosity test

Viscosity was assessed using a Viscometer Cone and Plate (Brookfield, USA). A 2 mL of NLC was carefully placed into the sample cup, ensuring the absence of bubbles and even distribution across the cup's surface.

Zeta potential test

The NLC was diluted in water at a ratio of 1:40, and a portion of the diluted solution was transferred into a

cuvette. Subsequently, place the cuvette into the sample container and proceed to get measurements.

Entrapment efficiency (EE) indirect test

Several NLC samples were loaded into a 1.5 mL microtube, followed by centrifugation at 15000 rpm for 10 min. The result of centrifugation was the supernatant, which was dissolved in a phosphate buffer saline of pH 7.4 ± 0.05 and ethanol (85:15), resulting in a total volume of 25 mL. The solution was diluted by 1 mL to 10 mL and then analysed at 276.6 nm using a UV spectrophotometer (Hitachi). In addition to preventing interference from the NLC matrix on the analyte analysis, the maximum wavelength is determined specifically on the NLC sample without the drugs. The EE was calculated with the equation:

$$EE\ (\%) = \frac{(Wa - Ws)}{Wa} x\ 100\%$$

where Wa is the amount of diclofenac used, and Ws is the quantity of free drug in the supernatant (verified transparent solution).

FTIR spectroscopy

FTIR analysis was used to verify the drug's identification and identify any interactions between the drug and carriers. The FTIR spectrometer (Perkin Elmer Instrument 1302F6802) was utilised to evaluate the native forms of diclofenac sodium, stearic acid, oleic acid, Tween 80, and diclofenac sodium NLC F1, F2, and F3. The samples were examined at room temperature. The collected spectra were scanned within the range of 400 to 4000 cm^{-1}.

Differential scanning calorimetry

Differential scanning calorimetry was used to conduct thermal analysis of pure diclofenac sodium and diclofenac sodium NLC F1, F2, and F3. All the samples were heated using aluminium pans. The temperature range for the analysis was 10-350°C, and the heating rate was 10°C/min.

Wavelength of NLC without diclofenac sodium

This measurement is conducted to check that the NLC matrix does not impact the measurement of the analyte. The analysis was conducted using a wavelength range of 200-350 nm. The maximum wavelength of sodium diclofenac is determined to be 276.6 nm.

Data analysis

The physical appearance of the diclofenac sodium NLC was evaluated using a One-Way Analysis of Variance (ANOVA) with a 95% confidence level. If a significant difference is found in the ANOVA test, the Tukey HSD post hoc Test is conducted to identify any different groups.

Results

Table I presents the results of the physicochemical properties, such as particle size and PDI, pH, viscosity, zeta potential, and entrapment efficiency.

Table I: Physicochemical properties of diclofenac sodium NLC (Mean ± SD, N=3)

Formula	Particle size (nm)	PDI	pH	Viscosity (cPs)	Zeta potential (mV)	EE (%)
F1 (6:4)	333.60 ± 144.29	0.416 ± 0.05	6.80 ± 0.03	378.33 ± 86.03	-41.37 ± 7.17	89.38 ± 3.69
F2 (7:3)	444.53 ± 36.01	0.404 ± 0.03	6.77 ± 0.04	521.30 ± 42.02	-33.97 ± 3.10	84.72 ± 3.68
F3 (8:2)	791.77 ± 85.57	0.448 ± 0.05	6.72 ± 0.05	435.30 ± 68.11	-31.80 ± 2.26	76.96 ± 3.29

Figure 1 depicts profiles of IR spectra of pure diclofenac sodium, stearic acid, oleic acid, Tween 80, F1, F2 and F3 of diclofenac sodium NLC in wave numbers 400-4000cm^{-1}. Profiles of DSC of pure diclofenac sodium, diclofenac sodium NLC F1, F2 and F3 can be seen in Figure 2. Figure 3 shows the wavelength of NLC without diclofenac sodium.

