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Review Article

# Nanostructured lipid carriers: A prospective dermal drug delivery system for natural active ingredients

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## Abstract

Nanostructured lipid carriers (NLCs) are versatile tools used for several purposes, including drug release modification, adhesion to the skin, film-forming ability followed by hydration of the superficial layers of the skin, as well as high penetration with permeation into and across deeper skin layers. During the formulation of active ingredients sourced from nature into dosage forms, NLCs play a crucial role in overcoming challenges associated with the process. These challenges include poor solubility and skin permeability, sensitivity to light, heat, and oxygen, leading to degraded quality, reduced potency, and probable risks of skin irritation or allergic reactions. Therefore, this review aimed to provide a comprehensive overview of NLCs as effective delivery system through the skin for natural active ingredients. The extensive discussion covers the advantages and disadvantages of a dermal delivery system for these ingredients, focusing on various types, lipids, and surfactants used in the formulation, preparation, and characterization process. Additionally, the recent developments in NLCs technology are explored. The result showed that NLCs would advance into a more efficient, precise, and safe system to transport natural active ingredients dermally.

## Keywords

Dermal drug delivery, Lipids, Nanostructured lipid carriers, Natural active ingredients, Surfactants

## Introduction

Natural active ingredients are chemical substances derived from various organisms, such as plants, microbes, or animals, renowned for pharmacological, therapeutic, antioxidant, and antibacterial effects. These ingredients have gained importance in modern medicine due to their potential as effective therapies for treating diseases with fewer side effects and cost-effectiveness with adequate administration compared to most pharmaceutical drugs (Thakur et al. 2011). In recent years, natural active ingredients have become increasingly popular in skincare products. This widespread application is attributed to therapeutic benefits to the skin, including wound-healing, antimicrobial, and anti-inflammatory properties (Kamel and Mostafa 2015; Shen et al. 2015; Sanad and Abdel-Bar 2017; Ghodrati and Farahpour 2018). These ingredients are often selected to target specific skin concerns or conditions, such as acne, aging, dryness, and inflammation (Okonogi and Riangjanapatee 2015; Chen et al. 2017; Pivetta et al. 2018).

Despite the numerous benefits, natural ingredients in topical dosage forms are still difficult to deliver through the skin without reducing their effectiveness (Thakur et al. 2011). A significant challenge is poor skin permeability, inhibiting penetration into the outermost layer and the stratum corneum. This phenomenon prevents natural ingredients from reaching the deeper layers for optimal effectiveness (Okonogi and Riangjanapatee 2015; Chen et al. 2016). Natural ingredients are also sensitive to light, heat, and oxygen, which potentially degrade and reduce their potency when exposed (Liu et al. 2015). Due to the variability in skin permeability, solubility, and other physical properties, formulating natural ingredients into skin products can be challenging (Wang et al. 2014). Compared to synthetic materials, natural ingredients can still cause skin irritation or allergic reactions in some people, raising safety concerns (Chen et al. 2016).

Lipid-based drug delivery systems (LBDDS) capable of mimicking the skin barrier function have been proposed to improve the delivery and performance of natural active ingredients (Aditya et al. 2014). LBDDS is known to enhance skin permeability and protect natural ingredients from degradation to improve stability and bioavailability while reducing toxicity (Qi et al. 2017; Poovi and Damodharan. 2018). At least five types of LBDDS have been identified, including lipid solutions or suspensions, emulsions, self-emulsifying or self-nanoemulsifying drug delivery systems, liposomes, and lipid particulate systems (solid lipid nanoparticles and nanostructured lipid carriers) (Akbari et al. 2015; Pradhana and Ritthidej 2023). LBDDS is often liquid form physically but may also be solid or semi-solid at room temperature when high melting lipids are used or adsorbed onto the carrier. Alternatively, it can also appear as lipid multi-particulates (Feeney et al. 2016). Figs 1, 2 show the schematic classification and the morphological models of some LBDDS (oil-in-water emulsion, solid lipid nanoparticle, and nanostructured lipid carrier).

Nanostructured lipid carriers (NLCs) are drug delivery system comprising a mixture of solid and liquid lipids as a core matrix. Furthermore, NLCs are second-generation lipid nanoparticles that have an unstructured matrix with high drug loading capacity, which are suitable for drug delivery system (Chen et al. 2014; Weber et al. 2014). Due to these unique characteristics, several studies have investigated NLCs as alternate carriers for the dermal delivery of pharmaceuticals, particularly natural active ingredients. Among the associated benefits discovered include biocompatible ingredients, drug release modification, adhesion to the skin, film-forming ability with hydration of the superficial skin layers, as well as increased penetration and permeation into deeper skin layers.

