JURNAL ILMU KEFARMASIAN INDONESIA
Indonesian Journal of Pharmaceutical Sciences
ISSN p-ISSN 1693-1831 (Print) e-ISSN 2614-6495 (Online) PUBLISHER : Faculty of Pharmacy Universitas Pancasila

Nanostructured lipid carrier (NLC) in topical preparations: a narrative review of components, manufacturing methods, characteristics and activities

Yayan Rizikiyan[1], Nining Sugihartini[2]*, Ichwan Ridwan Rais[2]

[1]*Faculty of Pharmacy, Universitas Muhammadiyah Ahmad Dahlan Cirebon, Indonesia*
[2]*Faculty of Pharmacy, Universitas Ahmad Dahlan, Indonesia*

*Corresponding Author: nining.sugihartini@pharm.uad.ac.id

Received: 13 August 2024/ Accepted: 24 April 2025

ABSTRACT: Nanostructured Lipid Carries NLCs have gained attention in formulation science and nanotechnology due to their biocompatible material and ability to enhance skin penetration. The goal is to create products that can effectively deliver active compounds to desired skin layers with minimal side effects. This review focuses on the use of functionalized NLCs in dermocosmetics, specifically looking at their composition, manufacturing method, characteristics, and role in delivering active compounds. The review obtained articles from databases such as Scopus, Pubmed, and Google Scholar, covering the years 2014-2024. Data search was conducted in May 2024. The search used keywords such as "NLC OR formulation OR dermal OR activity". By considering factors such as NLC composition, manufacturing method, and impact on compound delivery, researchers aim to optimize NLCs for use in topical preparations. This research contributes to the development of dermocosmetics that can address various skin problems more effectively. The search results from 32 articles gave an overview of the widely used NLC components: solid lipids: glycerol monostearate, compitrol 888 ATO, and tristearin; liquid lipids: myglyol, transcutol, and oleic acid; surfactants: poysorbat 80 and polysorbate 20. The widely used methods were ultrasonication and high pressure homogenization. Frequently performed characterizations include particle size, polydispersity index (PDI), zeta potential, and Entrapment Efficiency (EE). The pharmacological activity of active components loaded into NLCs increased than without NLCs. The active ingredient formulated in NLC can produce better activity compared to the active substance formulated directly in the conventional preparation. The application of nanostructured lipid carrier (NLC) nanoparticles on the skin is very beneficial. These nano systems have shown promising results and more commercial formulations, so it is expected to be done in further research.

KEYWORDS: Active compound delivery; characteristics; components; manufacturing methode; Nanostructured lipid carriers (NLC); topical.

INTRODUCTION

Nanostructured lipid carriers (NLC) is delivery systems for the delivery of drugs and other bioactives used in diagnosis, therapy, and treatment procedures. These nanocarriers may enhance the solubility and permeability of drugs, increase their bioavailability, and extend the residence time in the body, combining low toxicity with a targeted delivery. Nanostructured lipid carriers are the second generation of lipid nanoparticles differing from solid lipid nanoparticles in their composition matrix. The use of a liquid lipid together with a solid lipid in nanostructured lipid carrier allows it to load a higher amount of drug, enhance drug release properties, and increase its stability [1]. Poor drug release and loading drive the design of nanostructured lipid carriers (NLC), as NLC is a new drug carrier consisting of solid lipids and physiological liquid lipids and is fully biodegradable [2]. Nanoctructured Lipid Carrier (NLC) is a development of Solid Lipid Nanoparticles (SLN) which is the first generation lipid nanocarrier. The reason for this development is due to some observed limitations of SLNs such as drug release through the matrix during storage and lower drug loading efficiency. The idea behind NLC formulation is to incorporate the medicine into a combination of different ratios of liquid to solid lipid. To get over the constraints brought on by the SLN core's crystallinity, NLCs are made to have a less crystalline matrix without a compacted core. The processes used to prepare SLNs and NLCs are largely similar. Cold homogenization, hot homogenization, hot emulsification-ultrasonication are commonly used techniques for the preparation of SLNs and NLCs. The formulation parameter that shows the difference between the two is none other than their core/matrix composition. medications in NLCs are dissolved and/or

How to cite this article: Rizikiyan Y, Sugihartini N, Rais IR. Nanostructured lipid carrier (NLC) in topical preparations: a narrative review of components, manufacturing methods, characteristics and activities.JIFI. 2025; 23(1): 139-158.

ISSN: 2614-6495

liquefied in a mixture of liquid and solid lipids and dispersed in an aqueous phase including surfactants; in SLNs, medications are primarily dissolved or directly integrated into solid lipids[3][4].

Based on variations in lipid and oil mixture composition and various manufacturing methods, NLCs can be categorized into three types: NLC Type I, NLC Type II, and NLC Type III. NLC Type I is an imperfect crystal core. A partial substitution of liquid lipid or oil for solid lipid results in an incomplete crystal lattice or matrix. This phenomenon suggests that there is more room for drugs to be accommodated and permits greater drug loading. A highly organized or ordered matrix that would force the drug out of the core would not form when an imperfect crystal core forms, leaving greater room for drug integration. NLC Type II: This type is sometimes referred to as amorphous or unstructured. When liquid lipids are combined with solid lipids that remain in the α-polymorph after solidification and storage, an amorphous core is typically formed. Compared to type I NLCs, this is better since the medication stays entrenched in the amorphous matrix and no crystallization happens. Crystalline structured matrix is generated by solid lipid β polymorphs. NLC Type III: This dual type was created by extending the idea of w/o/w emulsion. Fundamentally, it is a form of NLC that is fat in water or oil in solid, and it can only be produced by phase separation methods. This strategy can be applied to NLC formulations to increase the drug loading capacity and stability when the medication exhibits greater oil solubility. These systems are distributed in aqueous fluids and contain uniformly distributed small droplets of oil within the solid lipid matrix [4][5].

NLC is currently in great demand because it has several advantages including having good biocompatibility, avoiding the use of organic solvents, NLC is easy to scale up and sterilize, and is inexpensive compared to surfactant-based carriers or carriers, can target drug release for pharmaceutical stability, allows drug delivery of lipophilic and hydrophilic drugs simultaneously, most lipids are biodegradable [6]. The advantages of NLC will certainly be easily obtained if we can formulate NLC optimally. This narrative review is conducted to facilitate further research on NLC, related to the components of the NLC formula, as well as the method of making NLC, the necessary characterization of NLC, and also the increase in activity of the active ingredients after being formulated in NLC preparations.

▪ MATERIALS AND METHODS

This narrative review uses articles obtained from online search results with databases from Scopus, Pubmed, Google Scholar. The data search was conducted in May 2024, to conduct a literature search on Nanostructured Lipid Carrier (NLC) drug delivery systems in topical preparations. Articles searched in the database were selected in English, publication year 2014-2024. The search keywords were "NLC OR formulation OR dermal OR activity. Only original (experimental) articles were used. Literature types such as review articles, book chapters and proceedings were not used in this review. The data extracted from the collected articles were as follows: NLC formula components, manufacturing method, characteristics, active ingredients contained in NLC, activity, and results of activity testing.

The inclusion criteria in this narrative review were research articles on NLC that described the formula components, manufacturing methods, characteristics and activity of the NLC. Exclusion criteria are articles in the form of reviews, book chapters and proceedings. The flow of literature search can be seen in Figure 1.

