Contents lists available at IOCS

Science Midwifery

journal homepage: www.midwifery.iocspublisher.org

Formula development and characterization of nanostructured lipid carriers (NLC) vitamin E acetate with solid lipids compritol and precirol

Syifa Salsabilla[1], Garnadi Jafar[2], Fenti Fatmawati[3]

[1,2,3]Farmasetika dan Teknologi Farmasi, Fakultas Farmasi, Universitas Bhakti Kencana, Kota Bandung, Indonesia

ARTICLE INFO

Article history:

Received Nov 16, 2024
Revised Nov 20, 2024
Accepted Nov 23, 2024

Keywords:

Antihyperpigmentation
Compritol
Nanostructured Lipid Carriers
Precirol
Vitamin E acetate

ABSTRACT

Vitamin E acetate has antioxidant activity that can prevent premature aging of the skin, but its nature is very lipophilic (log p±12.2) and has the potential to degrade. To overcome the problems of permeability and stability, vitamin E acetate needs to be developed in Nanostructured Lipid Carrier (NLC), which is a nano delivery system based on solid lipids and liquid lipids stabilized by surfactants as a colloidal system. The formulation of vitamin E acetate into NLC was carried out using the heat homogenization method, then sonicated using a probe sonicator. The materials used were 2% vitamin E acetate, 2-6% Compritol® and Precirol® solid lipids, 1% Myritol®, and 1-3% Chremophore and Plantacare® surfactants. The NLC results were then characterized by measuring particle size, zeta potential, polydispersity index, entrapment efficiency, and morphology. The characterization results showed that NLC vitamin E acetate had a particle size of 280-375 nm, a zeta potential of -23 mV to -28 mV, a polydispersity index <0.5, an entrapment efficiency of 92-97%, and a spherical morphology. The results showed that Nanostructured Lipid Carrier vitamin E acetate gave good results.

Corresponding Author:

Garnadi Jafar,
Farmasetika dan Teknologi Farmasi,
Fakultas Farmasi,
Universitas Bhakti Kencana,
Jl. Soekarno Hatta No. 754, Cipadung Kidul, Kec. Panyileukan, Kota Bandung, Jawa Barat 40614, Indonesia
Email: garnadi.jafar@bku.ac.id

INTRODUCTION

The skin is the most visible organ of the body, therefore skin aging can have an impact on a person's self-confidence. Skin aging is a process that occurs naturally with age, but can be accelerated by several factors, one of which is exposure to UV rays. Exposure to irradiation. Indonesia, which has year-round sun exposure, makes its population susceptible to hyperpigmentation (Sri & Estuningsih, 2020)(Lasmiani, 2024)(Pratiwi et al., 2024). Therefore, supplements containing antioxidants are needed to prevent premature aging due to oxidative stress.

Previous studies have shown that vitamin E can cause depigmentation by interfering with melanocyte membrane lipid peroxidation, increasing intracellular glutathione content, and inhibiting tyrosinase (Sarkar et al., 2013)(Lestari, 2022)(Winarni, 2023)(Novanda, 2024). The ester form of vitamin E, namely vitamin E acetate, shows good tolerability on the skin and is more stable because it is less sensitive to oxidative degradation (Silva et al., 2019). This compound is hydrophobic and has low solubility in water, with a molecular weight of 472.743 g/mol and a log P value of 12.07 ± 0.27 (Morais & Burgess, 2014). According to Xu et al. (2013), compounds with molecular weight ≥ 400 g/mol and log P ≥ 4 are difficult to absorb dermally, so it is known that vitamin E acetate has poor permeability. The problem of permeability is a challenge in the formulation of topical preparations, because active ingredients that do not penetrate well cannot provide the desired therapeutic effect.

Lipid-based nanoparticles are known to be an effective strategy to enhance the permeation of compounds into the skin. Solid Lipid Nanoparticles (SLN) are the first generation of lipid-based nanoparticles, consisting of a solid lipid matrix covered by a surfactant layer in an aqueous dispersion (Latter et al., 2019). Small particle size and strong adhesiveness can cause occlusive effects through film formation on the skin. Occlusive effects can reduce transepidermal water loss, increase skin hydration, and increase drug penetration (Ferreira et al., 2021).