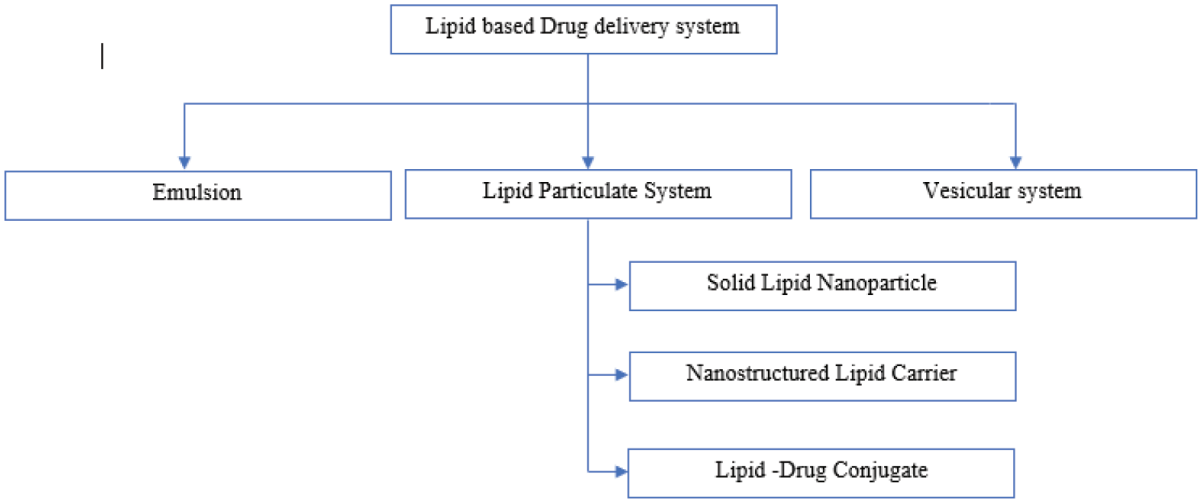


**Figure 1.** Lipid-based drug delivery system.

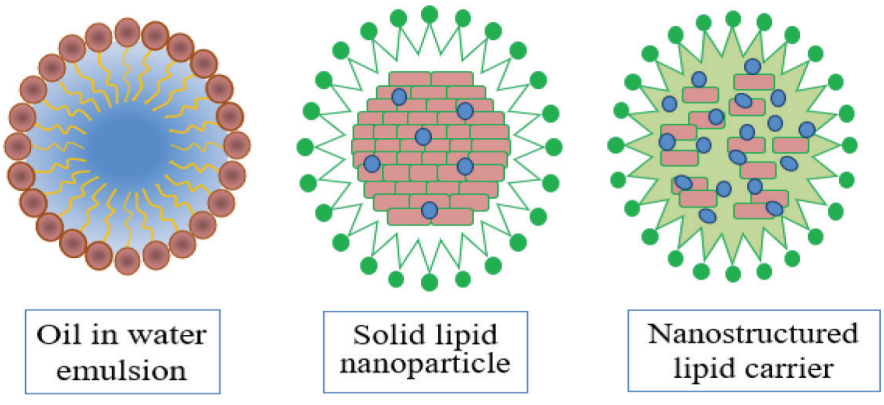


**Figure 2.** Morphological models of emulsion, SLN, and NLC.

Based on the background above, this review is designed to provide a comprehensive overview of NLCs as an effective delivery system through the skin for natural active ingredients. In addition to the dermal delivery system, the advantages and limitations are explored, including various types, lipids, and surfactants used in the formulation, preparation methods, and characterization. Recent developments are also discussed, showing the promising potential of NLCs for enhancing the dermal delivery of natural active ingredients.

An electronic search was conducted across PubMed, Springer Link, Science Direct, and Google Scholar to explore the application of NLCs in Dermal Drug Delivery System for Natural Active Ingredients. A comprehensive systematic search was performed by using several keywords, including Dermal drug delivery, NLCs, Natural active ingredients, NLCs for dermal delivery, NLCs for natural active ingredients, Natural active ingredients for dermal. Studies were included in the analysis after meeting the inclusion criteria, namely (1) the study was published between 2007 and 2023, and in English text (2) complete article, and (3) provides data that is appropriate to the scope of the review, specifically transdermal and topical dermal delivery. However, studies were excluded when published in a proceeding and not in a complete article.

## Dermal delivery system for natural active ingredient

Dermal delivery system plays a crucial role in transporting drugs or active ingredients through the skin to achieve therapeutic benefits (Brown et al. 2008). Over the past two decades, extensive research has been conducted to overcome the skin barrier, enhancing the effectiveness of pharmaceutical and cosmetic products (Kim et al. 2020). This method includes applying a substance to the skin, which is absorbed and delivered to the target organ or tissue.

Several advantages are associated with dermal delivery system over other drug administration techniques such as through the oral route or by injection. This method allows for a more consistent and predictable dose of medication, minimizing the risk of side effects related to other techniques. Due to convenience and non-invasiveness, patients who have difficulty swallowing pills or require long-term therapy prefer dermal delivery system. Furthermore, it is a versatile method suitable for both therapeutics and cosmetics to provide sustained as well as controlled release of drugs and other substances (Garcês et al. 2018; Kim et al. 2020).

Despite these numerous benefits, dermal delivery possesses some limitations, hindering its suitability for some drugs due to physicochemical properties. These include poor water solubility, slow permeability/absorption, and poor stability, with the skin barrier limiting the amounts of drugs penetrated. Additionally, skin irritation or other adverse effects may occur at the application site. To overcome these limitations, several strategies can be employed such as using carrier systems including nanostructured lipid carriers (NLCs) (Garcês et al. 2018; Mahant et al. 2018).

## Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers (NLCs) are delivery system comprising the combination of solid and liquid lipids as core matrix. This system has an unstructured matrix with a high loading capacity, enhancing its suitability as drug delivery system (Chen et al. 2014). NLCs were developed to address the limitations of early solid lipid nanoparticle (SLN) generation by incorporating a mixture of solid and liquid lipids, along with surfactants, to create a solid or semi-solid core matrix. Generally, surfactants play a crucial role in stabilizing the lipid core, resulting in improved size distribution, homogeneity, and stability of the final NLCs product, with particle diameter ranging from 10 to 1000 nm (Cirri et al. 2012; Guo et al. 2015; Karaman 2015; Garcês et al. 2018).

NLCs have gained significant attention in recent years due to their potential applications in dermal drug delivery. Specifically, NLCs have shown promise as a solution for limited drug penetration, showing improved stability, skin permeation, retention, and therapeutic efficacy. These unique characteristics contribute to the extensive use of NLCs in the dermal delivery of numerous therapeutics in skin disorders, indicating potential in treating skin diseases (Garcês et al. 2018; Mahant et al. 2018; Souto et al. 2020).

Several studies are focused on the development of NLCs for targeted dermal applications of antifungals such as luliconazole, quercetin, and fluconazole to show their potential in treating fungal skin infections (Nogueira et al. 2022). Luliconazole, an antifungal agent, showed high antifungal activity against *Trichophyton* spp., causing dermatophytosis. However, the limitations associated with Luliconazole include less skin retention, low aqueous solubility, and poor skin penetration. To overcome these drawbacks, Baghel et al. (2020) explored NLCs as a delivery system for luliconazole. Another study investigated the deposition and permeation of quercetin, a natural antifungal compound, from NLCs into the skin. The results showed that the amount of quercetin deposited into the epidermis and dermis from NLCs was significantly higher, suggesting enhanced delivery of antifungal agents into the skin (Elmowafy et al. 2021). Furthermore, the topical delivery of fluconazole, an antifungal drug, has been evaluated to show its potential therapeutic efficacy in treating cutaneous fungal infections. In the experiment, NLCs showed good skin-targeting effects, resulting in effective localized treatment and sustained release of fluconazole. The lowest number of colony-forming units (cfu/ml) was detected in subjects receiving fluconazole-loaded NLCs (Gupta et al. 2017).

Due to good skin-targeting effects, NLCs are a promising option for topical drug delivery. Previous studies

have tested the potential for treating psoriasis, dermatitis, bacterial infections, skin cancer, and atopic dermatitis (eczema) (Mahant et al. 2018; Wairkar et al. 2022). The results showed a significant efficiency in improving the dermal applications of N-acetyl glucosamine for skin diseases (Aliasgharlow et al. 2016) and lipophilic calcipotriol and hydrophilic methotrexate for psoriasis treatment (Jaiswal et al. 2014). Topical formulations have also been developed with this system to treat systemic inflammatory autoimmune diseases, such as rheumatoid arthritis. In other studies, NLCs are examined for the topical delivery of antioxidants, showing their ability to protect the skin from the harmful effects of free radicals and UV radiation, leading to oxidative stress and photoaging. Moreover, NLCs loaded with both alpha-mangosteen and resveratrol showed enhanced antioxidant activity when topically applied (Samprasit et al. 2022). It was also reported that propolis extract-loaded NLCs increased phenolic and flavonoid contents, indicating enhanced skin regenerative capacity (Elkhateeb et al. 2022). Additionally, the topical application of idebenone-loaded NLCs showed a high sun protection factor (SPF) value of 23, hindering 94–96% of ultraviolet-B rays (Salunkhe et al. 2013).

NLCs have also gained popularity in the cosmetic industry due to potential benefits, such as improved skin hydration, occlusion, bioavailability, and targeting (Chauhan et al. 2020). Arsenie et al. (2020) conducted a study utilizing nanostructured lipid carriers (NLCs) provided with three active ingredients—azelaic acid (AzA), white willow bark extract (WBE), and panthenol—in their investigation of cosmetic formulations. An advanced cosmetic formulation was produced by incorporating NLC-AzA-WBE-Ph into a Carbopol gel; this formulation guarantees an extensive hydration effect. The adherence of lipid nanoparticles to the epidermis results in the formation of a film, which subsequently induces an occlusion effect. An increase in occlusion can be achieved by either diminishing the particle size at a given lipid concentration or increasing the number of particles at a given lipid concentration (Muller et al. 2007). An example of the stabilizing impact of the NLC can be observed with the chemical compound retinol. Retinol has found wide use in the cosmetic industry as an active ingredient against wrinkles. Nonetheless, air oxidation of retinol constituted a significant obstacle to its implementation in the cosmetics industry. In an effort to optimize the components of NLC, Jun et al. (2021) utilized a variety of lipid species to create gradients of carbon chain C8-22, resulting in an amorphous structure. Sufficient spaces were estimated within the capsules to accommodate retinol through DSC analysis, which also revealed a lower enthalpy change and peak shift. The retinol-loaded NLC exhibited a restricted size distribution with a PDI value below 0.3, a scaled particle size of less than 200 nm, and an all-negative surface charge of approximately -50 mV. It retained a stable retinol concentration of 90% or higher after four weeks of storage at temperatures of 25, 40, and 50 °C.

