NANOSTRUCTURE LIPID CARRIER TECHNOLOGY IN DRUG DELIVERY: ROUTE OF ADMINISTRATION, PREPARATION METHOD, CHARACTERIZATION, AND APPLICATION FOR ANTI-AGING

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ABSTRACT
The new method, known as nanostructured lipid carrier (NLC) in drug delivery systems, has the potential to increase therapeutic efficacy, stability, and bioavailability. This systematic literature review aimed to provide a detailed summary of NLC technology in drug delivery systems, including routes of administration, preparation methods, characterization, and utilization for the delivery of anti-aging active ingredients in cosmetics. To collect scholarly articles on NLCs, we employed a systematic search method using Google Scholar and PubMed. After the screening process, 53 pertinent papers out of 102 articles were chosen for descriptive analysis. NLC exhibit significant promise in many drug delivery applications, including oral, topical, parenteral, and transmucosal routes, with many benefits, including improved bioavailability, stability, and drug penetration through the skin, cornea, and brain. Moreover, NLC technology has been effectively applied for the administration of drugs, including anti-aging drugs. Topical anti-aging preparations generally use synthetic or natural active ingredients. However, synthetic ingredients are often less stable and can irritate skin. NLC can protect and control the release of active ingredients, thereby reducing the risk of irritation. NLC can also improve the penetration of active ingredients into the deeper layers of the skin, allowing it to reach the dermis layer, which is responsible for most skin aging. The efficient absorption capacity of NLC technology in topical preparations presents new opportunities for anti-aging cosmetic product development owing to its effectiveness in skin penetration.

Keywords: Nanostructured Lipid Carrier (NLC), drug delivery system, drug penetration, anti-aging

INTRODUCTION

Nanostructured Lipid Carriers (NLC), composed of both solid and liquid lipids, represent a significant breakthrough in drug delivery systems and can address several challenges in the field of pharmaceuticals. This method is intended to increase the bioavailability, stability, and efficacy of pharmaceuticals using nanoscale particles (Yin *et al.*, 2017; Alavi *et al.*, 2022).

One of the primary benefits of NLC is their potential to improve the stability of medications that are quickly destroyed in harsh settings. NLCs contain lipids that act as protective barriers, limiting damage to drug molecules caused by light, oxygen, and enzymes (Murthy *et al.*, 2020). In addition, because of their nanometric size, NLC particles can penetrate body tissues and biological barriers more effectively. For example, cells and mucous membranes (Liang *et al*., 2020).

NLC technology has been applied to various drug systems, including the oral, topical, parenteral, and mucosal systems. Growing research has shown success in the treatment of various diseases, including cancer, antibiotics, antivirals, and inflammatory agents. A promising application of NLCs is in anti-aging products. NLCs can enhance the penetration of active ingredients into the deepest layers of the skin, which is a major factor in topical formulations (Suryawijaya *et al*., 2022). This allows the ingredients to reach the dermal layer, where the main aging process occurs (Ebtavanny *et al*., 2018).

NLC can be manufactured in a variety of ways, and choosing the right approach is crucial to ensure that the end product has the required features. Based on this, this systematic literature review aimed to provide a detailed summary of NLC technology in drug delivery systems, including routes of administration, preparation methods, characterization, and utilization for the delivery of anti-aging active ingredients in cosmetics.

RESEARCH METHOD

Tools and Materials

This article preparation study utilized the strategy of searching for references in national and international publications via the Google Scholar search engine, PubMed, and Scimago. A total of 102 articles were collected and the inclusion and exclusion criteria were filtered, resulting in 49 publications being examined. The data for the evaluation were analyzed using descriptive analysis.

Article Selection Criteria

This review article included publications published in Indonesian or English between 2014 and 2024 as well as original research articles on nanostructured lipid carriers (NLC). This review article excludes publications that are not related to the substance or topic being discussed.

Research Procedure

Initial Google Scholar searches for the terms "nanostructured lipid carriers," anti-aging, "antioxidants," and "cosmetic preparations" yielded 10 publications, PubMed 30 articles, and Scimago 62 articles, for a total of 102. Subsequently, the author applied the inclusion and exclusion criteria to the publications, resulting in a curated list of 49 papers for evaluation. Data for this evaluation were assessed using descriptive statistics. Figure 1 shows a journal flow chart.