However, the crystal structure of SLN can undergo modification over time during storage. This process occurs thermodynamically, associated with the release of energy and an increase in crystallinity. This phenomenon causes the packing of the solid matrix to become denser and reduces the space between lipid molecules. As a result, the active ingredients located at the interface of the lipid molecules are released from the lipid matrix and diffuse into the aqueous phase. In this phase, precipitation usually occurs (Latter et al., 2019).

The release of active ingredients from the matrix due to modification of solid lipids needs to be prevented to maintain stability, therefore a second generation of lipid-based nanoparticles called Nanostructured Lipid Carriers (NLC) has been developed. NLCs are not only composed of solid lipids, but are a mixture of solid and liquid lipids. The mixture forms oil regions within the solid matrix, which prevent or at least slow down the modification of the solid lipids over time. This results in higher storage stability. In addition, due to the addition of oil, more space is created between the solid lipid molecules, thus increasing the capacity for active ingredients (Latter et al., 2019).

Based on research Shettigar et al. (2021) ex vivo, the percentage of clarithromycin drug permeation in the NLC system (89.46%) was higher than in pure gel preparations (42%) and gels available on the market (65%). Clarithromycin is an antibiotic whose permeability will decrease if it passes through lipid barriers such as skin. The clarithromycin NLC system was successfully developed and showed good skin permeation and sustained antibiotic release. NLC components (lipids and surfactants) act as permeation enhancers through interactions with lipids in the stratum corneum layer, which facilitates the permeation of molecules into deeper layers of the epidermis.

Gu et al.'s (2018) study compared the permeability of SLN and NLC systems in vitro. The cumulative amount of active ingredients penetrated into the receptor media from NLC was 79.51 ± 9.64 µg/cm2 while from SLN was 53.94 ± 5.72 µg/cm2. The greater amount of drug penetrated from NLC compared to SLN is related to the addition of liquid lipids to NLC, which has the potential to loosen the stratum corneum in the same way as surfactants. The results showed that NLC had a stronger interaction with the skin compared to SLN.

RESEARCH METHOD

Tool

Glassware (Pyrex®), hot plate (Oxone®), magnetic stirrer (IKA® C-mag HS 10), probe sonicator (Lvymen® System CY-500), Particle Size Analyzer (PSA) (Malvern instruments Ltd), MPW-55 microcentrifuge, UV Spectrophotometer (Shimadzu UV-1800), Zetasizer (Zetasizer Nano

ZS; Malvern), Fourier Transform Infra-Red (FTIR) (Agilent Technologies Cary 630 FTIR), spray bottle, analytical balance (Mettler Toledo), minispin (Eppendorf, Germany), Transmission Electron Microscopy (TEM, JEOL JEM 1400, Japan).

Material

The materials used in the formulation included vitamin E acetate (dl-alpha tocopheryl acetate) 99.4% as the active ingredient (DSM Nutritional Products Asia Pacific Pte. Ltd, Singapore). Additional components were Precirol® and Glyceryl Behenate (Compritol ATO®) from Gattefose (Italy), Caprylic Triglyceride (Myritol®) from BASF Indonesia, and Chremophore from BASF. The surfactant Lauryl Glucoside (Plantacare®) was supplied by Evonik Industries, Singapore. Other substances included Aquadest and Methanol PA (Merck).

Fourier Transform Infrared Spectrophotometry (FTIR) Testing

To test the compatibility of excipients with active ingredients, testing was carried out using the Fourier Transform Infrared (FTIR) instrument on Precirol®, a mixture of Precirol®-Myritol®, a mixture of Precirol®-vitamin E acetate, and a mixture of Precirol®-Myritol®-vitamin E acetate. As well as Compritol®, a mixture of Compritol®-Myritol®, a mixture of Compritol®-vitamin E acetate and a mixture of Compritol®-Myritol-Vitamin E acetate. The samples were mixed and melted, then after solidifying, they were ground to obtain a fine powder. Furthermore, the samples were observed in the spectrum in the fingerprint area (wave number 500-1500 cm-1) (Tofani et al., 2016)

Differential Scanning Calorimetry (DSC) Testing

Several pans are prepared, one pan is used as a reference and the other for the sample. The sample is weighed according to the volume capacity of the pan using a micro or semi-micro scale. Then the sample is inserted into the pan. The cell cover on the DSC-60 device is opened, along with both furnace covers. The empty/reference pan is placed on the left detector plate and the sample pan on the right detector plate. The furnace cover and cell cover are reinstalled and testing is carried out at a temperature of 30°C to 300°C with a scanning rate of 10°C/minute (Jafar et al., 2022).