The use of NLCs requires certain qualities and properties for effective topical or transdermal administration. For instance, NLCs for cutaneous delivery of drugs typically have particles in the submicron size ranging from 40 to 1000 nm, based on the composition of lipids. A smaller particle ensures close contact with the stratum corneum (SC) to improve the skin penetration of the loaded active compound. When used topically, NLCs should be biocompatible and skin-safe, without causing irritation or other unpleasant effects (Chauhan et al. 2020).

In addition to size and safety considerations, NLCs should enable high drug loading to ensure a sufficient amount of the active ingredient is encapsulated for therapeutic efficacy. Drug loading is improved by optimizing formulation parameters, such as the types and concentrations of lipids, surfactants, and co-surfactants. Generally, NLCs have a higher drug-loading capacity than SLNs and encapsulate from 5% to over 20% active substances, accommodating 30% of some formulations. To guarantee stability, controlled release, and effective dermal distribution while avoiding potential side effects or irritation, the exact amount of the loaded drug should be optimized during the formulation process.

## Advantages and limitations

NLCs enhance the chemical stability of active ingredients by minimizing the release of loaded unstable compounds from the lipid structure and maintaining the physical quality of topical formulations during storage. Due to the less ordered structural arrangement, this improved version of SLNs also has a controlled-release characteristic and less proneness to aggregation when compared to emulsions. Other advantages include the ability of NLCs to reduce the water content of emulsion, ensure transdermal permeation with nanosized particles, prolonged half-life, and enable tissue-targeted drug delivery (Mahant et al. 2018; Nogueira et al. 2022). Additionally, NLCs enhance the efficacy and potency of active ingredients and can regulate the release of drugs while delivering active ingredients with varying polarity (Shi et al. 2016; Huang et al. 2017; Ahmad et al. 2018; de Barros et al. 2022).

Despite the promising drug delivery, NLCs technology has several drawbacks. These include the selection of surfactants cautiously to avoid irritation and sensitivity. Applications and efficiencies of NLCs in delivering proteins and peptide drugs and for targeted gene delivery are still not fully investigated. Furthermore, there are limited preclinical and clinical studies on NLCs (Khosa et al. 2018; Chauhan et al. 2020; Haider et al. 2020).

## Different types of NLCs

The summaries of three types of NLCs are stated below (Balamurugan and Chintamani 2018; Nogueira et al. 2022):

1. Type 1 NLCs (Imperfect).
   Type I NLCs have an imperfect crystal core structure due to the partial replacement of a portion of solid lipid with liquid or oil. Moreover, this type has a high loading capacity and excellent drug release profiles.
2. Type 2 NLCs (Amorphous/structureless).
   Mixing solid lipids with specific lipids that stay in α polymorph after solidification leads to the production of type 2 NLCs. The use of medium-chain triglycerides, hydroxyoctacosanyl, hydroxy stearate, or isopropyl myristate in conjunction with solid lipids has been found to yield the desired outcome. This type is generally preferred due to the absence of crystallization and the drug remains incorporated in the amorphous matrix. Consequently, drug release induced by the crystallization process to β forms during storage can be avoided.
3. Type 3 NLCs (Multiple).
   Type 3 NLCs are conceptually developed from w/o/w emulsion. When the loaded drug has high oil solubility, this method can be used to formulate NLCs with increased loading capacity and stability. In this method, small droplets of oil are consistently dispersed throughout a solid lipid matrix in an aqueous phase.

The morphological models of all types of NLCs are shown in Fig. 3.

## Lipids

NLCs are formulated using several excipients, including both solid (fats) and liquid lipids (oils), surfactants, and water. Creating the right lipid mixture is essential to producing NLCs with acceptable characteristics. Moreover, the selection of lipids and their proportions is based on the solubility of the active pharmaceutical ingredient and characteristics within the lipids such as types of carbon chains, length in solid lipids, polarity, solubility, and viscosity. Several lipids have been used to build a nano-lipid carrier matrix in NLCs, including phospholipids, fatty acids, wax esters, and triglycerides (Muller et al. 2007; Tamjidi et al. 2013; Wang et al. 2014; Khosa et al. 2018; Chauhan et al. 2020; Haider et al. 2020; Elmowafy and Al-Sanea. 2021; Pradhana and Ritthidej 2023)

### Phospholipids

Phospholipids contain a phosphate group and are commonly found in biological membranes. Due to good biocompatibility and stability, phospholipids have been frequently used to improve the stability of NLCs and drug delivery properties. Moreover, their application as lipids can affect the characteristics of the resulting NLCs, such as size, drug-loading capacity, and release pattern. For every formulation, suitable phospholipids are selected based on the specific needs of the drugs or the bioactive components to be encapsulated. Phospholipids that have been applied include soy lecithin, phosphatidylcholine, dipalmitoylphosphatidylcholine (DPPC), and synthetic phospholipids.

### Fatty acids

Fatty acids comprise a long chain of carbon atoms derived from natural sources, such as olive, coconut, and palm oils. Furthermore, fatty acids are frequently used in the formulation of NLCs to create a stable lipid matrix for drug delivery. Examples of commonly used fatty acids include oleic, stearic, palmitic, and arachidic acids. Oleic acid is a monounsaturated fatty acid serving as a liquid lipid component that modulates the drug-loading capacity and stability of the carriers. Stearic, palmitic, and arachidic (C20) acids are saturated fatty acids used as the solid lipid that shapes the carrier's structure and stability.