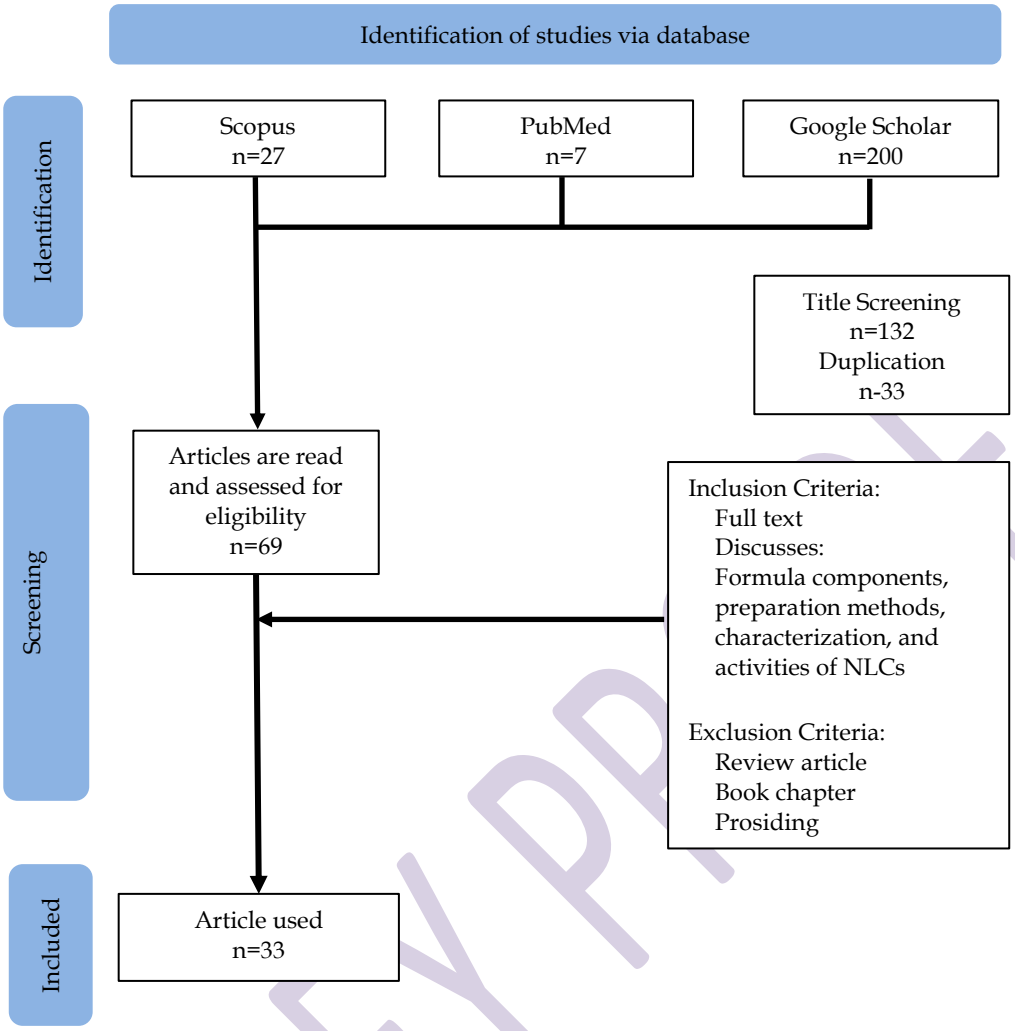

Figure 1. Literature search

▪ RESULTS

The results of the literature search on the formula components, manufacturing methods, characteristics, and activities of NLCs found in topical preparations in 33 selected articles are summarized in Table 1.

Table 1. Results of article search on nlc in topical preparations.

	NLC Component	Method of Preparation	Characteristics	Active Ingredient	Activity	Result
[7]	**Solid lipid:** glycerol monostearate (877.4 mg), **Liquid lipids:** Capmul MCM (101.8 mg) **Surfactant**: Myrj 1% w/v (52.20 mL)	Utrasonication	Particle Size: 199±8 nm PDI: 0.22±0.01 Zeta Potential: - EE: 92.5±0.9% DL: 2.3±0.1%	Econazole	Antifungal	Blank-NLC showed a particle size of 197 ± 4 nm and a polydispersity index of 0.23 ± 0.02 . Econazole-NLC were similar to those of blank-NLC. These characteristics of Econazole NLC would be beneficial to increase skin permeation in the form of NLC, improving the concentration-time dependent killing property by extension of exposure time. antifungal activity of Econazole-NLC was similar to that of raw Econazole. This means that Econazole-NLC has an activity equivalent to the antifungal activity of raw Econazole. Thus, Econazole-NLC could be an efficient formulation for the topical application of Econazole which was less toxic to human skin without the decrease of in vitro antifungal activity..
[8]	**Solid lipid:** Stearic Acid, **Liquid lipid:** Babchi Oil (Total lipid 3%, Solid lipid:Liquid lipid = 6:4) **Surfactant:** SLS **co-surfactant**: PEG-400 (Surfactant mixture 1.5%)	Melt emulsification method followed by ultra-sonication	f Particle Size: 132.5 ± 10.34 nm PDI : 0.224 ± 5.12 Zeta Potential : - % EE : 85.956 ± 5.78%	Barberin	Treatment skin acne	These results imply that the Barberine NLC gel showed more prolonged drug release as compared to Barberine NLC formulation, which is more desirable for long time efficacy of drug. The creation of NLC gels containing barberin may represent a viable strategy for the safe and efficient topical delivery of medication to treat acne vulgaris.

	NLC Component	Method of Preparation	Characteristics	Active Ingredient	Activity	Result
[9]	**Solid lipid:** Compritol 888 ATO (100 mg) **Liquid Lipid:** MCT 812 (50 mg) **Surfactant:** Myrj 52 (600 mg)	Emulsification and solution evaporation techniques	Particle Size: 18 - 20 nm PDI: 0.13 Zeta Potential: -2.59 to -2.77 mV EE: 96%	Corylin	UV-induced Skin Aging	Corylin solution cumulative amount of Corylin released was 65% within 24 h, Corylin-NLC cumulative amount of Corylin released was 25% and the cumulative amount of Corylin released from Corylin- NLC gel was 18% after 24 h. This study suggests a viable method to raise photoaging therapy's effectiveness. the skin of mice treated with high-dose Corylin NLC gel returned to smoothness, with only slight wrinkles. At the same time, mice in the low-dose Corylin group had smooth skin but a small amount of erythema.
[10]	**Solid lipids:** Softisan 100 **Liquid lipids:** Librafil **Surfactant:** Polysorbate 80 **Cosurfactant:** Kolliphor RH40	High pressure homogenization (Ultra-Turrax® (IKA, model T25))	Particle size: 70 nm - 200 nm PDI: 0.11 - 0.35 Zeta Potential: - EE: ~96%	Clotrimazole	Treatment antifungal Candida skin infections	The enhanced antifungal activity of clotrimazole-loaded nanoparticles prepared with rosmarinus or lavender was demonstrated in vitro studies against Candida albicans, Candida krusei, and Candida parapsilosis. This confirms that nanostructured lipid carriers (NLCs) containing essential oils from the Mediterranean region represent a promising approach for improving drug delivery.
[11]	**Solid Lipids:** Glyceryl Monostearate 5% w/w, Stearic Acid 55 w/w, Cetyl Palmitate 1-5%w/w **Liquid Lipid:** tea seed oil 1-3% **Surfactants**: Tween 20,, Tween 80, Plantacare 2000	High pressure homogenization (digital ULTRA-TURRAX IKA T 25)	Particle size: 152.5 ± 1.4 nm nm PDI: 0.108 ± 0.017 Zeta Potential: −48.8 ± 0.4 mV	Ocimum sanctum Linn	Anti-Aging	The most suitable NLC formulation was composed of 5% w/w cetyl palmitate, 3% w/w tea seed oil, 2.5% w/w Plantacare 2000→, and 91.5% w/w DI water. Given that NLC improved Rosmarinic Acid administration via the skin with a noteworthy skin retention of 27.1 ± 1.8% ($p < 0.05$), it was recommended as the best system.

	NLC Component	Method of Preparation	Characteristics	Active Ingredient	Activity	Result
[12]	**Solid lipids:** Compritol 888 ATO **Liquid lipids:** Miglyol-840 was taken in a ratio of 7:3 together with egg lecithin, **Aqueous phase:** prepared by dissolving Tween 80 in 5 ml of 20 mM acetate buffer pH 5.5 **Surfactant:** Tween 80	Melt emulsification technique	Particle Size: 127.2 ± 2.1 nm Zeta potensial: -22.5 mv PDI: - EE: 85.34 ± 1.05 % LE: 6.7 ± 0.4 %	DPK-060 (synthetic 17 amino acid peptide, structurally derived from human protein kininogen)	Antimicrobial, Anti-inflammatory, Atopic Dermatitis	Controlled release and permeation profile of NLC gel DPK-060 are better compared to free DPK-060. This study demonstrates that the DPK-060 NLC gel-based formulation can be a novel, safe, and effective therapy option for AD.
[13]	**Solid lipids:** 0livem 1000 (2 g) **Liquid lipids:** Tea seed oil **(8 g)** **Surfactant:** Tween 80 (2-4 g) Varisoft 442 (2.5-5 g)	High speed homogenization technique at hot temperature	Particle Size: NLC-T 90-100 nm, NLC-V 90-100 nm, NLC-V 80-100 nm PDI: 0.1 – 0.8 Zeta Potetial: -	Tea Seed oil	Hair growth	An efficient substitute for promoting hair growth is NLC-C (with combination surfactant Tween 80 and varisoft 442) hair grower.Clearly, using a hair serum with NLC-C lessens the feeling of oiliness, grease, and stickiness after application.
[14]	**Solid lipid:** Tristearin (3.35-4%) **Liquid lipids:** NLC-EA1: Miglyol (1.65%) NLC-EA2: Labrasol (1%) **Surfactant:** Poloxamer 188 (2.5%) w/v) solution (95%)	Hot homogenization and ultrasonication	NLC-EA1 Particle Size: 197+-2.1 nm PDI: 0.36 Potential Zeta: - NLC-EA2 Perticle Size: 189.6+-3.9nm PDI :0.33 Zeta Potential: -	Ellagic Acid	Antioxidant, Skin whitening	Overall, these findings demonstrate that adding EA to NLCs can increase their water solubility and enable a dosage reduction. Furthermore, both varieties of NLC-EA retained their low toxicity. In light of these observations, the antioxidant activity data reported for both types of NLC-EA a lower activity with respect to EA solution, but the profile emerged from these tests underlines how NLC EA1 and NLC EA2 preserve the excellent antioxidant capacity of the active.
[15]	**Solid Liipids:** Glyceryl Behenate (Compritol CG 888 ATO) **Liquid lipids:** PEG-8 caprylic/capric glycerides (PCCG), caprylic/capric	Ultrasonication and high pressure homogenization (HPH)	HPH: Particle Size:218.4 nm ± 3.4 PDI: 0.135 ± 0.018 Zeta Potential: - Ultrasound:	Thymol	Anti-acne	Thymol-NLC have been shown to provide a prolonged Thymol release. In addition, the Thymol-NLC and free Tymol were dispersed into several gelling formulations increasing NLC stability and showing to form gel threads with NLC embedded within them. Thymol was effectively added to NLCs and distributed throughout a gelling system, indicating that it is a good