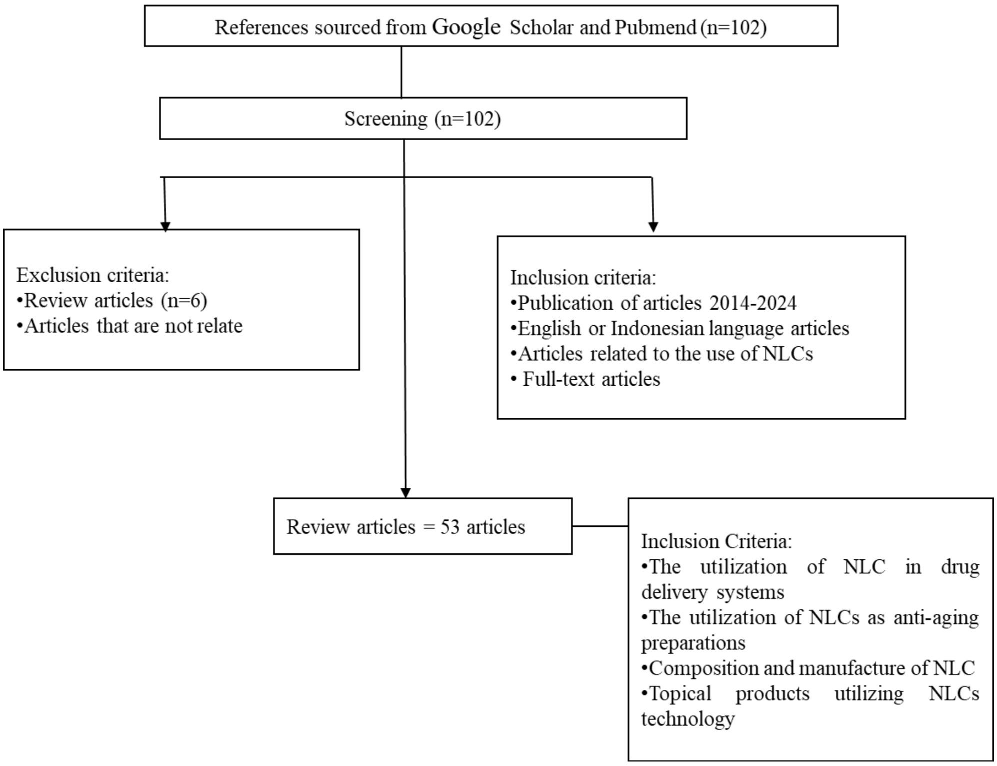

Figure 1. Flowchart of review writing method

RESULTS AND DISCUSSION

Nanostructured lipid carrier technology is an innovation in the pharmaceutical field that offers several advantages. NLCs are drug delivery systems designed using nanotechnology to improve the stability, effectiveness, and bioavailability (Yin *et al.*, 2017; Alavi *et al.*, 2022). In NLC, the medicine is integrated into a matrix composed of a mixture of solid and liquid lipids, resulting in nanometer-sized particles (Gautam, 2022). This structure enables NLC to have both a large drug loading capacity and the capability to control drug release in a sustained manner (Ni *et al.*, 2017).

One of the advantages of NLCs is their ability to increase drug stability, which makes them easily degraded or unstable under physiological conditions. NLC lipids serve as a protective barrier for drug molecules, preventing their degradation by external factors, such as light, oxygen, and enzymes. In addition, the nanoscale particle size of NLC allows for better penetration into body tissues, especially across barriers, such as cell membranes and mucosal layers (Nimtrakul *et al.*, 2020).

Another advantage of NLCs is their ability to release drugs (Yin *et al.*, 2017). Drug release can be regulated over a desired time by altering the composition and structure of the lipids. This is particularly useful in the treatment of diseases that require continuous and controlled drug administration to maintain therapeutic concentrations in the blood.

