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by Esti Hendradi

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RESEARCH ARTICLE

Characteristic of Nanostructured Lipid Carrier (NLC) Diclofenac Diethylammonium as Function of Ratio of Glyceryl Monostearate and Caprylic Acid

Esti Hendradi*, Faddlun Nur Hidayati, Tristiana Erawati
Department of Pharmaceutics, Faculty of Pharmacy, Universitas Airlangga, Campus C Jl Mulyorejo-Surabaya 60115, Indonesia.
*Corresponding Author E-mail: **estihendradiff@gmail.com**

ABSTRACT:
The present study investigated the characteristics of diclofenac diethylammonium-containing NLC as function of ratio of glyceryl monostearate (GMS) and caprylic acid (mygliol 80) of 65:35; 75:25 and 85:15. There were three formulas and the composition of each formula were diclofenac diethylammonium 1.16%; glyceryl monostearate and caprylic acid with ratio (65:35; 75:25 and 85:15); Tween 80 5%; and phosphate buffer pH 6.0 ± 0.1 as dispersion medium. The result showed that each formula had different characteristic of particle size and efficiency entrapment. Particle size was analized by Delsa^{TM}Nano, F I (65:35) had particle size 134.467 ± 26.601 nm with PI 11.776; F II (75:25) had particle size 2252.233 ± 727.370 nm with PI 0.348; and F III (85:15) had particle size 1500.867 ± 219.673 nm with PI 0.260. The present Entrapment Efficiency (EE) carried out by centrifuge method and result of F I, F II and F III were 88.342 ± 0.52%, 73.764 ± 0.511% and 70.754 ± 0.665%, respectively. The result was analyzed by statistic with ANOVA one-way method with degree of confident 95% (α = 0.005). Research result revealed that the best characteristics of diclofenac diethylammonium in terms of particle size and % Entrapment Efficiency (EE) was F I with ratio of GMS and caprylic acid (mygliol 80) 65:35.

KEYWORDS: Diclofenac Diethylammonium, NLC, Glyseryl Monostearate, Caprylic Acid, Tween 80.

INTRODUCTION:

Diclofenac is a phenylacetic acid derivative and a non-steroidal anti-inflammatory drug (NSAID). The mechanism is via inhibition of selective cyclooxygenase activity [1].The absorption of rapid oral administration, 40% - 50% diclofenac experience first pass metabolism with $t_{1/2}$ about 1-3 hours. Diclofenac can be accumulated in synovial fluid and thus potentially suitable for joint treatment [2]. Diclofenac is widely used for the treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis [3]. The most frequently reported adverse events in patients who were given diclofenac are peptic ulcers, vomiting, nausea, and epigastric pain. Intramuscular administration may cause pain and occasionally tissue damage at the injection site.[4]

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These problems can be avoided by administration of topical diclofenac[5]. The dose of diclofenac diethylammonium was 1.16% equivalent to 1% diclofenac sodium. Topical administration is recommended for chronic treatment such as rheumatism[6]. Target of its topical administration is the dermis layer[7]. Where the drug must penetrate through barriers including stratum corneum, outer layer of skin containing creatinine and dead cells[8]. Physicochemical characteristics and type of formulation are important factors in transdermal delivery[9]. Diclofenac diethylammonium is more lipophilic than diclofenac sodium so the drug can penetrate deeper into the skin [10].Lipid carriers such as microemulsions, nanoemulsions, solid dispersions, solid lipid nanoparticles (SLNs) and liposomes have been successfully used to increase transdermal drug solubility and bioavailability [11]. SLN is a nano-carrier system made from a mixture of solid lipids with a high-pressure homogenization method. Solid matrix in SLN provides high flexibility to control drug release (Muller et al, 2000). However, these lipid carriers have some limitations, in the case of a drug