	NLC Component	Method of Preparation	Characteristics	Active Ingredient	Activity	Result
	triglyceride (Miglyol 812) CCTG **Surfactant:** Tween 20		Particle Size: 250.9±2.9 nm PDI: 0.139 ± 0.023 Zeta Potential: -			option for topical treatment of acne vulgaris as it kills harmful bacteria while preserving a balanced skin microbiome.
[16]	**Solid lipids:** Precirol ATO 5 (450 mg) **Liquid lipids:** labrafac lipophile WL1349 (100 mg), Tween 80 (60 mg) **Surfactant:** poloxamer 407 (450 mg)	Emulsification 5 minutes with a high pressure homogenizer (Ultra Turrax T18 IKA, Germany), and an average of 5 minutes of sonication	Particle Size: 72 ± 11nm PDI: - Zeta Potential: -EE: 84.56 ± 4.48% DL: 2.33 ± 0.10	Curcumin	Antioxidant	Antioxidant activity of CUR was preserved and enhanced when entrapped into the NLCs. Moreover, the non-cytotoxic CUR-NLCs presented a moderate anti-migration/proliferation effect onto dermal cell lines and allowed CUR penetration into a Strat-M® membrane. The antioxidant effect of curcumin can be enhanced by modification of the NLC structure.
[17]	**Solid lipids:** cocoa butter (1.5%) shea butter **(**1.5%) **Liquid Lipids:** Capmul MCM EP (0.3%) **Surfactants:** Transcusol (2%) Tween 20 (2%)	tip-sonication	Particle Size 246 and 498 nm PDI: 0.166±0.042 - 0.196± 0.016 EE: 95.9±10.5% - 96.8+-2.1% LC: 0.91 ± 0.04% - 0.97 ± 0.07%	Orobol	Anti-aging	The NLCs formulation containing shea butter was successfully optimized for improving the stability of orobol and enhancing its in vitro topical skin delivery. The NLCs significantly enhanced the deposition of orobol into the Strat-M membrane and human cadaver skin. Moreover, the NLCs formulation did not cause any skin irritation in the human study. Thus, the shea butter-based NLCs formulation prepared in this study could be a promising topical skin delivery system of orobol for enhancing the anti-skin-aging effect without skin irritation.
[18]	**Solid Lipids:** Compritol ATO 888, Gelucire 44/14 **Liquid Lipid:** Miglyol 812N **Surfactant:** Solutol HS 15	Ultrasonication	Particle Size 181.2 - 265.6 nm, PDI: 0.134 - 0.261 Zeta Potential: -29.9 - 19.2 mV EE: -	Cyclosporin	Atopic dermatitis	After application of NLC based gel for 7 days, the redness was gradually reduced; skin crust was slowly improved compared to the untreated group.

	NLC Component	Method of Preparation	Characteristics	Active Ingredient	Activity	Result
[19]	**Solid Lipids:** Glycerol monostearate **Liquid Lipid:** capyrol 90 (Lipid compound = 4%, ratio 70:30) **Surfactant:** Tween 20 (2%)	Emulsification and Ultrasonication Methods	Particle Size 245,3 ± 42.2 - 627,0 ± 20.8 nm PDI: 0,057±0,04 - 0,595±0.06; Zeta Potential: -49,1±10,8 - -30,7±6,6	Etodolac	anti-inflammatory, analgesic, and antipyretic activity	Free ETD can be considered safe, because it did not reduce cell survival below 88% after 24 h. In addition, ETD slightly increased cell viability (from 88.5% to 92.3%) after 24 h incubation in keratinocytes line. The cell viability of fibroblast lines for free ETD was around 100%. ETDencapsulatedinNLCformulationsessentially did not affect the viability of the fibroblast and keratinocyte cells (p values > 0.05), except for compared to NLC2 and ETD-NLC2 formulations after 4 h of incubation (both cell lines) where slight statistical significance has been observed (p = 0.02–0.04). The fibroblasts viability after 24 h of incubation with all unloaded formulations was markedly higher than after 4 h, while the keratinocytes viability after 24 h was lower than after 4 h of incubation (especially for NLC3 formulation in which cell viability after 24 h was 49.6%). In conclusion, the test indicated that pure ETD and NLC formulations in the concentration of lipid phase in the range from 1.25 to 2.5 mg/mL were no cytotoxic (cell viability over 80%), while for the NLCin the lipid concentration 6.25 mg/mL significant decrease in cell viability (even 50%) was observed (p values < 0.01).
[20]	**Solid Lipids:** tri-palmitin (240, 180, 480, 360, 1200, 900 mg)r Tristearin **(**240, 180, 480, 360, 1200, 900 mg**)** **Liquid lipids:** Transcutol (60, 120, 120, 240, 300, 600 mg) **Surfactant:** Tween 80 (2% w/v)	High Pressure Homogenization (UltraTurrax T25, IKA, Germany)	Particle Size 113,9 ± 1,39 - 283,9 ± 0,58 nm PDI: 0,228 ± 0,01 - 0,386 ± 0,02 Zeta Potential: −29,80 ± 0,82 - −16,90 ± 1,49 mV	5-FU	Anti-skin cancer	These results can be explained with the nanoranged size and also occlusive effect of lipid nanoparticles. As expected; lipid nanoparticles weakened the barrier property of stratum corneum and facilitated the penetration of 5-FU. Penetration/permeation studies were carried out with NLC enriched hydrogel and 5-FU hydrogel by using Franz diffusion cells for 6 h and the samples were applied to the rat skin for characterized topical Developed a new form of semiconductor preparation enriched with NLC that is promising for topical treatment of skin cance

	NLC Component	Method of Preparation	Characteristics	Active Ingredient	Activity	Result
[21]	**Solid Lipid:** beeswax **Liquid lipid:** lavender and peppermint essential oils mixture (Lipid phase **= 9,68%)** **Surfactant:** Lutrol F68 (3,03%)	heat pressure homogenization	Particle Size: 192.6 ± 0.8 nm PDI: 0.161 ± 0.019 Zeta Potential:−25.3 ± 0,17 mV EE: 87.16 ± 2.1%	Riluzole, Glutamate Release Inhibitor	Anti-proliferation in amyotrophic lateral sclerosis (ALS)	The NLC delivery system containing RLZ in combination with natural essential oil is a promising strategy against hyperproliferative keratinocyte conditions. The anti-proliferative effects of RLZ in keratinocyte cells promoting cell death. Multiple RLZ mechanisms of action, from promotion of cell cycle arrest to apoptosis sensitization, including autophagy, among others, have been proposed to be beneficial to treat numerous cancer types, but other conditions involving hyperproliferation of cells might benefit from its actions. In this sense, RLZ-NLCs would allow for a long-lasting slow release of RLZ suitable to treat uncontrolled proliferation of skin cells in pathologies such as psoriasis, skin dermatoses, actinic keratosis and others.
[22]	**Solid Lipids:** Apifil® GC (A) orGelucire®50/13 (G) or Plurol® stearique WL 1009 (P) or Tefose® 2000 CG (T) (90 mg) **Liquid Lipids:** White soft paraffin (150 mg), Liquid Paraffin (100 mg) **Surfactant:** Propylene glycol (100 mg)	Probe sonication (sonicator probe Sonifier® Model 250)	Particle Size: 84.91±8.61 nm - 318,50±33,23 nm ; PDI: 0,16±0,02 - 0,49±0,2 Zeta Potential: 23,00±0,00 – 46,50±2,12 mV	Routine	Sun Protective And antioxidant	Values of calculated SPF: these are in thefollowing order NLC-T > NLC-P > NLC-G > NLC A Antioxidant activity: Routine/DMSO, NLC-T and NLC-T + 5% TiO_2 are found to be 85µg/ml, 19.5µg/ml and 43µg/ml, respectively.
[23]	**Solid Lipids:** Labrafil M 2130 CS **Liquid lipid:** Labrafil M 2125 CS (Binary mixture 0.31827 - 3.6819%w/w) **Surfactant:** Cremophor RH40 (0,977 - 6.02269% w	Emulsification with ultra-sonication method	Particle Size:191 ± 5.20 nm PDI: 0.33 ± 0.01 Zeta Potential: −10,00 mV ± 0.30 EE: 92.85 ± 0,25% (quercetin), 89.05 ±0.18% respectively. (resveratrol).	Quercetin and resveratrol	Treatment of skin cancer	combination's cytotoxicity and anti-metastasis ability was also assessed using the A431 skin cancer cell line. The created simulation demonstrated the importance of the NLC and the included medications for better skin cancer treatment; nevertheless, more research is necessary to determine how to use them clinically.