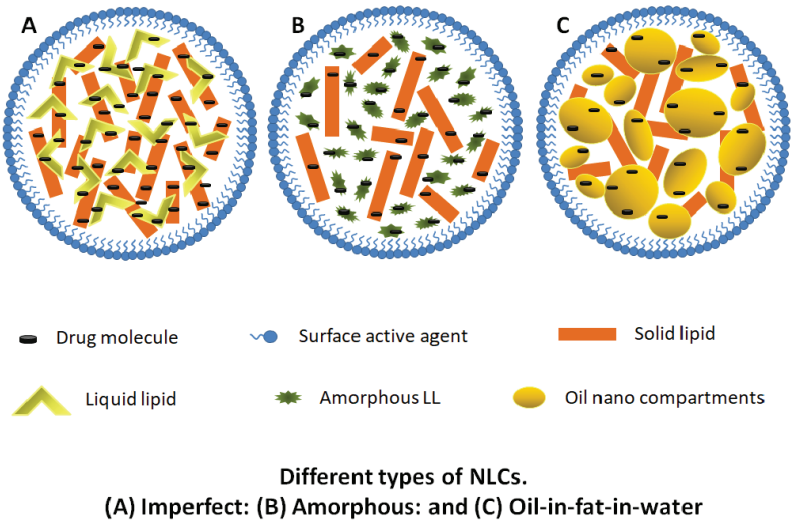


**Figure 3.** Morphological models of different types of nanostructured lipid carriers (NLCs).

### Wax esters

Wax esters are composed of a long-chain fatty acid and alcohol. With a high melting point and good stability, this lipid is suitable as a solid lipid carrier in NLCs. Furthermore, wax esters stabilize the carrier's lipid matrix and can be combined to produce the required properties. Some commonly used wax esters are palmitate esters, carnauba wax, beeswax, and propolis wax.

### Triglycerides

Triglycerides are composed of a glycerol molecule and three fatty acids. This type of lipid is used in the formulation of NLCs to improve the encapsulated active component chemical stability, film generation, and controlled occlusion. Furthermore, triglycerides produce cosmetics with favorable skin hydration and bioavailability. Some frequently used triglycerides are medium-chain triglycerides (MCTs), such as caprylic triglyceride, and glyceryl behenate.

### Cationic lipids

Cationic lipids are positively charged and are commonly used in NLCs for nucleic acid delivery, such as gene therapy. Furthermore, cationic NLCs (cNLCs) can be identified through the presence of at least one cationic lipid, which accounts for the distinct characteristics. Furthermore, their interaction with negatively charged nucleic acids through electrostatic interactions enhances encapsulation and delivery. DOTAP (1,2-dioleoyl-3-trimethylammonium-propane) and octadecylamine (OA) are examples of cationic lipids used in NLC formulation (Xu et al. 2022; Tucak-Smajic et al. 2023).

### Ionizable lipids

Depending on the surrounding pH, ionizable lipids can be protonated or deprotonated. This characteristic is essential in the transport of mRNA through lipid nanoparticles. Ionizable lipids, such as Dlin-MC3-DMA, SM-102, and ALC-0315 (Zhang et al. 2023), can be positively charged in acidic endosomal compartments. These characteristics enable endosomal escape and cytoplasmic delivery, which is crucial for lipid nanoparticles, particularly NLCs, in nucleic acid delivery, such as mRNA. Apart from Dlin-MC3-DMA, SM-102 has also received more attention for its use in lipid nanoparticle formulations for mRNA vaccines. In these nanoparticles, SM-102 serves as a lipid system component behind their ability to carry mRNA payloads into cells. ALC-0315 is a third ionizable lipid found in approved lipid nanoparticles, playing a significant part in nucleic acid transport (Gonzalez-Rioja et al. 2023).

Several factors are considered during the selection of lipids in developing a nanolipid carrier structure for natural ingredients. The selected lipid should possess the ability to solubilize the natural ingredient while maintaining its stability and activity. Compatibility with the natural ingredient and biocompatibility are also crucial, ensuring no adverse effects on the skin or other tissues. Additionally, good thermodynamic stability and desirable physicochemical properties are required. The melting point, viscosity, and surface tension of the lipid should be appropriate for processing and formulation.

## Surfactants

Surfactants play a crucial role in shaping the colloidal properties such as viscosity and capacity of NLCs to dissolve hydrophobic components and preserve the stability of nanosized lipid particles. Furthermore, the selection for NLC formulation is based on several factors, namely desired route of administration, hydrophilic-lipophilic balance (HLB), potential lipid and particle size modification, including contributions to in vivo lipid degradation. Surfactants have an amphiphilic structure that lowers surface tensions and promotes particle partitioning into hydrophilic (attracted to water) and hydrophobic (attracted to lipids) groups. This behavior is considered in selecting and obtaining physicochemically compatible surfactants and lipids. The HLB value measures the hydrophilicity/lipophilicity degree of a surfactant molecule from the strength and size of its lipophilic and hydrophilic moieties. Surfactants can be cationic, amphoteric, anionic, or non-ionic. Pluronic F68, polysorbate (Tween), polyvinyl alcohol, poloxamer 188, and sodium deoxycholate, are the most widely used hydrophilic emulsifiers. Lecithin and Span® 80 are two examples of lipophilic and amphiphilic emulsifiers frequently added to the NLC formula. Moreover, the combination of more than one emulsifier leads to the effective inhibition of inhibits particle aggregation (Muller et al. 2007; Tamjidi et al. 2013; Wang et al. 2014; Khosa et al. 2018; Chauhan et al. 2020; Haider et al. 2020).