explosion of the SLN system causing the lipid phase to turn into a highly ordered crystal that leaves no room for the active ingredient; Lower drug loading caused by the drug solubility in solid lipids; and the concentration of particles in aqueous dispersions which ranges from 1% to a maximum of 30% [12] To overcome such limitations, new lipid carriers, called nanolipid carriers (NLCs) are developed. NLC is prepared from a mixture of solid lipids and liquid lipids. The solid lipids that are widely used are glyceryl behenate, soy phosphatidycholine, glyceryl monostearate, cetyl alcohol, and stearyl alcohol. Triglycerides such as carnuba wax, oleic acid, caprylic acid, soybean lipids and olive oil are generally used as liquid lipids[13].The mixture of solid lipids and liquid lipids provides several advantages, which make the system physically and chemically stable against drug phase separation drug during storage. Most drugs are more dissolved in liquid lipids than those in solid lipids which cause problems in NLCs preparation using hot homogenizing techniques [14]. NLC provides an occlusive effect on the skin by increasing skin hydration so that cell density decreases and dilates the intercellular distance, so that drug molecules can penetrate into the skin[14]. Lipids and surfactants serve as enhancers by increasing drug permeation and affecting the stratum corneum[15].

Several methods for generating NLCs including high pressure homogenization; evaporation; double emulsion; precipitation techniques; spray drying; and high-speed homogenization followed by ultrasonication [16] In this study, diclofenac diethylammonium -containing NLC system was pepared using glyceryl monostearate and caprylic acid in ratio of 65:35 (FI); 75:25 (FII); and 85:15 (FIII). The physicochemical characteristics of prepared NLC were investigated, including particle size, pH, viscosity, particle morphology, thermal analysis, infrared spectra and entrapment efficiency. Concentration of diclofenac diethylammonium was measured by UV-Vis Spectrophotometry using three wavelengths (266 nm, 276 nm and 286 nm).

MATERIALS AND METHODS:

Materials:

Materials used in this study, if not otherwise stated, have a degree of pharmaceutical grade in purity. Diclofenac diethylammonium (Aarti Drugs Limited); caprylic acid (Sigma Aldrich); glyceryl monostearate was purchased from Kurniajaya; Tween 80 (Croda); Ethanol 96%, KBr with p.a quality of E Merck. Phosphate buffer pH 6.0 ± 0.1 was made from 0.1 M sodium dihydrogenphosphate and a 0.1 M disodium hydrogenphosphate quality p.a (E Merck).

Preparation of NLC:

Diclofenac diethylammonium NLC system is prepared by hot homogenizing method. First, diclofenac diethylammonium was powdered before it was mixed. Glyceryl monostearate and caprylic acid were melted at 60°C on hotplate until completely melted. The aqueous phase was phosphate buffer (pH 6.0 ± 0.1) and Tween 80 which was preheated at 65°C. The water phase was introduced to the lipid phase and mixed using an Ultra-turax homogenizer at a rotational speed of 3600 rpm for 30 minutes in 3 cycles. The formula was further removed from the hotplate and stirred at 1500 rpm for 30 minutes until the samples reached room temperature.

Table 1 Composition of diethylammonium diclofenac-containing NLC

Material	weight (gram)		
	F I	F II	F III
Diclofenac diethylammonium	0.580	0.580	0.580
Glyceryl monostearate*	4.875	5.625	6.375
Caprylic acid*	2.625	1.875	1.125
Tween 80	2.500	2.500	2.500
Phosphate Buffer pH 6.0 ± 0.1	39.420	39.420	39.420
Total	50	50	50

* total lipid : 15% x 50g = 7.5 g

Standard Solution:

The standard solution of diclofenac diethylammonium was produced by preparing a series of solutions in phosphate buffer pH 6.0 ± 0.1 (Table 2).