	NLC Component	Method of Preparation	Characteristics	Active Ingredient	Activity	Result
[24]	**Solid Lipids:** Witepsol1 S51 (694 mg) **Liquid lipids:** Oleic acid (300 mg) **Surfactant:** Polysorbate 60 Polysorbate 80 (200 mg)	high-shear homogenization followed by the ultrasound	**MTX_NLC-P60** Particle Size: 292±2 nm PDI: 0,18±0,02 Zeta Potential: −39±3 mV. EE: 64±2% **MTX_NLC-P80** Particle Size: 292±9 nm PDI: 0,12±0,02 Zeta Potential: -37±3 nm EE: 64±4%	methotrexate	Psoriasis	MTX-loaded NLC-P60 ($P < 0.01$) when compared with free MTX. After 8 h the amount of MTX permeated through skin was 5.8 0.2 and 4.2 0.1% from NLCs-P60 and -P80, respectively while for free MTX was 3.6 0.2%. The outcomes demonstrated the possibility of NLC for methotrexate delivery in topical psoriasis therapy.
[25]	**Solid Lipid:** Precirol ATO 5 **Liquid Lipid:** Captex 300 (Solid lipid:Liquid lipid=1:1) **Surfactant:** Poloxamer 407 (0.5–2% w/v)	Hot homogenization (T 25 digital Ultra-Turrax)	Particle Size:278±10 nm PDI: 0.231±0.05 EE: 22.29±1.23%	methotrexat	Psoriasis	MTX-NLC gel showed the gradual release with more effective eradication of psoriatic manifestations when topically applied. The findings of this formulation pave the way for treatment of psoriasis with the topical colloidal formu lation of MTX. However, significance of MTX-NLC gel may only be established, when evaluated clinically.
[26]	**Solid lipids:**Glyceryl mono-stearate (0,8 %), Cholesterol (0,1 %), Stearic Acid (0,8 %). **Liquid lipid:** Oleic acid (0,3%) **Surfactant:** Span 60 (0,4%), Span 80 (0,4%), tween 20 (0,2%)	high-speed homogenization followed by ultra-probesonication method	**KA-NLC3** Particle Size 172.9 ±7.1 nm Zeta Potential: 39.1 ±2.7 mv EE: 76.4 ±0.1% DL: 17.6±1.3%	Kojic Acid	Hyperpigmentation	Kojicic Acid in NLC increases percutaneous delivery of Kojic Acid. Concentrations below 250 µg/mL were determined as suitable concentrations for KA-NLC_3. It seems to be biocompatible formulation for the cosmetics aims.
[27]	**Solid Lipid:** tristearin **Liquid Lipid:** Labrasol (Mixture 1%, 4:1) Captex 300 **Surfactant:** Tween 80	High thermal pressure homogenization	Particle Size: 268.3±2.5nm PDI: 0.218 ± 0.0012 Zeta Potential: -16.35 ± 0,21 mv EE: 87.29 ± 1.6%	Adapalene and Vitamin C (ascorbyl -6-	anti Acne Vulgaris	The NLCs showed higher skin-targeting potential in contrast to that seen with free ADA, and the adjuvant effect of antioxidant helped to aggravate the potential of ADA during the course of chronic therapy. NLCs as novel vehicles for adapalen skin administration and the beneficial effects of vitamin C in topical treatment.

	NLC Component	Method of Preparation	Characteristics	Active Ingredient	Activity	Result
				palmitate)		
[28]	**Solid Lipid:** Gelucire 53/13 **Liquid Lipid:** coconut oil (Solid lipid: liquid lipid=6:4, 2%)) **Surfactant:** Tween 80 and Transcutol P (ration 2:1)	Double emulsification	Particle iSze: 207.2 nm PDI: 0.257 Zeta Potential: -11.9 mV	5-flurouracil and cannabidiol	Treatment of non-melanoma skin cancer	Conventional formulation significantly reduces the tumor volume but FU-CBD-NLCs exhibit a higher inhibition rate. The higher tumor inhibition indicates that nanoformulations exhibit better penetration of 5-FU and CBD into the tumor environment. The produced gel presents itself as a potentially effective formulation method for the management of skin cancer.
[29]	**Solid Lipids:** Precirol ATO 5 **Liquid Lipids:** Capyrol 90 (Lipid Mixture ratio 70:30, 60:40, 50:50) **Surfactant:** Poloxamer 188 (19.17 2.35 g/mL) Tween80(196.29 14.08 g/mL)	Double emulsion (w/o/w)	Particle Size: 331.8±29.1 - 509.2 18.3nm PDI: 0.031± 0.03 - 0.36±0.01 EE EGF: 79.0 ±1.9 - 81.1 0.8% EE Curcumin: 99.2±0.0 - 99.4 0.1%	epidermal growth factor (EGF) and curcumin	Chronic diabetic wound healing	The wound closure rate with EGF–Cur-Mix increased more than that with EGF–Cur-NLC over time. EGF–Cur-NLC accelerated wound closure and improved the antioxidant activity in the wound. EGF–Cur-NLC accelerated wound healing by inducing an antioxidant e ect and by stimulating the migration/proliferation of keratinocytes and fibroblasts
[30]	**Solid Lipid**: Compritol 888 ATO 8% w/w) **Liquid lipid:** Labrafac (2% w/w) Transcutol P (27% w/w) **Surfactant:** Poloxamer 407 (5% w/w)	Phase inversion and temperature cycling method	Particle Size: 154.7 ± 10.5 nm PDI: 0.38 ± 0.02 Zeta Potential: −19.4±4.1 mV EE: 99.0 ± 0.008%	Itraconazole	Antimikrobial	Topical application of ITC-LNC in a gel vehicle increased dermal retention of ITC in excised human skin relative to a conventional gel and ITC-NLC gel. In a preclinical study, both ITC-loaded nanocarrier-based gels and conventional ITC gel therapies proved qualitatively efficacious for the treatment of induced cutaneous candidiasis in rats with no histo pathological changes in the epidermal and dermal layers of the skin when applied for 14 consecutive days
[31]	**Solid Lipid:** Compritol®888ATO **Liquid Lipid:** Linseed oil (Lipid consentration = 120 mg) **Surfactant:** Tween 80 (30 mg)	Probe Sonicator	Particle Size: 210.86 nm PDI: 0.263 Zeta Potntial: -26.79 mV EE: 86.74%	β-caryophyllene	Antioxidant	gnificant antioxidant activity, could be the explanation for the effective antioxidant potential in the BCP-NLC. The observed antioxidant ac tivity of the BCP-NLC was 80.12%, while the antioxidant activity of ascorbic acid was de termined to be 94.92%, antioxidants. It is hypothesized that the synergistic impact of BCP in combination with Transcutol P, which possesses significant antioxidant activity, could be the explanation for the effective

	NLC Component	Method of Preparation	Characteristics	Active Ingredient	Activity	Result
						antioxidant potential in the BCP-NLC. The observed antioxidant activity of the BCP-NLC was 80.12%, while the antioxidant activity of ascorbic acid was determined to be 94.92% NLC containing beta-caryophyllene have the potential to be studied for use as a method of topical administration on skin abnormalities with increased skin retention and effectiveness.
[32]	**Solid Lipid:** Myristic acid (C14:0) (1 – 15,5%) **Liquid Lipid:** natural plants oil (Sunflower, corn oil, peanut, olive oil, Sweet almond, castor, virgin coconut, Eucalyptus oil) (1-1,5%) (Solid lipid:liquid lipid ratio=60:40, 40:60) **Surfactant:** Span 80 (2%)	mini-emulsions methodologywith Ultrasonication step	Particle size 156.8±5.52 nm - 194.5± 25.65 nm PDI: 0.197 - 0.294 Zeta Potential: -46mV - -61mV	natural plants oil (Sunflower, corn oil, peanut, olive oil, Sweet almond, castor, virgin coconut, Eucalyptus oil)	Antimikrobial	The NLC-SF and NLC-CO systems, which havea very similar saturated vs.unsatu rated composition, showed asignificant difference in antimicrobialactivity, withNLC-SF showing a stronger inhibitionon bacterial growth than NLC-CO. It may indicate that other bioactive compounds from NPO (e.g., polyphenolic compounds) compositions could have a higher antimicrobial impact than the present FFAs. One potentially useful approach for the treatment of skin infections is the incorporation of natural oils into NLC formulations.
[33]	**Solid Lipid:** Cetyl palmitate (8% w/w) **Liquid ipid:** Transcutol®P (2% w/w), medium chain triglycerides, (MCT) (2% w/w), Oleic acid (2% w/w) **Surfactant:** Tego®Care 450 (1,8% w/w) or Poloxamer 188 (2,5% w/w)	High pressure homogenization	Particle Size: 163.2±1.2 - 175.5±1.9 nm PDI: 0.009±0.011 - 0.087±0.023Zeta Potential: -57.0±1.7 - -29.0±0.5 mV EE: almost 100%	Cannabidiol	Antiinflamatory	CBD extract solution at a concentration of 0.8 g/mL inhibited IL-6 production induced by LPS by 15.7%. CBD-NLC4 (37.0%) and CBD-NLC3 (24.3%) showed higher inhibition percentages than the CBD extract solution even though they showed lower CBD release.
[34]	**Solid Lipid:** Compritol® ATO 888 **Liquid Lipid:** Oleic acid (Solid lipid: Liquid lipid = 65:35, 70:30, 75:25) **Surfactant**:	microemulsion Thecnique	Particl Size: 137.9±0.45 - 211.4±0.02 nm PDI: 0,224 – 0,462 Zeta Potential: −20.5 - −16.3 mV EE:	Clobetasol	Various skin disorders, such as vitiligo, atopic dermatitis,	The anti-inflammatory activity of the optimized formu lation was evaluated by the carrageenan-induced hind paw inflammation method on Wistar albino rats. The percentage inhibition value of CP-NLC gel (test) was compared to marketed TEMOVATE gel (standard). Test formulation not only decreased the inflammation