Table 1 shows the examples of natural active ingredients loaded into NLCs, and their preparation mechanism, including the lipids and surfactants used from numerous published articles.

## NLC Preparation methods

Natural ingredients can be loaded into nano lipid carriers to create advanced product formulation in numerous techniques and systems. These include high-pressure homogenization (HPH), high-shear homogenization followed by ultrasonication, microemulsion, solvent emulsification/evaporation, membrane contactors, phase inversion (separation), and coacervation (Ganesan and Narayanasamy 2017; Khosa et al. 2018; Chauhan et al. 2020; Duong et al. 2020; Haider et al. 2020).

**Table 1.** List of different natural active ingredients incorporated into nanostructured lipid carriers (NLCs) in the literature.

| Natural active ingredient | Excipient Use | | Particle size (nm) | Reference |
|---|---|---|---|---|
| | Lipid | Surfactant | | |
| Alfa lipoic acid | MCT, Campritol 888-ATO | Soya lecithin | 60.1 | Li et al. 2021 |
| Astaxanthin | Stearic acid, Glyceryl palmitostearate (Precirol® ATO 5) | Poloxamer 407 | 100 | Salatti-dorado et al. 2019 |
| Baicalin | Miglyol® 812, Precirol® ATO 5 | Pluronic® F68 | 92 | Shi et al. 2016 |
| | GMS, MCT | Soybean lecithin | 244.7 | Luan et al.2015 |
| Cardamom essential oil | Olive oil, Cocoa butter | Tween 80 | <150 | Keivani-Nahr et al. 2018 |
| Curcumin | Caprylic/capric triglyceride, GMS | Soya lecithin, Pluronic F-127 | 263.9 | Chen et al. 2016 |
| | Caprylic/capric triglycerides, stearic acid | Tween 80 and Pluronic F127 | 225.8 | Behbahani et al. 2019 |
| | MCT, stearic acid | Tween 80 | 200–500 | Chanburee and Tiyaboonchai 2017 |
| Curcuminoid | MCT, Precirol® ATO 5 | Poloxamer 188, Span 80 | 148–225 | Dolatabadi et al. 2021 |
| Ferulic Acid | IPM | Kolliphor RH40, Labrafil, Softisan 100 | <150 | Carbone et al. 2020 |
| | Cetyl palmitate, Gliceryl Oleate, isopropyl myristate, isopropyl palmitate, and isopropyl stearate (IPS) | | <100 | Carbone et al. 2014 |
| Ganoderma triterpenoids | MCT, Oleanolic acid, GMS | Poloxamer F68 | 164.42 | Shen et al.2015 |
| Genistein | GMS, MCT | Poloxamer F68 | 304.8 | Andrade et al. 2014 |
| Hesperetin | MCT, Gliseryl behenate | Sorbitan monooleate, POE-40 hydrogenated castor oil (HCO-40), | 100 | Simao et al. 2020 |
| | GMS, hexadecyl palmitate, amaranth oil, pumpkin seed oil | Tween 20, phosphatidylcholine, Synperonic PE | 110–125 | Lacatusu et al. 2018 |
| Quarcetin | MCT, Stearic acid | Soya lecithin | 215.2 | Chen-yu et al. 2012 |
| | MCT | Tween 80, Span 20, lecithin | 34–47 | Aditya et al. 2014 |
| *Rosmarinus officinalis* L., Lavandula *Origanum vulgare* and *Thymus capitatus* essential oils | Isopropyl myristate (IPM) | Kolliphor RH40 (Polyoxyl 40 hydrogenated castor oil), Labrafil (Oleoyl Macrogol-6 Glycerides), Softisan 100 (Hydrogenated Coco-Glycerides) | < 200 | Carbone et al. 2018 |
| Silybin | GMS, MCT | lecithin, Pluronic F68 | 232.1 | Jia et al. 2010 |
| Thymol | Calendula oil, illipe butter | Pluronic F68 | 107.7 | Pivetta et al. 2018 |
| Turmeric extract | Miglyol 812, Campritol 888-ATO | Poloxamer 407 | 112.4 | Karimi et al. 2018 |
| Ursolic acid | Capryol-90, Glyceryl Monostearate (GMS) | Tween 80 | 120 | Ahmad et al. 2018 |

## High-pressure homogenization (HPH)

A high-pressure homogenizer (HPH) is a compartment where excipients are passed through a micro-size nozzle at a high pressure ranging from 100 to 2000 bar. This process exerts mechanical and thermodynamic pressures on the excipients, generating high shear stress from strong turbulent eddies and cavitation forces, simultaneously reducing pressure along the nozzle. HPH can break down the lipid matrix and emulsify natural ingredients into nanosized droplets, offering technical feasibility that facilitates production upscaling to formulate NLCs. However, this mechanism produces sub-micrometer particles, which is the main drawback of HPH.