Table 2. A serial concentration of diclofenac diethylammonium in phosphate buffer pH 6.0 ± 0.1

Drug Concentration (ppm)	Pipetted Volume (ml)	Total Volume (ml)
2.008	0.5	50.0
6.024	3.0	100.0
10.040	5.0	50.0
15.060	7.5	100.0
20.080	5.0	50.0
25.100	12.5	100.0

Homogeneity:

The homogeneity of diclofenac diethylammonium-containing NLC was determined by extracting 50.0 mg NLC with 96% ethanol and sonicated for 2 minutes at 35000 Hz. The samples were then diluted to 10.0 ml with phosphate buffer pH 6.0 ± 0.1 and sonicated again for 15 minutes. Next, samples were pipetted 1.0 ml and diluted to 10.0 ml using phosphate buffer pH 6.0 ± 0.1 and filtered (Whatman® milipore 0.45 µm). The absorbance was measured by Spectrophotometer at 3 wavelength; 266 nm, 276 nm and 286 nm.

Percent recovery was calculated using following equation:

$$\% \text{ Recovery} = \frac{Ct}{Cs} \times 100$$

The Ct is the measured concentration and Cs is the initial concentration in the samples. The coefficient of variation (CV) was calculated and it is considered homogenous if CV is less than 6%.

Organoleptic:
Organoleptic characteristics of the diclofenac diethylammonium-containing NLC were visually observed in terms of color, odor and consistency.

Particle Size:
The NLC's particle size and distribution were determined using Delsa™ Nano. NLC was diluted in a CO2 free aquadest. The particle size was determined at an angle of 165° and a temperature of 25°C. Particle size was measured from average fluctuations in light scattering intensity.

pH:
The pH of the prepared NLCs was measured using pH meter. Prior to measurements, the pH meter was calibrated with standard buffer solution pH 6.0. The electrode was immersed into the samples and waited until the reading is completed.

Viscosity:
The viscosity of the NLC samples was measured using a Brookfiled Cone and Plate viscometer. Approximately 1 g sample was placed in the middle plate, its position was raised up to the position beneath the cone. The sample was in the shear between the static plate and the rotating cone. The shear speed was increased or decreased by a dial selector and the resulting viscosity was displayed on scale.

Viscosity was calculated using following equation:

$$U = C \frac{T - Tf}{v}$$

in which: C = a constant
T = displayed torque
Tf = Torque on the axis of the shearing stress (extrapolated from the linear part of the curve)
v = cone speed per minutes

Particle Morphology:
Examination of particle shape and morphology was carried out using Transmission Electron Microscopy (TEM) technique. NLC samples were added with PTA (Phosphotungstic Acid) in a ratio of 3:1 then placed in a specimen holder which is a copper plate (Cu). The specimen holder was then dried at room temperature for 10-15 min, ready to be analyzed.

Thermal Analysis:
Thermal analysis was performed using Differential Thermal Analysis (DTA). This analysis was aimed to determine the interaction between components in the NLC system which is indicated by changes in thermogram and melting point shift.

Samples of 3-5 mg were inserted into aluminum crucible pan, crimped and inserted into the sample holder. Samples were heated in rate of 5°C/min. The obtained thermogram shows the melting point of the materials contained in the sample.The thermogram of diclofenac diethylammonium-containing NLC was compared with the glyceryl monostearate and the diclofenac diethylammonium.

Infra Red Spectrophotometry:
Infrared spectroscopy examination aims to determine the compatibility between diclofenac diethylammonium and glyceryl monostearate solids used in the NLC system. Spectral examination was performed on diclofenac diethylammonium, glyceryl monostearate and NLC diclofenac diethylammonium formulas [17] Samples were mounted in KBr pellet prepared by weighing 1 mg of sample and mixed with 200 mg of dried KBr powder and compressed using hydraulic pump. The pump is equipped with water vapor apparatus to produce translucent thin plate. The plates were then scanned at 400-4000 cm^{-1} wavelengths.