NLCs also have great potential for various drug delivery applications, including oral, topical, parenteral, and transmucosal applications. The research and development of NLCs continues to grow, with many studies showing success with various types of drugs, including anticancer drugs, antibiotics, antiviral drugs, and anti-inflammatory drugs. Several types of drugs use nanostructured carrier technology in their drug delivery systems.

Table I. Various Drug Delivery Systems Utilizing NLC Technology

NLC Route System	Drug Activity	Active Ingredients	Key Advantages of NLC	References
NLC intramuscular	Anticancer	Doxorubicin-gemcitabine and vincristine	Improve bioavailability and specific targets	(Ni *et al.*, 2017)
NLC Intratumoral	Anticancer	Docetaxel		(Lee *et al.*, 2018)
NLC Subcutaneous	Anticancer	Paclitaxel and gemcitabine		(Liang *et al.*, 2020)
NLC Intravena	Anti tumor	Gefitinib		(Deepak *et al.*, 2023)
	Artery coroner	Resveratrol		(Astley *et al.*, 2021)
	Antivirus	Ivermectin		(Xu *et al.*, 2024)
NLC Topical	Anti inflammatory	Lornoxicam	Extends drug release and better skin penetration	(Kharwade and Mahajan, 2019)
		Capsaicin		(Wang *et al.*, 2017)
	Antifungal	Econazole nitrat		(Gujjar *et al.*, 2019)
		Luliconazole		(Baghel *et al.*, 2020)
		Voriconazole		(Tian *et al.*, 2017)
	Antioxidant	Melatonin		(Hatem *et al.*, 2018)
	Anti-aging	Protopanaxadiol		(Kim *et al.*, 2019)
	Dermatology	Constraints		(Madan *et al.*, 2020)
NLC Oral	Antimicrobial	Sulfamethoxazole	Improves the stability of the drug and protects against gastric degradation	(Alavi *et al.*, 2022)
	Antidiabetes	Berberine chloride		(Yin *et al.*, 2017)
	Diuretic	Hydrochlorthiazide		(Cirri *et al.*, 2018)
	Anticancer	Gemcitabine and paclitaxel		(Liang *et al.*, 2017)
NLC Bukal	Antipsychotics	Paliperidone	Improves bioavailability and therapeutic effects	(AlMulhim *et al.*, 2023)
NLC Ophthalmic	Eye medicine	Lomefloxacin	Increases corneal penetration	(Gautam, 2022)
		Eplerenon		(Abdelhakeem *et al.*, 2021)
		Natamycin and ciprofloxacin		(Youssef *et al.*, 2022)
NLC intranasal	Neurodegenerative drug	Astaxanthin	Increases transmission to the brain	(Shehata *et al.*, 2023b)
		Astaxanthin and donepezil		(Shehata *et al.*, 2023a)
NLCs for DNA vaccines	Vaccine	Ivermectin	Improves stability and immune response	(Ahmadpour *et al.*, 2019)

Skin aging is characterized by a loss of structural stability and functional integrity, resulting in diminished functional and maximal capacity due to accumulated damage from intrinsic and extrinsic factors (Liang *et al.*, 2023). Genital instability, cellular aging, and telomere shortening all contribute to intrinsic skin aging. Extrinsic aging is exacerbated by external factors such as ultraviolet (UV) contamination, smoking, and alcohol use. These environmental factors accelerate the aging process, resulting in premature skin aging (Quan, 2023).

Anti-aging refers to various methods and techniques used to slow down or reverse the aging process, particularly in skin. The main goal of anti-aging is to preserve the skin by reducing the signs of aging, such as fine lines and loss of elasticity (Leelapornpisid *et al.*, 2014; Avadhani *et al.*, 2017). Exogenous dietary antioxidant supplementation and/or pretreatment with antioxidant-based lotions prior to sun exposure may be effective for treating age-related skin diseases. Many secondary metabolites defend against UV rays, and these substances may protect the skin from photoaging (Petruk *et al.*, 2018).

The use of NLCs as topical preparations for anti-aging products, both synthetic and natural, is a major advancement in the cosmetic and dermatology industries. NLC offer several significant anti-aging benefits. First, NLC can increase the penetration of deeper skin layering ingredients, which is a major challenge in topical formulations (Suryawijaya *et al.*, 2022). Small particle size allows the active ingredient to penetrate the epidermal layer and enter the dermis, causing most indications of age, such as wrinkles, lack of elasticity, and hyperpigmentation (Ebtavanny *et al.*, 2018).