Creation of NLC

The oil phase consisting of solid lipids and liquid lipids was added with the active ingredient vitamin E acetate, melted and heated to a temperature of 60°C. The water phase consisting of surfactants and distilled water was heated to a temperature of 60°C. The water phase was mixed into the oil phase by stirring using a magnetic stirrer for 15 minutes in a hot state. Particle size reduction was carried out on the mixture using a probe sonicator for 15 minutes. After that, the sample was cooled at room temperature for 10 minutes (Jafar et al., 2022).

Characterization of NLC

Characterization of NLC vitamin E acetate was carried out using particle size parameters, Polydispersity index, and zeta potential. This measurement was carried out using a Malvern ZSP Zetasizer (UK) at room temperature (25oC). 10 drops of the NLC vitamin E acetate sample were taken, then distilled water was added up to 10 mL and put into a disposable cuvette. The structure of NLC vitamin E acetate was observed using Transmission Electron Microscope (TEM) instrument. The sample was diluted with distilled water and placed on a film-coated copper grid, then one drop of phosphotungstic acid was added to dry overnight at room temperature. The dried sample was then visually evaluated using TEM (Sirikhet et al., 2021).

Adsorption Efficiency (EE)

A total of 1.5 mL of NLC vitamin E acetate was put into a Vivaspin® tube, then centrifuged at 13,000 rpm for 60 minutes (1 cycle) with a centrifugator. The filtrate was separated and diluted with methanol, then the absorbance was measured and the concentration was determined. %EE was calculated based on the following formula (Tofani et al., 2016):

$$\%EE = \frac{\text{total zat aktif} - \text{zat aktif bebas}}{\text{total zat aktif}} \times 100\%$$

RESULTS AND DISCUSSIONS

Table 1. NLC formula and NLC characterization results of Vitamin E acetate

Code	Formulation						Particle size (nm)	PdI	Zeta Potential (mV)	Entrapment Efficiency (%)
	Active Ingredients	Liquid Lipids	Solid Lipids		Surfactant					
	VIT E (%)	MYR (%)	CMP (%)	PRE (%)	PLA (%)	CHRE (%)				
F1	2	1	6	-	1	-	197.50 ± 1.20	0.36	-30.87 ± 0.60	97.08
F2	2	1	2	-	3	-	59.66 ± 0.60	0.13	-29.63 ± 0.81	97.64
F3	2	1	4	-	2	-	98.04 ± 0.96	0.21	-29.67 ± 0.59	95.88
F4	2	1	5	-	1.5	-	133.73 ± 1.25	0.25	-31.57 ± 0.46	96.65
F5	2	1	3	-	2.5	-	75.85 ± 0.91	0.30	-29.07 ± 0.67	96.67
F6	2	1	-	6	-	1	279.50 ± 5.59	0.25	-24.30 ± 0.56	96.71
F7	2	1	-	2	-	3	106.10 ± 1.97	0.33	-10.27 ± 0.15	96.58
F8	2	1	-	4	-	2	173.57 ± 1.63	0.17	-21.17 ± 0.42	96.61
F9	2	1	-	5	-	1.5	136.40 ± 2.72	0.35	-21.37 ± 0.15	95.29
F10	2	1	-	3	-	2.5	247.33 ± 4.19	0.25	-15.50 ± 0.30	96.04

The preliminary testing stage aims to see the characteristics of the raw materials used in the NLC vitamin E acetate formulation, including FTIR testing and DSC testing. FTIR testing was conducted to determine the compatibility between the raw materials to be used in the NLC formulation. The spectrum pattern in Figure 1 shows that the mixture of Precirol® solid lipids with Myritol® and vitamin E acetate appears to resemble the spectrum of single Precirol® and no new peaks were found at wave numbers 500-1500 cm-1. These results are in line with research Nasiri et al., (2020)which states that there is no new peak in the FTIR spectrum indicates no interaction between materials. So that the raw materials can be used in the NLC formulation because no incompatibility was found.