Entrapment Efficiency:
Entrapment efficiency was obtained by calculating the concentration of the free drug in the aqueous phase. 1 gram NLC was dispersed into 10 ml phosphate buffer pH 6.0 ± 0.1 and stirred at 500 rpm for 5 min to dissolve the free drug in the water phase. The dispersion was centrifuged for 10 min at 3000 rpm and the precipitate was separated (NLC particles). Furthermore, 1.0 ml of filtrate was diluted in 10.0 ml phosphate buffer pH 6.0 ± 0.1. Samples were filtered using Millipore 0.45 µm and scanned with a Spectrophotometer at 3 wavelength 266 nm, 276 nm and 286 nm. The concentration of the free drug in the water phase was obtained by introducing absorbance into the standard curve regression equation. Entrapment efficiency was calculated using following equation:

$$EE\ (\%) = \frac{A_2}{A_1} \times 100$$

EE(%) is entrapment efficiency, A_2 is drug concentration trapped in NLCs, and A_1 is initial loaded drug concentration [18].

RESULTS AND DISCUSSIONS:

Homogeneity:

The purpose of homogeneity test was to ensure that the diclofenac diethylammonium in the NLC system is homogeneous. Therefore, the result of entrapment efficiency (EE) was not caused by the difference of drug concentration but due to difference of formula composition. Recovery of diclofenac diethylammonium in the FI was 102.376 ± 1.517% with a coefficient of variation (CV) of 1.481%; Recovery of FII was 103.613 ± 1.953% with CV of 1.885%; and recovery of FIII was 105.049 ± 0.781% with CV 0.743%. The coefficient of variation of diclofenac diethylamonium in FI, FII and FIII was less than 6% so that all formulas were considered homogeneous. Percent recovery% of all formulas were still within the required range for semisolid, 85-115%.

Table 3. Homogeneity data of diclofenac diethylamonium-containing NLCs in all formula

Formula	Replication	% Recovery	Average ± SD	% CV
I	1	103.808	102.376 ± 1.517	1.481
	2	100.787		
	3	102.531		
II	1	104.616	103.613 ± 1.953	1.885
	2	104.861		
	3	101.362		
III	1	105.945	105.049 ± 0.781	0.743
	2	104.691		
	3	104.511		

Organoleptic:

All formulas of Diclofenac diethylamonium NLC of exhibited the same white color and slightly odor (Figure 1). Their consistency increases as the amount of solid lipid increases. Similar condition was experienced by [12] in research on NLC. Solid lipids have high melting point and rigid structure that provide high consistency [19]

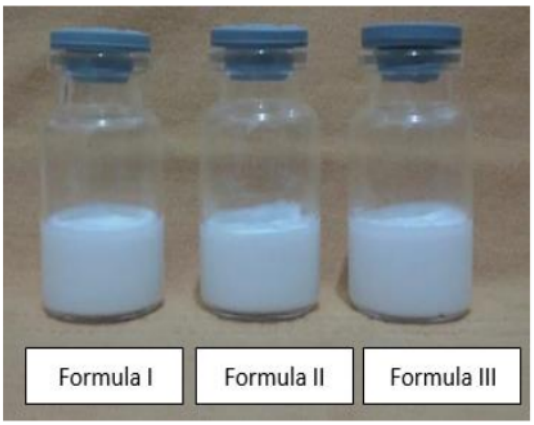


Figure 1. Physical appearance of diclofenac diethylamonium-containing NLCs

Particle Size:

Particle size of FI was 134.467 ± 26.601 nm, but the polydispersity index (PI) was very high i.e. 11.776 ± 3.044, the particle distribution was not homogeneous. FII and FIII showed particle sizes of 2252.233 ± 727.370 nm and 1500.867 ± 219.673 nm and a low polydispersity index, ie 0.348 ± 0.038 and 0.260 ± 0.076, respectively. The large amount of total lipid might have caused lack of agitation resulting in larger particle size, increasing viscosity and movement of NLC particles was restricted. Moreover, a low concentration of surfactant (5%) was not sufficient to break the lipid particles into nano size and could not stabilized it. FI contains lower amount of glyceryl monostearate compared to FII and FIII, where its function was as emulsifier and stabilizer [19] Therefore, FI experienced less stable lipid particles and less controllable and led to the higher PI.