The active ingredients used in NLC anti-aging topical preparations usually come from synthetic or natural sources. However, synthetic active ingredients often have low stability and can cause skin irritation. NLC can address this problem by protecting the active ingredient from degradation by environmental factors and controlling its gradual release, thereby reducing the risk of irritation and increasing the effectiveness of therapy (Leelapornpisid *et al.*, 2014). Active ingredients, such as plant extracts, essential oils, and bioactive compounds, are becoming increasingly popular in anti-aging formulations. These natural ingredients are advantageous because they are generally more biocompatible and have fewer side effects than synthetic materials. However, the stability and solubility of natural active ingredients are often challenging.

The use of NLC allows for the development of multifunctional anti-aging products. For example, topical preparations can combine several ingredients that work synergistically to treat various aspects of the skin such as hydration, antioxidants, and stimulation (Chu *et al.*, 2019). This not only increases the effectiveness of the product, but also provides ease of use for consumers.

Table II. Cosmetic Active Ingredients in Formulations Using NLC Technology

Source of Materials	Active Ingredients (%)	Use	Test Methods	Reference
Natural	Green Tea Extract (0.1%)	Antioxidant	In Vitro	(Suryawijaya *et al.*, 2022)
	Tagetes erecta Linn (30%)	Anti wrinkle	In Vitro	(Leelapornpisid *et al.*, 2014)
	Cucurbita pepo L and *Hibiscus cannabinus* L (6%)	Antioxidant	In Vitro	(Chu *et al.*, 2019)
Synthetic	α- tocopherol (10%)	Antioxidant	In Vitro	(Ijaz and Akhtar, 2020)
	Tretinoin (98%)	Anti-aging	In Vivo	(Ghate *et al.*, 2016)
	Ubiquinone (1%)	Anti-aging	In Vivo	(Ebtavanny *et al.*, 2018)
	Hesperitin (0,1%)	Anti-aging	In Vitro	(Nurrohim *et al.*, 2022)

The manufacture of nanostructured lipid carriers (NLCs) is highly diverse, and the selection of an appropriate method is essential to ensure the desired characteristics of the final product. Various techniques used in the creation of NLC include the following:

1. Emulsification and Evaporation of Solvents

   Lipids, solids, and liquids are dissolved in volatile solvents such as methanol or ethanol. Active components were dissolved in the same solvent. The lipid solution containing the active component was then slowly added to the water phase containing the surfactant with vigorous stirring to generate an oil-in-water emulsion. The emulsion was boiled to remove organic solvent. As the solvent evaporates, lipids precipitate as nanoparticles, creating NLCs that contain the active components. The resultant NLC can then be filtered to remove excess surfactants and contaminants (Lee *et al.*, 2018; Liang *et al.*, 2020).
2. Diffusion and Evaporation of Solvents

   This procedure involved mixing the lipid solution in an organic solvent with water. During mixing, the organic solvent diffuses from the lipid solution into the aqueous phase, resulting in lipid precipitation in the form of nanoparticles. Evaporation of organic particles is carried out by continual swirling to completely remove the solvent, leaving stable nanolipid particles (Ni *et al.*, 2017).
3. High-Pressure Heat Homogenization

   This procedure involves melting the solid lipids and adding liquid lipids to form a hot lipid phase. Surfactants or cosurfactants were added to the water to generate the water phase. Furthermore, the heated lipid phase combined with the melted solid phase while continually stirring to form a microemulsion. To reduce the particle size, the heated microemulsion was homogenized using high pressure. Various homogenization processes can be used, depending on the required particle size. Subsequently, the nanoemulsion was cooled and transformed into NLC (Patil *et al.*, 2016; Nimtrakul *et al*., 2020).
4. High-Pressure Cold Homogenization

   This method is similar to high-voltage homogenization in that it involves mixing the lipid phase with a cold-water solution held at a temperature of 2–6°C while constantly whirling. This rigid NLC suspension was homogenized using a high-pressure homogenizer at a low temperature. This strategy is applicable to pharmaceuticals and materials that are not resistant to high heat (Duong *et al.*, 2019).
5. Hot Melt Extrusion