	NLC Component	Method of Preparation	Characteristics	Active Ingredient	Activity	Result
	poloxamer 188 (1,25; 1,5; 1,75 %e,v)		63.24±0.71 - 78.50±0.03% DL: 12.38±0.24 - 14.36±0.78 (% w/w)		pruritus eczema, and psoriasis	by a greater magnitude but also sustained the effect for a prolonged period..
[35]	**Solid Lipid:** Glyceryl mono stearate (0,7 g) **Liquid Lipid:** Capric acid (0,3 mL, **Surfactant:** lecitin (0,5 mL), tween 80 (0,2 mL)	Emulsion-evaporation-solidification	Particle Size: 41.57 ± 1.96 - 44.28 ± 2.32nm PDI: 0.290 - 0.348 Zeta Potential: − 31.5 ± 6.87 to − 43.1 ± 4.69 mV EE: 83.29±0.47% DL: 1.43 ± 0.01 - 3.97% ± 0.02	Propolis	Antioxidant, antibacterial and antifungal, wound healing.	Propolis-NLCs possessed a potent antioxidant activity compared with ascorbic acid ($p < 0.0001$) and propolis-EXTR. The propolis-NLCs exhibited DPPH inhibition of 58.50, 62.07, and 65.47% for the samples containing 25, 50, and 75 mg propolis, respec tively. It has also been reported that the antioxidant activity of the propolis-NLCs was attributed to their high content of phenolic and non-phenolic compound contents that could preventively attack free radicals during the oxidation reaction. Propolis-NLCs exhibited 26 mm IZD B. subtilis ATCC 6633 with 125 µg/mL MIC, 27 mm IZD for S. aureus ATCC 25,923 with 31.25 µg/mL MIC, and 18 mm IZD against Salmonella spp. with 125 µg/mL. Similarly, the IZD was 14 mm for E. coli ATCC 25,922 and S. epidermis with MIC 500 µg/mL and 250 µg/mL successively. Contrastively, we observed that the gel containing the propolis-EXTR manifested a lower antibacterial activ ity against the tested strain.
[36]	**Solid Lipid:** Pericrol (500 mg) **Liquid Lipid:** Labrafac (125 mg) **Surfactant:** tween 80 (1%)	Hot emulsification followed by probe sonication methods.	Particle Size: 96.17±0.919 nm, PDI: 0,257 Zeta Potential -15.2± 0.566 mV.the fixing efficiency is 70.5 ± 1.65% and the	Curcumin	Skin Deposition	The curcumin use is limited due to its poor solubility and bioa vailability. The NLC based formulation can be utilized for topical de livery of curcumin to improve its targeting ability to skin layers with prolonged retention in the skin layers. The prepared curcumin-NLC dispersion exhibited controlled release compared to free drug. The ex vivo drug release study revealed the improved permeation and reten tion of curcumin in the skin layers. The NLC dispersion exhibited high antibacterial activity, and the skin irritation study revealed that the prepared formulation is safe for topical application.

	NLC Component	Method of Preparation	Characteristics	Active Ingredient	Activity	Result
[37]	**Solid Lipid:** Compritol®888 ATO **Liquid Lipid:** Miglyol® 812(Lipid compound 2% w/v) **Surfactant:** polysorbate 80 (1% w/v)	microemulsion	Particle size: 153.54±2.09nm PDI: 0,01 Zeta Potential: 36.20±0.93 mV EE: 92.29±1.54% DL: 2.84±0.04%	Argan Oil	Skin Hydration	Conclusively it was demonstrated that FA loaded NLCs offered enhanced solubility of the drug FA and favored deposition of FA into the epidermis, which is the site of the hyper-proliferation of keratinocytes and site for psoriasis development. Selective accu mulation of FA in the epidermis might eliminate adverse side effects associated with systemic exposure. The incorporation of the therapeutic moiety into nanoparticles (FA loaded NLCs) suc cessfully provided a better therapeutic effect in order to manage the hyperproliferation of keratinocytes.
[38]	**Solid Lipid:** Glyceryl monostrearat **Liquid Lipid:** Azadirachta indica seed Oil (Solid lipid:Liquiud lipid **=** 70:30, total 3%**)** **Surfactant:** tween 80 (10%)	Hot melt emulsification and ultrasonication	Particle Size: 296.9 nm nm PDI: - Zeta Potential: −23.6 mV to −38 mV EE: 92.7% DL: 85.97%	Vetiveria zizanoides Oil	prickly heat treatmentP	A comparatively broader zone of growth inhibition i.e., (2570 ± 189 mm) was observed for the optimized NLC containing gel as compared to vetiver oil alone (11±31±0±21 nm). Placebo gel of carbop A potentially effective product for the treatment of sweat flakes is perfumed root oil gel based on NLC.
[39]	**Solid Lipid:** *Cetyl alcohol* **Liquid Lipid:** Oleic Acid (mixture lipid compound 2%) **Surfactant:** tween 80 (3-5%) **Co-Surfactant:** Propyleneglycol (6-8%)	High-Speed Stirring and Ultra-Sonication	Particle Size: 189,8 – 632,8 nm PDI: 0,387-0,582 Zeta Potential: - 7,37 mV	Callus Mulberry Leaf Extract	Tyrosinase enzyme inhibitor	The callus extract of mulberry leaves (Morus alba L.) and the NLC gel of mulberry leaf callus extract (Morus alba L.) can provide strong tyrosinase enzyme inhibition activity with IC50 values of 72.51 µg/ml and 79.69 µg/mL.

DISCUSSION

Component NLC

The main components of NLC are solid and liquid lipids. Most NLCs also use surfactant in their components, although not all use them. Solid lipids that are commonly used as NLC components are mono-, di-, and triglyceryl monostearate, such as Precirol®ATO5 (glycery distearate), Compitrol®888ATO (gliceryl dibehenate), Dynasan 114® (glyseryl trimyristate, C14), Dynassan®116 (glycery tripalmitate, C16), Dynasen®118 (glyseryl tristearat, C18), Imwitor®900K (a mixture of mono and diosilgliserol based on hydrogenated fatty acids containing 40–55% glyseryle monostearat), and Softisan®100 (mixture of triglicerides composed of fatty acid with chains from C10 to C18) [40], Witepsol1S51 mixture (65–80%), diglycerides (10–35%), and monoglycerids (15%-15%), Gelu®(50/13), Plurol, Steurol®, W.L.

Stearic acid, a saturated fatty acid with an 18-carbon chain (C18), is a frequently used fatty acid. When applied to NLC, it makes the lipid matrix more flexible, which presents a chance to hold a lot of drug molecules. [40]. Another class of lipids derived from fatty acids is fatty alcohols, which also have high safety and tolerance. Examples include cetyl alcohol and stearyl alcohol [41]. Because this kind of lipid can disrupt the skin's lipid storage, it can be utilized in conjunction with absorption boosters. Because this kind of lipid can disrupt the skin's lipid storage, it can be utilized in conjunction with absorption boosters. Another family of frequently used solid lipids are ceramides, which are mostly made up of fatty alcohols and fatty acid esters. Additional examples include palmite seed, cocoa butter, bee candles, and carnauba candles. The three solid lipids that are most frequently employed in the NLC formula, according to search results on 33 articles, are Pericrol ATO 5 (4 articles) [16][25][29] [36], glycerol monostearate (6 articles) [7][11][19][26][35][38]; and compitrol 888 ATO (8 articles) [9][12][15][18][30][31][34][37]. Other solid lipids used in the 33 reviewed articles are Staric acid [8][26]; Tristearin [14][20][27]; softisan 100 [10], Olivem 1000 [13], Cocoa buter and Shea butter [17], Tri-palmitin [20], Beeswax [21], Apifil® GC (A), Gelucire®50/13 (G), Plurol® stearique WL 1009 (P), Tefose® 2000 CG (T) [22][28]; Labrafil M 2130 CS [23], Witepsol1 S51 [24], Cholesterol [26], Myristic acid [32], cetyl palmitate [33], Cetyl alcohol [39].

Almond oil, olive oil, oleic acid, squalene (shark liver oil), ricin, or ricin oil are among the oils high in fatty acids that fall under the category of liquid lipids. The most widely used medium chain triglycerides are capryol (monocaprilate propylen glycolate), labrafac (medium chain triglyceride derived from caprilic acids), labrafil ides associated with polyethylene glycol esters (PEG) (gliser-Maisine (glyceryl monolinolate), lambrycol (monolaurate glycol propylene), and migliol ®810 and ®812 (caprilic acid esters) [42]. According to the findings of a library search for 33 articles, liquid lipids that are most frequently utilized are Miglyol (5 articles) [12][14][15][18][37]; Oleic Acid (4 articles) [24][26][34][39]; Transcutol (3 articles) [20][30][33]; and Labrafac (3 articles) [16][30][36]. Other liquid lipids are Labrafil [10][23]; Capyrol [19][29]; Capmul MCM [7][17]; Captex 300 [25][27]; MCT 812 [9]; PEG 8 caprylic [15]; Capric acid [35]; white soft paraffin and liquid paraffin [22]. Some articles use natural plant oil as a liquid lipid, for example Babchi oil [8], Tea seed oil [11][13] Coconut oil [28], Linseed oil [31], Sunflower oil, corn oil, peanut oil, olive oil, Sweet almond oil, castoroil, virgin coconut oil, Eucalyptus oil [32], Azadichta indica seed oil [38].