One-way ANOVA statistical analysis showed that particle size and distribution of FI were different from FII and FIII. However, there was no differences in particle size and particle distribution between FII and FIII.

pH:

The average pH of FI was 5.45 ± 0.007, FII 5.52 ± 0.007 and FIII was 5.71 ± 0.008. These data were then statistically tested using one-way ANOVA. The results showed that there were significant differences between FI, FII and FIII. The pH value of NLC was decreased when the caprylic acid concentration was increased. The caprylic acid is composed of an acidic fatty acid so that when it was added to the formula, the NLC pH was dropped proportionally depending on its concentration. The pH value was controlled using phosphate buffer pH 6.0 ± 0.1, however, the pH of the all formulas was still decreasing. Glyceryl monostearate may also affect the pH since the acidic value of glyceryl monostearate was increased over heating [19] The NLC component was too acidic so that the buffering capacity was not sufficient in maintaining the changing of pH. Buffer capacity was determined by buffer composition. Low buffer concentration causes low buffering capacity. In this study, the concentration of sodium dihydrogen phosphate and disodium hydrogen phosphate was 0.1 M. Therefore, in this case the buffer component concentration needs to be increased. Although pH values did not match the desired pH, all formulas was still in range of pH of the skin i.e. 4.5 to 6.5 [20].

pH was associated with ionised and unionised form, diclofenac diethylammonium pH is 6.4 – 8.4 [13] so in pH 5 diclofenac diethylammonium would be ionised but because the drug was weak base, ionised form less than unionised form, so active ingredients could be a great entry into skin and NLC dispersion still efective.

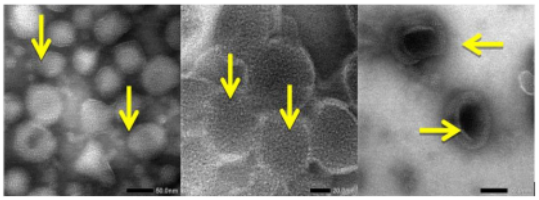
pH was associated with ionised and unionised formand diclofenac diethylammonium has pH in range of 6.4 – 8.4 [21] So if it is exposed to environment with pH 5, diclofenac diethylammonium would be ionised. However, as the drug was a weak base, then the ionised form would be less than the unionised form. The active ingredient is able to penetrate into the skin and NLC dispersion is still effective.

Viscosity:

The diclofenac diethylamonium NLC system is administered topically, and targeting the epidermis. In order to give effect, the drug must penetrate through skin. Prior to penetrating the skin, it has to be released from the NLC. One of factors affecting the drug release is viscosity. Based on the measurements, the viscosities of FI, FII and FIII were 441.3 ± 269.7 cPs,; 924.0 ± 216.7 cPs and 1266.3 ± 267.4 cPs respectively. If the amount of glyceryl monostearate increases, the viscosity also increases and the particles were less mobile, thus, diclofenac diethylamonium was also difficult to release from the NLC particles. Statistical data showed significant differences in viscosity of FI and FIII, but there was no significant differences between FII and FIII. Thus, with a lipid ratio of 75:25 to 85:15, it did not make a significant difference in the viscosity of the NLC system of diclofenac diethylamonium.

Particle Morphology:

Particle morphology was examined by Transmission Electron Microscopy (TEM) and they are presented in figure 2. In addition to the particle morphology, TEM can also show the particle size of NLC. Based on the observations, the NLC morphology of FIII with the highest concentration of glyceryl monostearate, has more spherical form than FI and FII. Glyceryl monostearate in FIII was the highest than the other formula. This solid lipid has high melting point than the liquid lipid so that when it is stored below its melting point, the particles are more easily compacted and stable.



A B C

Figure 2. Particle morphology of the NLC captured using TEM with magnification of 80000X. A: FI; B: FII; C: FIII.