## High-shear homogenization (HSH) and ultrasonication

High-shear homogenization is a straightforward dispersal method for producing NLCs. The process commences with melting solid lipid at 5–10 °C, followed by stirring the heated lipid with an aqueous phase (surfactant) to the same temperature at high speed to form an emulsion. Subsequently, the mixture is dispersed through a homogenization valve and ultrasonicated to reduce the size of the resulting droplets. The warm emulsion is gradually cooled to a temperature at which lipids crystallize to create nanosized dispersions and ultracentrifuged to obtain concentrated dispersions. The resulting lipid nanoparticles have physicochemical and biopharmaceutical characteristics suitable for topical applications. However, the combination of this technique generates microparticles as a byproduct that impairs the nanocarrier quality. In addition, ultrasonication can introduce metal contaminants to the formulation.

## Microemulsion

Microemulsion is a simple method for developing NLCs, although the use of organic solvents is not recommended. This method exposes active drugs to high temperatures, which can be challenging for thermolabile substances. Initially, the bulk lipid is melted at 10 °C higher above its melting point, followed by the solubilization of the drug. The melted phase is added to the heated aqueous phase, such as surfactant and co-surfactants, and disturbed mechanically to produce an oil-in-water (o/w) microemulsion.

Subsequently, the microemulsion can be cooled rapidly to 2–3 °C in an ice-water bath while simultaneously agitated or added to the cold aqueous phase dropwise. The sudden temperature change causes lipids to crystallize, forming NLCs.

## Solvent emulsification/evaporation

Precipitating an o/w emulsion in an aqueous phase is essential to create NLCs using the solvent emulsification/evaporation method. In an aqueous phase, bulk lipids dissolved in a water-impermeable organic solvent are emulsified and the remaining solution is immediately precipitated to form nanoparticles. Compared to microemulsion, solvent evaporation does not include thermal stress induction but entails the dissolution of natural ingredients in a suitable solvent and evaporation, leaving behind nanosized lipid particles. However, organic solvents such as acetone, dichloromethane, ethyl acetate, and acetic acid may be present in the final product, which is a limitation of this technique.

## Membrane contactors

Melted lipid is forced through the membrane pores by a cylindrical device called a membrane contactor, resulting in the formation of tiny droplets. These droplets are removed by surfactants while moving through the aqueous phase inside the membrane module. The aqueous phase is maintained at the lipid melting point. NLCs are created when nanoparticles near the pore outlets are cooled to room temperature. This technique can change the membrane pore size to alter particle size.

## Phase inversion temperature (PIT)

Phase inversion is the interconversion between o/w and w/o emulsions due to thermal modifications, occurring at 'phase inversion temperature' (PIT). In this method, nanoparticles are formed by several mechanisms, including spontaneous inversion through freezing-and-heating cycles and lipid crystallization induced by irreversible thermal shocks that break emulsions.

## Coacervation

The technique forms nanoparticles from the coacervation of oppositely charged lipids and natural ingredients. In coacervation, NLCs are prepared by acidifying a micellar solution consisting of alkali salts of fatty acids. Before acidification, a polymeric stabilizer is added to water and heated to create a stock solution. To create a clear solution, the stock solution is heated above its Krafft temperature, while continuously agitated. The sodium salts of fatty acids are added, evenly distributed, and heated. The drug (dissolved in ethanol) is added to the clear solution while stirred continuously until a separate phase is formed. The mixture is added with coacervate gradually by acidification to produce a suspension. Subsequently, the suspension is cooled in a water bath and constantly agitated to obtain well-dispersed drug-loaded nanoparticles. Among the above techniques, several NLCs have been developed and tested using HPH due to its inclusion of cooling technology, energy efficiency, sustainability, and environmental friendliness. The preparation methods of NLCs are tabulated in Fig. 4, while Table 2 summarizes both the techniques and lipids used.

**Table 2.** Overview of methods, solid lipids, and liquid lipids used to prepare nanostructured lipid carriers (NLCs).

| Method | Solid Lipid | Liquid Lipid | Particle size (nm) | Reference |
|---|---|---|---|---|
| Emulsion evaporation | GMS (monoglyceride) | Caprylic/capric triglyceride (triglyceride) | 263.9 | Chen et al. 2016 |
| | Stearic acid (fatty acid) | Caprylic/capric triglyceride (triglyceride) | 263.9 | Chen et al. 2016 |
| | Stearic acid (fatty acid) | MCT (triglyceride) | 215.2 | Chen-yu et al. 2012 |
| Hot melt emulsification | Compritol 888 ATO (fatty acid ester) | MCT (triglyceride) | 60.1 | Li et al. 2021 |
| | Illipe butter (triglyceride) | Calendula oil (fatty acid, triacylglycerol) | 107.7 | Pivetta et al. 2018 |
| High-pressure homogenization | GMS (monoglyceride) | MCT (triglyceride) | 164.42 | Shen et al. 2015 |
| | GMS (monoglyceride) | Oleanolic acid | 164.42 | Shen et al. 2015 |
| | Precirol® ATO 5 (fatty acid ester) | Miglyol® 812 (triglyceride) | 92 | Shi et al. 2016 |
| High-shear homogenization | Compritol 888-ATO (fatty acid ester) | Miglyol 812 (triglyceride) | 112.4 | Karimi et al. 2018 |
| | Compritol 888-ATO (fatty acid ester) | MCT oil (triglyceride) | 148-225 | Dolatabadi et al. 2021 |
| | Cocoa butter (triglyceride) | Olive oil (triglyceride) | <150 | Keivani-Nahr et al. 2018 |
| | Precirol® ATO 5 (fatty acid ester) | Squalene (triterpenoid hydrocarbon) | 190–310 | Huang et al. 2008 |
| | Precirol® ATO 5 (fatty acid ester) | MCT (triglyceride) | 148–225 | Dolatabadi et al. 2021 |
| Microemulsion | Stearic acid (fatty acid) | Caprylic/capric triglycerides (triglyceride) | 225.8 | Behbahani et al. 2019 |
| | Stearic acid (fatty acid) | MCT (triglyceride) | 200–500 | Chanburee and Tiyaboonchai 2017 |
| Phase inversion temperature | Glyceryl behenate (fatty acid) | MCT (triglyceride) | 100 | Simao et al. 2020 |
| Probe-ultrasonication | Stearic acid (fatty acid) | Oleic acid (fatty acid) | 240 | Kelidari et al. 2016 |