The use of solid lipids and liquid lipids in the 33 reviewed articles produces NLC characteristics, including particle size, PDI, zeta potential, and %EE that meet the requirements. However, There are two articles was found where one of its formulas has a particle size exceeds the recommended size of 50-300 nm [42], the particle size particle size reaches 498 nm [17], with solid lipid and liquid lipid components shea butter and capmul MCM. The highest particle size reaches 632,8 nm, with solid lipid and liquid lipid components cetyl alcohol and oleic acid [39]. The smallest particle size is 18 – 20 nm, with components of solid lipids and liquid lipids compritol 888 ATO dan MCT 812 [9].

To achieve improved functional properties and physical stability, surfaces of non-ionic or ionic (anionic, cationic) surfactants that are soluble in oil and water are typically employed in the production of NLC rather than a single surfactant [40]. Surfactant are used in water-containing NLC, with a mechanism to lower surface tension between oil and water phases. Tyloxapol, polysorbates (Tween 20, 40, 60, 80), sorbitons (Span 20, 40, 60, 80), esters of sorbitol, and triblock copolymer of polyoxypropylene

(poloxamers) are the most often utilized nonionic surfactants in the manufacturing of NLC. Moreover, laurate, oleate, palmitate, and stearate acid esters are frequently utilized. Non-ionic surfaces are favored for use because of their non-irritative and non-toxic profile. This is especially true for cutaneous and transdermal formulations, as non-ionic-charged molecules do not interfere with the lipids that make up the surface, unlike surface agents with ionic charges. Polysorbat or tween 80 (15 articles) [10][11][12][13][20][24][27][28][29][31][35][36][37][38][39]; Polysorbat or tween 20 (5 articles) [11][15][17][19][26]; and Poloxamer 188 (4 articles) [14][29][33][34]; are the two most often used surfactants, according to the search results of 33 articles. Other surfactant used in the 33 reviewed articles are Myrj [7][9]; Sodium Lauryl Sulfate [8], Plantacare 2000 [11], Varisoft [13], Poloxamer 407 [16][23][30]; Transcutol [17][28], Solutol HS [15][18]; Lutrol F68 [21], Propylenglycol [22], Cremophore RH40 [23], Polysorbat or Tween 60 [24], Span 60 and Span 80 [26][32], Tego care 450 [33], Lecitin [35].

NLC Manufacturing Method

Several methods have been effectively employed to produce NLC. These include phase inversion, double emulsions, ultrasonic, membrane contractor techniques, high pressure homogenization (HPH), microemulsion, emulsification solvent evaporation method, emulsion solvent diffusion method, solvent injection (or solvent transfer method), and phase inversion. Nonetheless, HPH is the recommended approach because it has been utilized in the pharmaceutical sector to create nutritional emulsions and is thus a suitable approach for large-scale [42]. The advantages of HPH are short production times, ease of production, organic solvent-free operation, and scale-up feasibility [2]. High-pressure homogenization methods are performed using Ultra Turrax devices, is the second most used in the 33 reviewed articles [10][11][15][16][20][21][26][27][33]. Some commonly used types are T25 and T18. The most widely used manufacturing method in the 33 articles reviewed is ultrasonication as many as 13 articles [7][8][13][14][15][17][18][22][24][26][31][38][39], even more because there are some articles combining ultrasonication methods with other methods. Like a combination of emulsification [19][23][32][36], combination with high pressure homogenization [15][26]. The instrument used in the ultrasound method is the ultrasonicator or probe sonicator. Another method used in the 33 reviewed articles are microemulsion method [34][37]; solvent emulsification-diffusion method [12], solvent emulsification-evaporation method [9][35]; double emulsion method [28][29]; phase ınversion temperature (PIT) method [30].

Characteristic NLC

Similar to other colloidal carriers, NLC characterisation is crucial for evaluating the delivery system's discharge kinetics, stability, and quality. This is a challenging job for NLC since the lipid's complex properties and small size make the system dynamic. Characterization methods include measurement of particle size and distribution, structural properties, particle surface load and morphology, changes in crystallinity, polymorphism and lipid thermal behavior. Most studies don't examine the general trait above in their research. Characteristics that most researchers do are particle size, polydispersity index (PDI), and zeta potential. Some researchers added the characteristics of Entrapment Efficiency (EE) and Drug Loading (DL)[43]. Particle size and distribution are important characteristics that have an influence on the stability, solubility, release rate and biological performance of NLC. The average NLC diameter ranges from 10 to 1000nm. However, the 50-300 nm range is recommended for location-specific administration, mainly for chemotherapeutic drugs and illnesses of the central nervous system. diameters between 50 and 300 nm facilitate barrier crossing, enhance cellular absorption, and have a quick action, whilst diameters over 300 nm offer prolonged drug delivery. Additionally, during storage, particle size should remain within a specific range as it indicates the stability of NLC. Particle size increases during storage are a sign of physical instability and agglomeration [42].

The electrical potential of a particle that is not on its surface but rather extends into a diffusion layer is known as the Zeta potential (ZP), and it is associated with the movement of particles in a liquid matter known as a gliding or sliding field. It is intimately linked to the stability of the suspension and the shape of the particle surface. ZP is dependent on the particle as well as its surroundings, including pH, ionic strength, and the kind of ions present, unlike particle size or molecular weight. Important details regarding the long-term stability and clumping propensity of nanoparticles are provided by the ZP. Overall, there is remarkable stability with the ZP ± 60mV. However, a minimum of ± 30 mV is needed

for satisfactory stability of electrostatically stabilized nanodispersions, and a minimum of ± 20 m ZP is needed in situations where stability is achieved through electrostatic and sterile stabilization. [44].

The term "particle morphology" describes an object's outside features, such as its surface's form and structure. Compared to ball particles, anisometric particles have a higher surface area and a shorter diffusion path. Non-ball particles require a higher amount of surface agent to stabilize them because of their bigger surface area. Moreover, pharmacokinetics, biodistribution, drug load, encapsulation effectiveness, and targeted NLC administration are all strongly impacted by particle form. Additionally, it is crucial for receptor binding, cellular absorption, and cell interaction [45]. In order to obtain a stable NLC, it is necessary to characterize the crystallinity and degree of lipid modification. Furthermore, the state of the crystals and the modification of the lipids can affect the absorption efficiency and kinetics of the release. Most NLC production processes involve the formation of hot microemulsions, by heating the lipids above the melting point and then saturating them by dispersing them in a liquid stabilizer solution. Most NLC lipid mixtures produce a decrease in the melly point which causes the lipid to crystallize at temperatures well below the malty point. Crystallization and lipid compression occur only when the mixture is cooled below its critical crystallization temperature [42].

Entrapment Efficiency (EE) is a crucial component that must be maximized during the formulation design process because it influences both the drug release and the formulation's economic viability. This represents the effectiveness of the NLC formulation and is expressed as a percentage of the drug trapped in the nanoparticles. Because lipophilic medicines dissolve uniformly in lipids, their trapping efficiency is great. Additionally, following cooling, hard solid lipid particles form, increasing clamping and keeping the medication confined in the lipid system. Higher EE is indicated by lipids with defects in their crystal structure. The presence of liquid lipids in NLC causes crystal structures to become more defective, which raises EE [42].

NLC Activity

Activity of NLC depends on each active ingredient contained in the NLC. of the active ingredients in NLC in the topical preparation on 33 articles reviewed are anti fungus, anti acne, anti aging, antimicrobial, anti-inflammatory, atopic dermatitis, sunscreen, psoriasis, anti hyperpigmentation, anti skin cancer, antioxidants, various skin disorders, such as vitiligo, atopic dermatite, pruritus eczema, and sweat flakes. One reviewed article suggests that NLC inserted in orobol as an anti-aging, can enhance the stability of orobols and improve topical delivery on the skin [17]. It suggested that a wide variety of active ingredients can be inserts into the filling carrier system in the NLC delivery system. The active ingredients are usually substances with low solubility in water, fatty oils [46][47], essential oils [48], and other substances that have problems with their water-solubility. Nano-structured lipid carrier containing a variety of active ingredients in it, has the potential to enhance retention and effectiveness in the skin. So the preparation that the active ingredient formulated in NLC can produce better activity compared to the active substance formulated directly in the conventional preparation. This can be seen from the penetration test results and activity test of each reviewed article. For example, Thymol-NLC have been shown to provide a prolonged Thymol release. In addition, the Thymol-NLC and free Tymol were dispersed into several gelling formulations increasing NLC stability and and showing to form gel threads with NLC embedded within them. Thymol was effectively added to NLCs and distributed throughout a gelling system, indicating that it is a good option for topical treatment of acne vulgaris as it kills harmful bacteria while preserving a balanced skin microbiome [15]. Antioxidant activity of curcumin was preserved and enhanced when entrapped into the NLCs. Moreover, the non-cytotoxic CUR-NLCs presented a moderate anti-migration/proliferation effect onto dermal cell lines and allowed CUR penetration into a Strat-M® membrane [16]. The NLCs formulation containing shea butter was successfully optimized for improving the stability of orobol and enhancing its in vitro topical skin delivery. The NLCs significantly enhanced the deposition of orobol into the Strat-M membrane and human cadaver skin. Moreover, the NLCs formulation did not cause any skin irritation in the human study. Thus, the shea butter-based NLCs formulation [17].