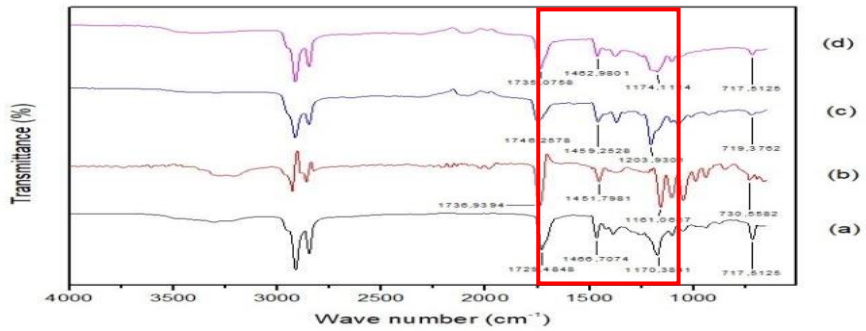


Figure 1. FTIR spectra of (a) Precirol® solid lipid; (b) mixture of Precirol® and Myritol®; (c) mixture of Precirol® and vitamin E acetate; (d) mixture of Precirol®, Myritol®, and vitamin E acetate

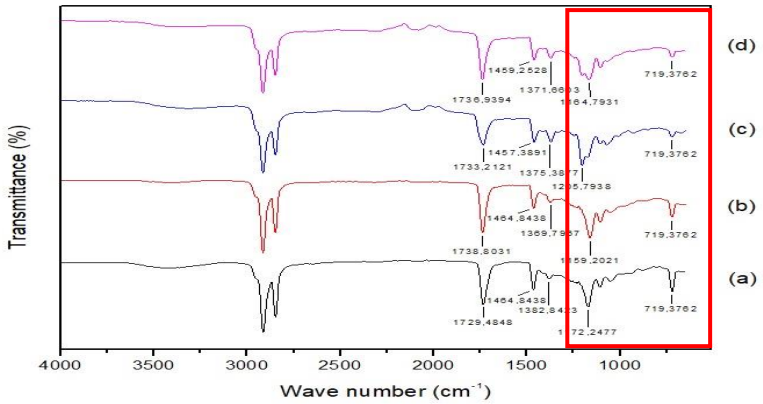


Figure 2. FTIR spectrum(a) Compritol® solid lipid; (b) mixture of Compritol® and Myritol®; (c) mixture of Compritol® and vitamin E acetate; (d) mixture of Compritol®, Myritol® and vitamin E acetate

The spectrum pattern of the solid lipid mixture of Precirol® and Compritol with Myritol® and vitamin E acetate appears to resemble the spectrum of single Precirol® and single Compritol® and no new peaks were found at wave number 500-1500 cm-1. These results are in line with the research (Shettigar et al., 2021) which states that there is no new peak in the FTIR spectrum indicates no interaction between materials. So that the raw materials can be used in the NLC formulation because no incompatibility was found.

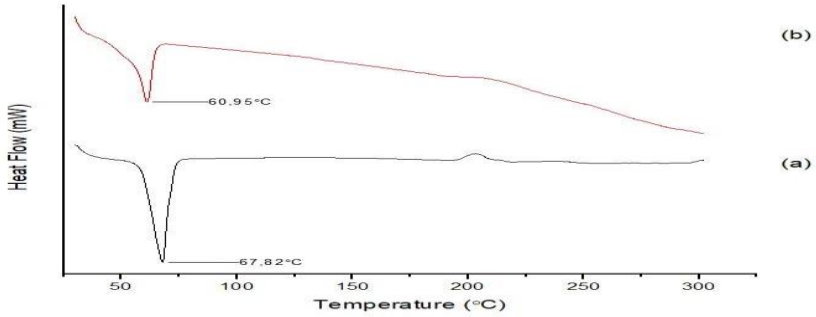


Figure 3. DSC spectra of (a) Precirol® alone and (b) mixture of Precirol® with vitamin E acetate