   This technology involves pumping the starting material into containers, followed by ultrasound to produce NLC. The solid lipids were combined and fed into an extruder container using a volumetric feeder. Solid lipids and aqueous solutions were introduced at the extrusion temperature using a peristaltic pump. This mixture was extruded at the melting temperature of the components, resulting in a pre-emulsion. The heat pre-emulsion was sonicated to reduce the size of the NLC (Shadambikar *et al.*, 2021).
6. Microemulsions

   The microemulsion technique involves the incorporation of liquid lipids to melt solid lipids. The solution was then combined with water to create a microemulsion. Cold water was used to swiftly cool the microemulsion and heat the NLC dispersion system. The difference between microemulsions and water affects the size of the NLC particles. This technique is simple to use to generate NLC, but requires large amounts of surfactants and cosurfactants (Li *et al.*, 2017).
7. Solvent Injection

   The lipid phase is dissolved in a water-soluble solvent or a combination of such solvents, which are then heated to dilute solid lipids. The resultant organic phase was promptly inserted into an aqueous solution containing surfactants or buffer solutions while continuously stirring. Solvents spread via lipid deposition and the production of lipid nanocarriers. Particle size was determined by the diffusion rate of the solvent and emulsifier content (Duong *et al*., 2020).

The use of NLC technology in topical formulations can increase user acceptance. The resulting nanoparticles have better properties in terms of absorption, distribution, and texture on the skin to provide a more comfortable and non-sticky use experience. Therefore, the use of NLC technology as a carrier in topical preparations presents novel prospects for the advancement of anti-aging cosmetic formulations, owing to its effective and efficient skin absorption capacity.

Table III. Topical Preparations Utilizing NLC Technology

Types of Preparations	Active Ingredients	NLC characterization techniques	Activity	References
Cream	Retinyl Palmitate	Transmission Electron Microscopy (TEM)	Antioxidant	(Sriarumtias *et al.*, 2017)
	Asam Caffeic	Entrapment Efficiency TEM, and FTIR	Anti inflammatory	(Kamath *et al.*, 2023)
	Tretinoid	Malvern Zetasizer, Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC) and FTIR	Anti-aging	(Ghate *et al.*, 2016)
Gel	Aceclofenac	TEM and SEM	Anti inflammatory	(Garg *et al.*, 2021)
	Lornoxicam	Malvern Zetasizer, TEM, and DSC	Edema Treatment	(Gao *et al.*, 2019)
	Spironolactone	Malvern Zetasizer and TEM	Antiacne	(Kelidari *et al.*, 2016)
	Erythromycin	Entrapment Efficiency and ultraviolet (UV) spectrophotometer	Antibacterial	(Zafar *et al.*, 2022)
Emulsion	Routine	Malvern Zetasizer and TEM	Eye treatment	(Chakole, 2024)
	Lulicnazol	Entrapment Efficiency, DSC, and Attenuated Total Reflectance Fourier Transform Infrared (ATR-FTIR)	Antifungal	(Nosratabadi, 2024)
	Ketoconazole	Malvern Zetasizer	Antifungal	(Rahayu *et al.*, 2022)
Lotions	Baccuri Butter	Malvern Zetasizer, Spektrofotometri UV, Atomic Force Microscopy (AFM)	Sunscreen	(De Araújo *et al.*, 2024)

CONCLUSION

Lipid carrier (NLC) nanostructures are novel drug delivery systems that can improve the stability and bioavailability of active pharmaceutical ingredients. NLCs have been successfully used to administer a variety of drugs, including anticancer drugs, antibiotics, antivirals, anti-inflammatory agents, and anti-aging agents, via oral, topical, parenteral, and transmucosal routes. In anti-aging applications, NLC can improve the penetration of active ingredients into deeper layers of the skin, allowing them to reach the dermis layer, which is responsible for most skin aging. The application of NLC technology as a carrier in topical preparations provides new opportunities for the development of anti-aging products in cosmetic preparations, because it has a more effective and efficient absorption capacity through the skin.

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