▪ CONCLUSION

A review that discusses NLC related to components, manufacturing methods, characteristics, and activity enhancement of active ingredients is needed to form a stable and optimal NLC formula. Components that are widely used are: Solid lipids are Glycerol monostearate, Compitrol 888 ATO, and Tristearin; Liquid lipids are Myglyol, Transcutol, and Oleic Acid; surfactants are Polysorbate or tween 80, and Polysorbate or tween 20. The widely used manufacturing method is ultrasonication. The characterizations are particle size, polydispersity index (PDI), and zeta potential. Some researchers add the Entrapment Efficiency (EE) characteristic. The active ingredient formulated in NLC can produce better activity compared to the active substance formulated directly in the conventional preparation. The application of nanostructured lipid carrier (NLC) nanoparticles on the skin is very beneficial. These nano systems have shown promising results and more commercial formulations, so it is expected to be done in further research. Because the lipid structure of the carrier has a close resemblance to that of our biomembranes, drugs channelled using NLC are more profitable than polymer systems. NLC-based active ingredient delivery systems are applicable to a range of topical treatments and cosmetic items. Owing to its biocompatibility, stability, increased drug load, and biological appropriateness of NLC research subjects will be highly valued in the medical field.

Ackonwledgements: The author thanked the Universitas Muhammadiyah Ahmad Dahlan Cirebon and the Universitas Ahmad Dahlan for providing excellent infrastructure facilities for the literary review.

REFERENCES

[1] C. Viegas, A. B. Patrício, J. M. Prata, A. Nadhman, P. K. Chintamaneni, and P. Fonte, "Solid Lipid Nanoparticles vs. Nanostructured Lipid Carriers: A Comparative Review," *Pharmaceutics*, vol. 15, no. 6, p. 1593, May 2023, doi: 10.3390/pharmaceutics15061593.

[2] V.-A. Duong, T.-T.-L. Nguyen, and H.-J. Maeng, "Preparation of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers for Drug Delivery and the Effects of Preparation Parameters of Solvent Injection Method," *Molecules*, vol. 25, no. 20, p. 4781, Oct. 2020, doi: 10.3390/molecules25204781.

[3] C.-L. Fang, S. A. Al-Suwayeh, and J.-Y. Fang, "Nanostructured Lipid Carriers (NLCs) for Drug Delivery and Targeting," *Recent Pat Nanotechnol*, vol. 7, no. 1, pp. 41–55, Nov. 2012, doi: 10.2174/1872210511307010041.

[4] V. R. Salvi and P. Pawar, "Nanostructured lipid carriers (NLC) system: A novel drug targeting carrier," *JDrug Deliv Sci Technol*, vol. 51, pp. 255–267, Jun. 2019, doi: 10.1016/j.jddst.2019.02.017.

[5] S. Shidhaye, R. Vaidya, S. Sutar, A. Patwardhan, and V. Kadam, "Solid Lipid Nanoparticles and Nanostructured Lipid Carriers – Innovative Generations of Solid Lipid Carriers," *Curr Drug Deliv*, vol. 5, no. 4, pp. 324–331, Oct. 2008, doi: 10.2174/156720108785915087.

[6] A. Sharma and A. Baldi, "Nanostructured Lipid Carriers: A Review," 2018, doi: 10.4172/2329-6631.1000191.

[7] Y. G. Na *et al.*, "Development and evaluation of a film-forming system hybridized with econazole-loaded nanostructured lipid carriers for enhanced antifungal activity against dermatophytes," *Acta Biomater*, vol. 101, pp. 507–518, Jan. 2020, doi: 10.1016/j.actbio.2019.10.024.

[8] M. Qureshi *et al.*, "Berberine loaded dermal quality by design adapted chemically engineered lipid nano-constructs gel formulation for the treatment of skin acne," *J Drug Deliv Sci Technol*, vol. 66, Dec. 2021, doi: 10.1016/j.jddst.2021.102805.

[9] Z. Zhao *et al.*, "Development and evaluation studies of Corylin loaded nanostructured lipid carriers gel for topical treatment of UV-induced skin aging," *Exp Gerontol*, vol. 153, p. 111499, Oct. 2021, doi: 10.1016/j.exger.2021.111499.

[10] C. Carbone *et al.*, "Clotrimazole-loaded mediterranean essential oils NLC: A synergic treatment of Candida skin infections," *Pharmaceutics*, vol. 11, no. 5, May 2019, doi: 10.3390/pharmaceutics11050231.

[11] W. Chaiyana *et al.*, "Dermal delivery enhancement of natural anti-ageing compounds from *Ocimum sanctum* linn. Extract by nanostructured lipid carriers," *Pharmaceutics*, vol. 12, no. 4, Apr. 2020, doi: 10.3390/pharmaceutics12040309.

[12] A. Javia, A. Misra, and H. Thakkar, "Design and pharmacodynamic evaluation of DPK-060 loaded Nanostructured lipid carrier embedded gel for dermal delivery: A novel approach in the treatment of atopic dermatitis," *Colloids Surf B Biointerfaces*, vol. 217, p. 112658, Sep. 2022, doi: 10.1016/j.colsurfb.2022.112658.

[13] P. Riangjanapatee *et al.*, "Development of Tea Seed Oil Nanostructured Lipid Carriers and In Vitro Studies on Their Applications in Inducing Human Hair Growth," *Pharmaceutics*, vol. 14, no. 5, 2022, doi: 10.3390/pharmaceutics14050984.

[14] S. Singh Hallan *et al.*, "Ellagic Acid Containing Nanostructured Lipid Carriers for Topical Application: A Preliminary Study," *Molecules*, vol. 25, no. 6, p. 1449, Mar. 2020, doi: 10.3390/molecules25061449.

[15] C. Folle *et al.*, "Gel-Dispersed Nanostructured Lipid Carriers Loading Thymol Designed for Dermal Pathologies," *Int J Nanomedicine*, vol. Volume 19, pp. 1225–1248, Feb. 2024, doi: 10.2147/IJN.S433686.

[16] R. Calderon-jacinto, P. Matricardi, V. Gueguen, G. Pavon-djavid, E. Pauthe, and V. Rodriguez-ruiz, "Dual Nanostructured Lipid Carriers/Hydrogel System for Delivery of Curcumin for Topical Skin Applications," *Biomolecules*, vol. 12, no. 6, 2022, doi: 10.3390/biom12060780.

[17] M.-H. Kim *et al.*, "Lipid Nanoparticles for Enhancing the Physicochemical Stability and Topical Skin Delivery of Orobol," *Pharmaceutics*, vol. 12, no. 9, p. 845, Sep. 2020, doi: 10.3390/pharmaceutics12090845.

[18] S. Wairkar, D. Patel, and A. Singh, "Nanostructured lipid carrier based dermal gel of cyclosporine for atopic dermatitis-in vitro and in vivo evaluation," *J Drug Deliv Sci Technol*, vol. 72, 2022, doi: 10.1016/j.jddst.2022.103365.

[19] A. Czajkowska-Kośnik *et al.*, "Nanostructured Lipid Carriers Engineered as Topical Delivery of Etodolac: Optimization and Cytotoxicity Studies," *Materials*, vol. 14, no. 3, p. 596, Jan. 2021, doi: 10.3390/ma14030596.

[20] G. Amasya, B. Aksu, U. Badilli, A. Onay-Besikci, and N. Tarimci, "QbD guided early pharmaceutical development study: Production of lipid nanoparticles by high pressure homogenization for skin cancer treatment," *Int J Pharm*, vol. 563, pp. 110–121, May 2019, doi: 10.1016/j.ijpharm.2019.03.056.

[21] X. Llorente *et al.*, "Riluzole-Loaded Nanostructured Lipid Carriers for Hyperproliferative Skin Diseases," *Int J Mol Sci*, vol. 24, no. 9, 2023, doi: 10.3390/ijms24098053.

[22] R. Kamel and D. M. Mostafa, "Rutin nanostructured lipid cosmeceutical preparation with sun protective potential," *J Photochem Photobiol B*, vol. 153, pp. 59–66, Dec. 2015, doi: 10.1016/j.jphotobiol.2015.09.002.

[23] M. Imran *et al.*, "Topical nanostructured lipid carrier gel of quercetin and resveratrol: Formulation, optimization, in vitro and ex vivo study for the treatment of skin cancer," *Int J Pharm*, vol. 587, Sep. 2020, doi: 10.1016/j.ijpharm.2020.119705.