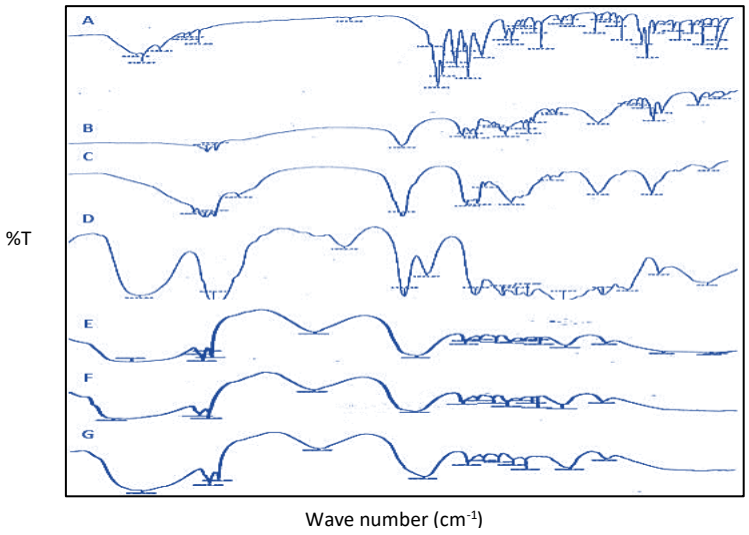

Figure 1: Profiles of IR spectra of pure diclofenac sodium (A), stearic acid (B), oleic acid (C), Tween 80 (D), F1 (E), F2 (F) and F3 (G) of diclofenac sodium NLC in wave numbers 400-4000cm^{-1}

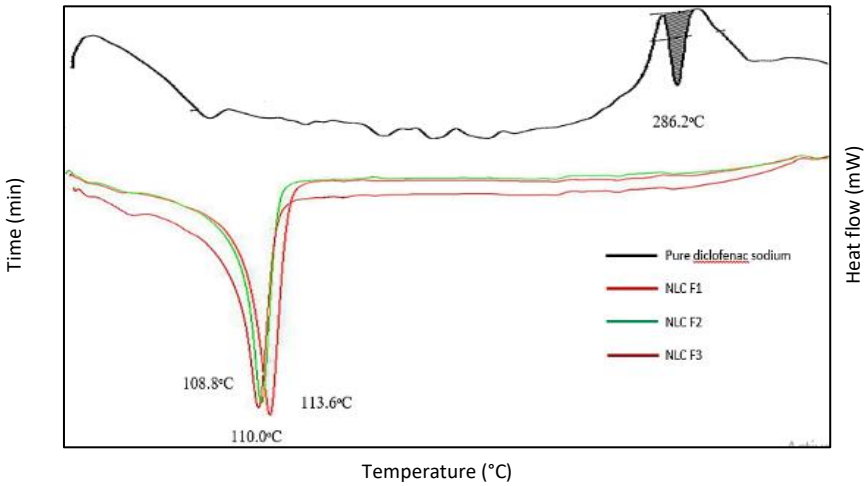

Figure 2: Profiles of DSC of pure diclofenac sodium, diclofenac sodium NLC F1, F2 and F3

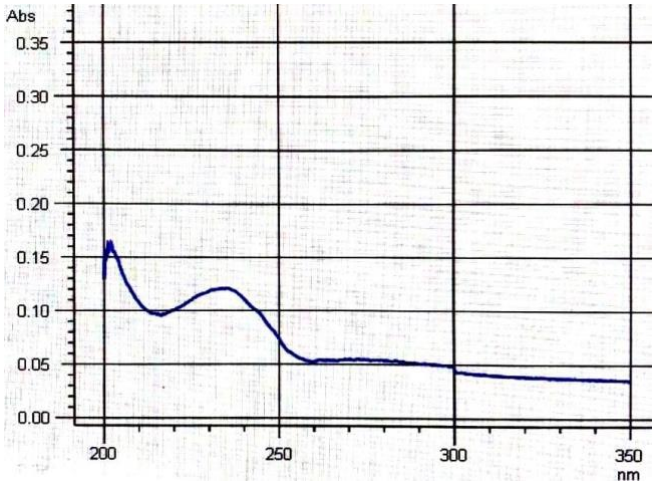

Figure 3: Wavelength of NLC without diclofenac sodium

Discussion

Organoleptic results show significant differences in the consistency of NLC, which is increasing because of a higher concentration of solid lipids (Annisa *et al*., 2016). The white colour of NLC is due to diclofenac sodium. All formulas have the same menthol odour.

The physicochemical properties of diclofenac sodium NLC are shown in Table I. Based on the outcomes of particle size measurements, F1 exhibits the smallest particle size. Conversely, F3 has greater sizes, potentially because of its low concentration of oleic acid. Increasing the quantity of liquid lipids reduces the size of the NLC particles that will be attained. A significant quantity of surfactant is necessary to prevent the aggregation of lipid particles due to the 8:2 ratio between stearic acid and oleic acid. Based on ANOVA followed by statistical analysis of the HSD test, the results showed a *p*-value < 0.05. F1 and F2 have nearly identical particle diameters. Meanwhile, F3 exhibits a significantly different particle size than F1 and F2. F3 exhibits a propensity to agglomerate when the particle size is increased.