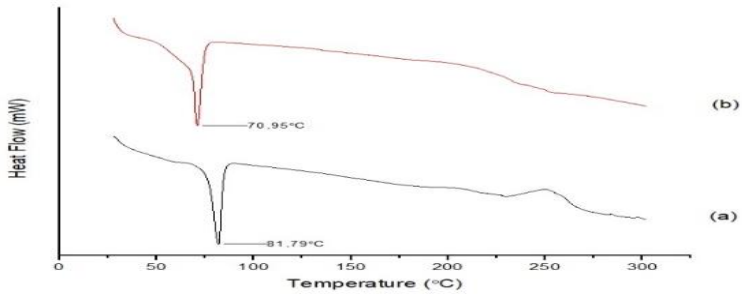
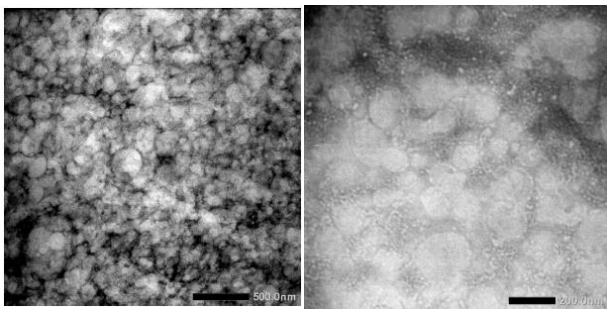


Figure 4. DSC spectra of (a) Compritol® solid lipid; (b) mixture of Compritol® and vitamin E acetate

The DSC spectrum shows that the single Precirol® solid lipid endothermic peak occurs at 67.82°C while the mixture of Precirol® with vitamin E acetate at 60.95°C. The spectrum also shows Compritol's single ingredient endothermic peak is at 81.79°C and the mixed ingredient endothermic peak is at 70.95°C. Based on these results, it can be seen that vitamin E acetate has the effect of shifting the solid lipid peaks of Precirol® and Compritol® to lower temperatures (Jafar et

al., 2021). Observations were made visually using a TEM instrument on the NLC vitamin E acetate sample with a magnification of 8,000 times. This stage aims to observe the morphology of the NLC system that has been made.



(b)

Figure 5. Results of TEM Visualization of NLC Vitamin E Acetate (a) NLC Vitamin E acetate Precirol-Chremophore (b) NLC Vitamin E acetate Compritol-Plantacare at 8000x magnification

After going through the manufacturing process, NLC vitamin E acetate was produced with a volume of each formula of ±30 mL, in the form of a milky white liquid. The results of the NLC manufacturing were then characterized. The characterization stage aims to determine the success of the NLC formulation by ensuring that the NLC vitamin E meets the requirements including particle size, Polydispersity Index (PdI), zeta potential, entrapment efficiency (%EE).

Characterization parameters are particle size, polydispersity index, zeta potential and adsorption efficiency. Based on the test results, it is known that NLC vitamin E acetate has a particle size in the range of 58.75-346.47 nm at H30. These results are in line with research Souto et al., (2020)which states that the size of NLC particles is in the range of 40-100 nm. According toMüller et al., (2016)Particle sizes above 400 nm can affect long-term stability, such as the possibility of flotation or creaming. While NLCs with sizes below 200 nm tend to experience recrystallization.

The polydispersity index of NLC vitamin E acetate ranged from 0.13 to 0.36. These results are in line with researchRohmah et al., (2019)which states that the PdI value that is getting closer to 0 indicates that the particles are getting more homogeneous. This is supported by the statement Garg et al., (2017)that the PdI value is less than 0.5 indicates that all particles are in a narrow range and the distribution is considered monodisperse.

The zeta potential value of NLC vitamin E acetate is in the range of -31.57 to -10.27. These results are in line with research Chauhan et al., (2020) which states that a zeta potential value of more than +20 mV or less than -20 mV is predicted to have good stability. According to Jafar et al., (2019), the higher the zeta potential value, the greater the repulsive force between particles, thus preventing aggregation.

% EE NLC Vitamin E acetate is in the range of 95.29-97.64%. These results are in line with research Aisiyah et al., (2019)which states that %EE of more than 80% indicates a high amount of active ingredients adsorbed in the NLC system, and the higher the %EE, the greater the loading capacity. According toSriarumtias et al., (2017)The high %EE of the NLC system is due to the composition of the NLC matrix consisting of solid lipids and liquid lipids. When solidified, the presence of liquid lipids forms irregular spaces in the matrix which increases the space for active ingredients.

The results of TEM observations on NLC vitamin E acetate visualized spherical nanoparticles, dispersed in the system homogeneously and measuring <500 nm. The TEM results also confirmed the results of particle size characterization and PdI with the PSA instrument.

Particles that are in a narrow range and distributed homogeneously are indicated by PdI values of less than 0.5 (Garg et al., 2017).