[24] M. F. Pinto, C. C. Moura, C. Nunes, M. A. Segundo, S. A. Costa Lima, and S. Reis, "A new topical formulation for psoriasis: Development of methotrexate-loaded nanostructured lipid carriers," *Int J Pharm*, vol. 477, no. 1–2, pp. 519–526, Dec. 2014, doi: 10.1016/j.ijpharm.2014.10.067.

[25] V. Avasatthi, H. Pawar, C. P. Dora, P. Bansod, M. S. Gill, and S. Suresh, "A novel nanogel formulation of methotrexate for topical treatment of psoriasis: optimization, *in vitro* and *in vivo* evaluation," *Pharm Dev Technol*, vol. 21, no. 5, pp. 554–562, Jul. 2016, doi: 10.3109/10837450.2015.1026605.

[26] K. Khezri, M. Saeedi, K. Morteza-Semnani, J. Akbari, and A. Hedayatizadeh-Omran, "A promising and effective platform for delivering hydrophilic depigmenting agents in the treatment of cutaneous hyperpigmentation: kojic acid nanostructured lipid carrier," *Artif Cells Nanomed Biotechnol*, vol. 49, no. 1, pp. 38–47, Jan. 2021, doi: 10.1080/21691401.2020.1865993.

[27] A. Jain *et al.*, "A synergistic approach of adapalene-loaded nanostructured lipid carriers, and vitamin C co-administration for treating acne," *Drug Dev Ind Pharm*, vol. 42, no. 6, pp. 897–905, Jun. 2016, doi: 10.3109/03639045.2015.1104343.

[28] N. Hasan *et al.*, "Advanced multifunctional nano-lipid carrier loaded gel for targeted delivery of 5-flurouracil and cannabidiol against non-melanoma skin cancer," *Environ Res*, vol. 233, p. 116454, Sep. 2023, doi: 10.1016/j.envres.2023.116454.

[29] H.-J. Lee, M. Jeong, Y.-G. Na, S.-J. Kim, H.-K. Lee, and C.-W. Cho, "An EGF- and Curcumin-Co-Encapsulated Nanostructured Lipid Carrier Accelerates Chronic-Wound Healing in Diabetic Rats," *Molecules*, vol. 25, no. 20, p. 4610, Oct. 2020, doi: 10.3390/molecules25204610.

[30] N. A. El-Sheridy, A. A. Ramadan, A. A. Eid, and L. K. El-Khordagui, "Itraconazole lipid nanocapsules gel for dermatological applications: In vitro characteristics and treatment of induced cutaneous candidiasis," *Colloids Surf B Biointerfaces*, vol. 181, pp. 623–631, 2019, doi: 10.1016/j.colsurfb.2019.05.057.

[31] M. Ghazwani, U. Hani, M. H. Alqarni, and A. Alam, "Beta Caryophyllene-Loaded Nanostructured Lipid Carriers for Topical Management of Skin Disorders: Statistical Optimization, In Vitro and Dermatokinetic Evaluation," *Gels*, vol. 9, no. 7, p. 550, Jul. 2023, doi: 10.3390/gels9070550.

[32] D. P. C. de Barros, P. Reed, M. Alves, R. Santos, and A. Oliva, "Biocompatibility and Antimicrobial Activity of Nanostructured Lipid Carriers for Topical Applications Are Affected by Type of Oils Used in Their Composition," *Pharmaceutics*, vol. 13, no. 11, p. 1950, Nov. 2021, doi: 10.3390/pharmaceutics13111950.

[33] B. Morakul, V. B. Junyaprasert, K. Sakchaisri, and V. Teeranachaideekul, "Cannabidiol-Loaded Nanostructured Lipid Carriers (NLCs) for Dermal Delivery: Enhancement of Photostability, Cell Viability, and Anti-Inflammatory Activity," *Pharmaceutics*, vol. 15, no. 2, Feb. 2023, doi: 10.3390/pharmaceutics15020537.

[34] U. Nagaich and N. Gulati, "Nanostructured lipid carriers (NLC) based controlled release topical gel of clobetasol propionate: design and in vivo characterization," *Drug Deliv Transl Res*, vol. 6, no. 3, pp. 289–298, 2016, doi: 10.1007/s13346-016-0291-1.

[35] O. M. Elkhateeb, M. E. I. Badawy, A. E. Noreldin, H. M. Abou-Ahmed, M. H. El-Kammar, and H. A. Elkhenany, "Comparative evaluation of propolis nanostructured lipid carriers and its crude extract for antioxidants, antimicrobial activity, and skin regeneration potential," *BMC Complement Med Ther*, vol. 22, no. 1, Dec. 2022, doi: 10.1186/s12906-022-03737-4.

[36] V. K. Rapalli *et al.*, "Curcumin loaded nanostructured lipid carriers for enhanced skin retained topical delivery: optimization, scale-up, in-vitro characterization and assessment of ex-vivo skin deposition," *European Journal of Pharmaceutical Sciences*, vol. 152, p. 105438, Sep. 2020, doi: 10.1016/j.ejps.2020.105438.

[37] M. Pradhan, D. Singh, S. N. Murthy, and M. R. Singh, "Corrigendum to 'Design, characterization and skin permeating potential of Fluocinolone acetonide loaded nanostructured lipid carriers for topical treatment of psoriasis' [Steroids 101 (2015) 56–63]," *Steroids*, vol. 106, p. 93, Feb. 2016, doi: 10.1016/j.steroids.2016.02.002.

[38] D. Rawat, C. B. Tripathi, P. Parashar, M. Singh, G. Kaithwas, and S. A. Saraf, "Development and Characterization of Nanostructured Lipid Carriers of <I>Vetiveria zizanoides</I> Oil for Therapeutic Potential in Prickly Heat Treatment," *J Pharm Sci Pharmacol*, vol. 2, no. 2, pp. 162–171, Jun. 2015, doi: 10.1166/jpsp.2015.1054.

[39] Faizatun, "Formulasi Gel NLC Ekstrak Kalus Daun Murbei Hasil Induksi dengan NAA dan BAP (Formulation of NLC Gel from Callus Mulberry Leaf Extract Induced by NAA and BAP)," *JURNAL ILMU KEFARMASIAN INDONESIA*, vol. 12630, no. 1, pp. 123–129, 2020.

[40] P. Severino, S. C. Pinho, E. B. Souto, and M. H. A. Santana, "Polymorphism, crystallinity and hydrophilic–lipophilic balance of stearic acid and stearic acid–capric/caprylic triglyceride matrices for production of stable nanoparticles," *Colloids Surf B Biointerfaces*, vol. 86, no. 1, pp. 125–130, Aug. 2011, doi: 10.1016/j.colsurfb.2011.03.029.

[41] V. Sanna, G. Caria, and A. Mariani, "Effect of lipid nanoparticles containing fatty alcohols having different chain length on the ex vivo skin permeability of Econazole nitrate," *Powder Technol*, vol. 201, no. 1, pp. 32–36, Jul. 2010, doi: 10.1016/j.powtec.2010.02.035.

[42] A. Khosa, S. Reddi, and R. N. Saha, "Nanostructured lipid carriers for site-specific drug delivery," *Biomedicine & Pharmacotherapy*, vol. 103, pp. 598–613, Jul. 2018, doi: 10.1016/j.biopha.2018.04.055.

[43] A. Deep *et al.*, "Formulation and in vivo pharmacodynamics studies of nanostructured lipid carriers for topical delivery of bifonazole," *ACTA Pharmaceutica Sciencia*, vol. 59, no. 1, p. 559, 2021, doi: 10.23893/1307-2080.APS.05902.

[44] P. Jaiswal, B. Gidwani, and A. Vyas, "Nanostructured lipid carriers and their current application in targeted drug delivery," *Artif Cells Nanomed Biotechnol*, vol. 44, no. 1, pp. 27–40, Jan. 2016, doi: 10.3109/21691401.2014.909822.

[45] N. P. Truong, M. R. Whittaker, C. W. Mak, and T. P. Davis, "The importance of nanoparticle shape in cancer drug delivery," *Expert Opin Drug Deliv*, vol. 12, no. 1, pp. 129–142, Jan. 2015, doi: 10.1517/17425247.2014.950564.

[46] D. P. C. de Barros, P. Reed, M. Alves, R. Santos, and A. Oliva, "Biocompatibility and antimicrobial activity of nanostructured lipid carriers for topical applications are affected by type of oils used in their composition," *Pharmaceutics*, vol. 13, no. 11, Nov. 2021, doi: 10.3390/pharmaceutics13111950.

[47] M. Ijaz and N. Akhtar, "Fatty acids based α-Tocopherol loaded nanostructured lipid carrier gel: In vitro and in vivo evaluation for moisturizing and anti-aging effects," *J Cosmet Dermatol*, vol. 19, no. 11, pp. 3067–3076, Nov. 2020, doi: 10.1111/jocd.13346.

[48] N. Ayshah Rosli, R. Hasham, A. Abdul Aziz, T. Ubaidah Noh, and K. Jemon, "Nanostructured lipid carrier loaded with Zingiber officinale oil to enhance transdermal bioactive delivery for topical formulation," *Microchemical Journal*, vol. 200, p. 110470, May 2024, doi: 10.1016/j.microc.2024.110470.