PDI describes the level of uniformity in a system, where the smaller the PDI value, i.e. 0, the more uniform distribution of particles in a monodispersing system, and PDI values < 1 indicate polydisperse samples (Luo *et al.,* 2017; Danaei *et al.,* 2018). The PDI values of the NLC system range from 0.404 to 0.448, as shown in Table I. The polydispersity index of F3 is higher due to the increased solid lipid content, which has been found to result in particle aggregation (Phatak & Chaudhari, 2013). The statistical analysis indicates that F1, F2, and F3 have a similar polydispersity index, as represented by a *p*-value > 0.05.

The pH measurement results of all formulas were included in the skin pH ranges of 4.00 to 6.80 so that irritation to the skin can be avoided (Kon *et al*., 2017). The pH of F1 is higher due to the increased liquid lipid content, where increasing the concentration of oleic acid will lead to an elevation in the pH level of diclofenac sodium NLC. pH data are shown in Table I. Based on statistical analysis indicates that F1, F2, and F3 have a similar pH value, as represented by a *p*-value > 0.05.

The purpose of viscosity testing was to enable NLC to adhere to the skin surface, extend the drug's residence time within the skin, increase penetration, and increase the availability of the drug at work in a controlled manner as well as to avoid systemic absorption (Hendradi *et al*., 2017). Viscosity data are shown in Table I. The viscosity of the NLC system ranges from 378.33 to 521.30. Based on statistical analysis indicates that F1, F2, and F3 have a similar viscosity, as represented by a *p*-value > 0.05.

Zeta potential measurement is a crucial parameter for assessing the possibility of dispersion, aggregation, or flocculation in the NLC system. According to zeta potential measurements conducted with the Zetasizer, it is evident that all three formulas exhibit zeta potential values exceeding -25 mV. This observation suggests the NLC system is stable (Khater *et al*., 2021). Based on statistical analysis indicates that F1, F2, and F3 have a similar zeta potential, as represented by a *p*-value > 0.05.

Entrapment efficiency data are shown in Table I. EE is a step used to determine the percentage of active substances trapped in the NLC system. From the results of determining the % EE, it can be seen that in the comparison of lipids making up the NLC, all of them give quite high entrapment results (> 76%). Increasing the concentration of liquid lipids would reduce particle size, impacting the retention of diclofenac sodium NLC because formulations with high concentrations of liquid lipids can dissolve more drug molecules. Furthermore, the entrapment of diclofenac sodium is also affected by the solubility of diclofenac sodium in lipid components. The solubility of diclofenac sodium in oleic acid is approximately 180 mg/10 g (Rao *et al*., 2015). Enhanced drug solubility in both liquid and solid lipids might increase entrapment efficiency (Shah *et al.,* 2012). Based on ANOVA followed by statistical analysis of the HSD test, the results showed a p-value < 0.05. F1 and F2, F2 and F3 have nearly identical entrapment efficiency. Meanwhile, F3 exhibits a significantly different entrapment efficiency than F1.

FT-IR spectroscopy was conducted to assess the compatibility of the original diclofenac sodium with stearic acid, oleic acid, and Tween 80, which were utilised to manufacture NLC. The original diclofenac sodium exhibits distinct infrared peaks at the following wavenumbers: 3287.27 cm^{-1} (N-H), 766.19 cm^{-1} (C-Cl), 1469.51 cm^{-1} (C=C), and 1557.14 cm^{-1} (C=O). Referring to Figures 1E, F, and G, there was no disparity in the absorption process. These findings indicate that varying the proportions of stearic acid and oleic acid in the three NLC formulations does not alter the chemical composition, and there is no chemical reaction between sodium diclofenac and the NLC constituents.

The melting point of pure diclofenac sodium and diclofenac sodium NLC F1, F2 and F3 were ascertained using DSC. Figure 2 in this study shows that pure diclofenac sodium has a melting point of 286.2°C. The peak of diclofenac sodium did not appear throughout the entire formula after being manufactured into diclofenac sodium NLC. Diclofenac sodium's peak shift suggests it has become stuck in the NLC system. In

diclofenac sodium of NLC F1, F2, and F3, a noticeably significant peak falls between 108.8 to 113.6°C. because polymorphism of stearic acid might result from interactions between NLC components. An addition of 1 to 5 percent of tween surfactant can cause this.

Figure 3 demonstrates that the NLC matrix does not affect the measurement of the analyte due to its wavelength. In NLC without diclofenac sodium, no absorption is observed at a wavelength of approximately 276.6 nm, corresponding to the maximum wavelength of sodium diclofenac.

Conclusion

To summarise, this work demonstrates that different ratios of stearic acid and oleic acid affect both the particles' size and the entrapment's efficacy. The combination of sodium diclofenac NLC F1 with a 4% concentration of oleic acid was selected as the most optimal due to its smaller particle size and higher entrapment efficiency.

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