CONCLUSION

Nanostructured Lipid Carrier (NLC) formula of vitamin E acetate can be developed using solid lipid Compritol ATO® and surfactant Plantacare® and solid lipid Precirol® and surfactant Chremophore®. NLC vitamin E acetate in surfactant formula F1-F10 showed good characterization results, with particle size parameters ranging from 58.75-346.47 nm, polydispersity index <0.5, zeta potential -31 mV to -10.27 mV, and entrapment efficiency of 92-97%. The results of morphological testing using TEM to evaluate the morphological shape of NLC showed that the particles were spherical (round).

References

Aisiyah, S., Harjanti, R. & Nopiyanti, V. (2019). Pengaruh Panjang Rantai Karbon Lipid Padat terhadap Karakteristik Nanostructured Lipid Carrier Resveratrol. *JPSCR : Journal of Pharmaceutical Science and Clinical Research*, *4*(2), 69. https://doi.org/10.20961/jpscr.v4i2.34408

Chauhan, I., Yasir, M., Verma, M. & Singh, A. P. (2020). Nanostructured lipid carriers: A groundbreaking approach for transdermal drug delivery. *Advanced Pharmaceutical Bulletin*, *10*(2), 150–165. https://doi.org/10.34172/apb.2020.021

Ferreira, K. C. B., Valle, A. B. C. D. S., Paes, C. Q., Tavares, G. D. & Pittella, F. (2021). Nanostructured lipid carriers for the formulation of topical anti-inflammatory nanomedicines based on natural substances. *Pharmaceutics*, *13*(9). https://doi.org/10.3390/pharmaceutics13091454

Garg, N. K., Sharma, G., Singh, B., Nirbhavane, P., Tyagi, R. K., Shukla, R. & Katare, O. P. (2017). Quality by Design (QbD)-enabled development of aceclofenac loaded-nano structured lipid carriers (NLCs): An improved dermatokinetic profile for inflammatory disorder(s). *International Journal of Pharmaceutics*, *517*(1–2), 413–431. https://doi.org/10.1016/j.ijpharm.2016.12.010

Jafar, G., Abdassah, M., Rusdiana, T. & Khairunisa, R. (2021). Development and characterization of precirol ato 88 base in nanostructured lipid carriers (Nlc) formulation with the probe sonication method. *International Journal of Applied Pharmaceutics*, *13*(special issue 3), 43–46. https://doi.org/10.22159/IJAP.2021.V13S3.08

Jafar, G., Agustin, E. & Puryani, D. (2019). Pengembangan Formula Solid Lipid Nanoparticles (SLN) Hidrokortison Asetat. *Jurnal Pharmascience*, *6*(1), 83. https://doi.org/10.20527/jps.v6i1.6080

Jafar, G., Salsabilla, S. & Santoso, R. (2022). Development and Characterization of Compritol Ato® Base in Nanostructured Lipid Carriers Formulation With the Probe Sonication Method. *International Journal of Applied Pharmaceutics*, *14*(Special Issue 4), 64–66. https://doi.org/10.22159/ijap.2022.v14s4.PP04

Lasmiani, N. M. E. (2024). *Penentuan Potensi Tabir Surya dan Nilai Sun Protection Factor (SPF) Sediaan Krim Ekstrak Etanol Bunga Kenanga (Cananga odorata (Lamk.) Hook.) dengan Metode Spektrofotometri Uv-Vis*. Universitas Mahasaraswati Denpasar.

Latter, G., Grice, J. E., Mohammed, Y., Roberts, M. S. & Benson, H. A. E. (2019). Targeted topical delivery of retinoids in the management of acne vulgaris: Current formulations and novel delivery systems. *Pharmaceutics*, *11*(10). https://doi.org/10.3390/pharmaceutics11100490

Lestari, W. (2022). *Photoaging*. Syiah Kuala University Press.

Morais, J. M. & Burgess, D. J. (2014). In vitro release testing methods for vitamin e nanoemulsions. *International Journal of Pharmaceutics*, *475*(1), 393–400. https://doi.org/10.1016/j.ijpharm.2014.08.063

Müller, R. H., Alexiev, U., Sinambela, P. & Keck, C. M. (2016). *Nanostructured Lipid Carriers (NLC): The Second Generation of Solid Lipid Nanoparticles*.