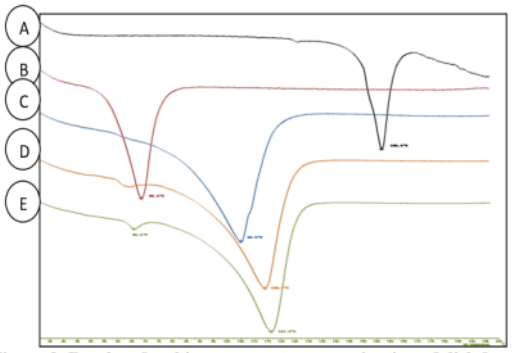


Figure 3. Results of melting temperature examination of diclofenac diethylamonium NLC preparations using DTA.

A: Diclofenac diethylamonium (155.3°C), B: Glyceryl monostearate (66.3°C), C: Formula I (99.9°C), D: Formula II (106.5°C), E: Formula III (107.6°C)

Based on observations of DTA thermogram it can be seen that there is a shift in the melting point of glyceryl monostearate in the NLC system in formulas I, II and III.

Infra Red Spectrophotometry:

Figure 4 showed results of infrared spectra of FI, FII and FIII. There was no difference between the spectra of NLC of FI, FII and FIII. Each formula showed no difference in absorbance, and some functional groups in each NLC compound were still observed including C-Cl, O-H and C-O. This suggests that there was no interaction between diclofenac diethylamonium and NLC components.

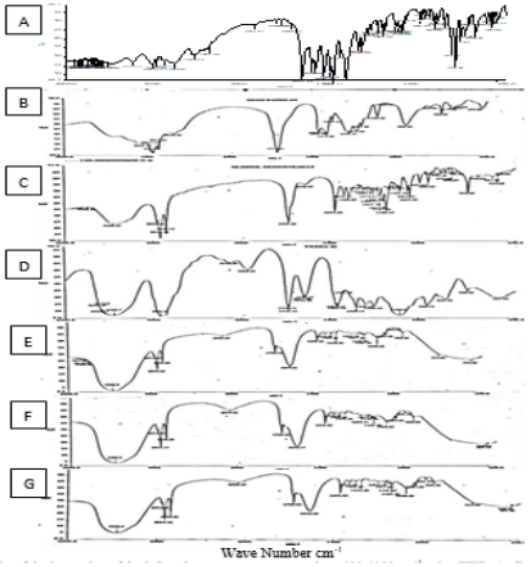


Figure 4. The results of the inspection of the infrared spectrum at wave numbers 400-4000 cm^{-1} using FTIR.

A: Diclofenac diethylamonium; B: caprylic acid; C: glyceryl monostearate; D: Tween 80; E: Formula I; F: Formula II; G: Formula III

Entrapment Efficiency (EE):

The entrapment efficiency of diclofenac diethylamonium in FI was the highest, i.e. 88.342 ± 0.52%. FII was 73.764 ± 0.511% and FIII was 70.754 ± 0.665%. In theory, higher liquid lipid content in NLCs can increase drug solubility in the NLC system so that the EE increases [14] In addition, higher concentrations of liquid lipids might disrupt the solid lipid crystals and turn them into amorphous. Burst of drug may not occur during storage and entrapment efficiency was higher. Based on statistical analysis using one way ANOVA, it showed that there was a significant difference between FI, FII and FIII.

CONCLUSION:

The diclofenac dichylamonium NLC system of the three formulas were white in color, the pH increases with increasing caprylic acid (miglyol), the viscosity increases with the increase of glyceryl monostearate, whereas the IR spectra showed the same result of the three formulas. The smallest particle size of the NLC system was FI with the ratio of glyceryl monostearate and caprylic acid was 65:35. The highest Entrapment Efficiency of diclofenac diethylamonium in NLC system was FI with the ratio of glyceryl monostearate and caprylic acid 65:35.

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Characteristic of Nanostructured Lipid Carrier (NLC) Diclofenac Diethylammonium as Function of Ratio of Glyceryl Monostearate and Caprylic Acid

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GENERAL COMMENTS

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