Nasiri, F., Faghfouri, L. & Hamidi, M. (2020). Preparation, optimization, and in-vitro characterization of α-tocopherol-loaded solid lipid nanoparticles (SLNs). *Drug Development and Industrial Pharmacy*, *46*(1), 159–171. https://doi.org/10.1080/03639045.2019.1711388

Novanda, N. A. (2024). *PENGARUH PEMBERIAN GEL EKSTRAK BUAH TOMAT TERHADAP KADAR TRANSFORMING GROWTH FACTOR BETA (TGF-β) DAN INTERLEUKIN-10 (IL-10)(Studi Eksperimental Pada Mencit yang Terpapar UVB)*. Universitas Islam Sultan Agung Semarang.

Pratiwi, L., KM, M., Anggraini Ambarsari, S., KM, M., Annarahayu, L., Keb, S. T., KM, M., Nawangsari, H.,

ST, S. & Keb, M. (2024). *Kesehatan Wanita Indonesia*. CV Jejak (Jejak Publisher).

Rohmah, M., Raharjo, S., Hidayat, C. & Martien, R. (2019). Formulasi dan Stabilitas Nanostructured Lipid Carrier dari Campuran Fraksi Stearin dan Olein Minyak Kelapa Sawit. *Jurnal Aplikasi Teknologi Pangan*, *8*(1), 23–30. https://doi.org/10.17728/jatp.3722

Sarkar, R., Arora, P. & Garg, Kv. (2013). Cosmeceuticals for hyperpigmentation: What is available? *Journal of Cutaneous and Aesthetic Surgery*, *6*(1), 4. https://doi.org/10.4103/0974-2077.110089

Shettigar, P., Koland, M., Sindhoor, S. M. & Prabhu, A. (2021). Formulation and Evaluation of Clarithromycin Loaded Nanostructured Lipid Carriers for the Treatment of Acne. *Journal of Pharmaceutical Research International*, *September*, 26–38. https://doi.org/10.9734/jpri/2021/v33i40b32260

Silva, S., Ferreira, M., Oliveira, A. S., Magalhães, C., Sousa, M. E., Pinto, M., Sousa Lobo, J. M. & Almeida, I. F. (2019). Evolution of the use of antioxidants in anti-ageing cosmetics. *International Journal of Cosmetic Science*, *41*(4), 378–386. https://doi.org/10.1111/ics.12551

Sirikhet, J., Chanmahasathien, W., Raiwa, A. & Kiattisin, K. (2021). Stability enhancement of lycopene in Citrullus lanatus extract via nanostructured lipid carriers. *Food Science and Nutrition*, *9*(3), 1750–1760. https://doi.org/10.1002/fsn3.2156

Souto, E. B., Baldim, I., Oliveira, W. P., Rao, R., Yadav, N., Gama, F. M. & Mahant, S. (2020). Expert Opinion on Drug Delivery SLN and NLC for topical , dermal , and transdermal drug delivery. *Expert Opinion on Drug Delivery*, *00*(00), 1–21. https://doi.org/10.1080/17425247.2020.1727883

Sri, Y. & Estuningsih. (2020). PERBANDINGAN APLIKASI TERAPI AKUPUNKTUR DENGAN SUSU FERMENTASI KEFIR UNTUK MENGHAMBAT PROSES PENUAAN DINI yang tidak mengikuti peraturan sesuai dengan terapi akupunktur dan atau minum kerfir sesuai yang sudah dijadwalkan ; dan wanita yang mempunyai penyak. *Jurnal Kesehatan Kusuma Husada*, 153–160.

Sriarumtias, F. F., Darijanto, S. T. & Damayanti, S. (2017). Formulasi Dan Uji Potensi Antioksidan Nanostructured Lipid Carrier (Nlc) Retinil Palmitat. *Acta Pharmaceutica Indonesia*, *42*(1), 25–31. https://doi.org/10.5614/api.v42i1.4563

Tofani, R. P., Sumirtapura, Y. C. & Darijanto, S. T. (2016). Formulation, characterisation, and in vitro skin diffusion of nanostructured lipid carriers for deoxyarbutin compared to a nanoemulsion and conventional cream. *Scientia Pharmaceutica*, *84*(4), 634–645. https://doi.org/10.3390/scipharm84040634

Winarni, N. (2023). *PENGARUH SERUM EKSTRAK DAUN SUKUN (Artocarpus Altilis) TERHADAP KADAR TNF-a DAN SOD (Studi experimental pada marmut yang dipapar sinar UVB)*. Universitas Islam Sultan Agung Semarang.