GMS: Glyceryl monostearate; MCT: medium-chain triglyceride.

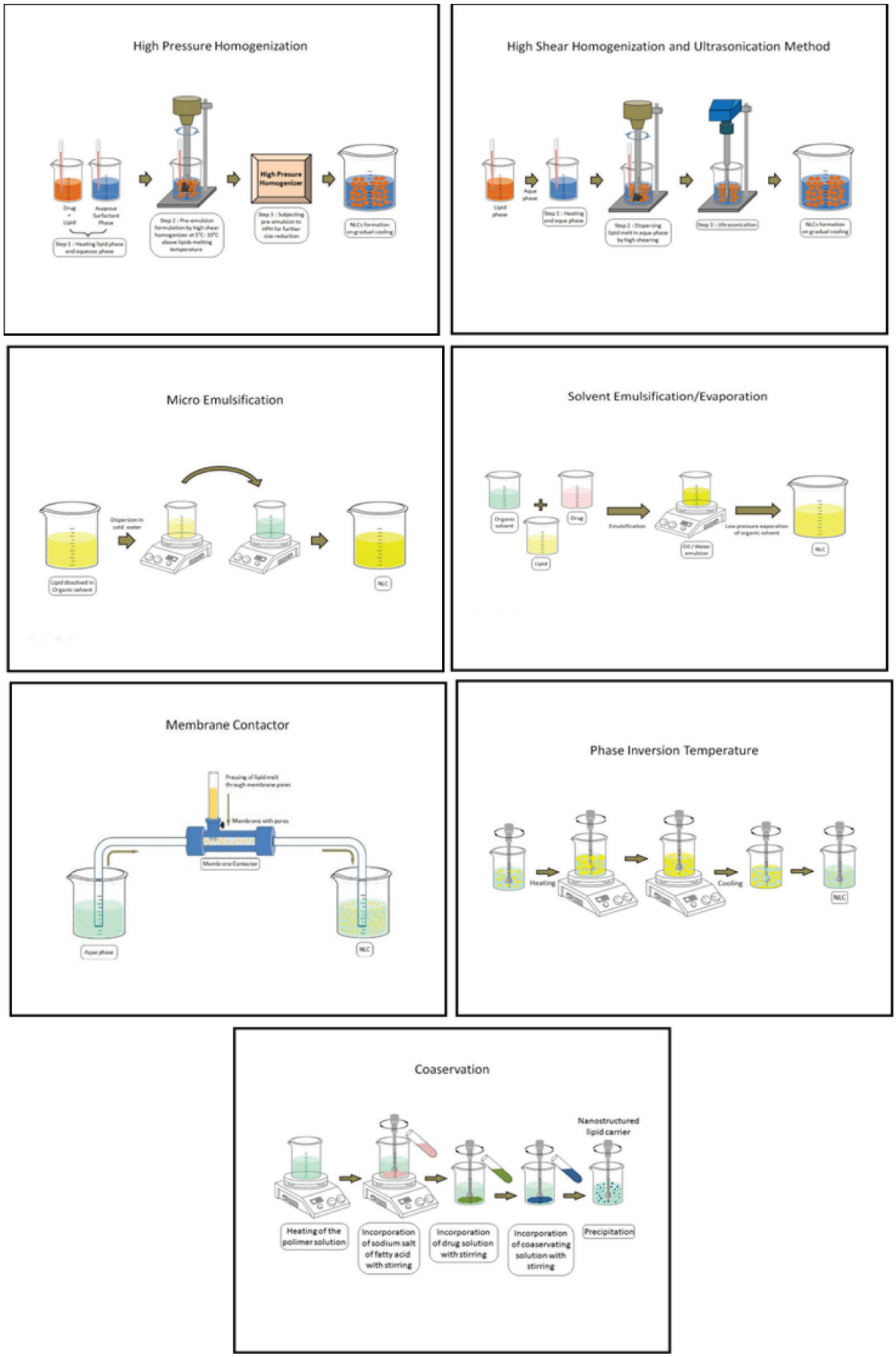


**Figure 4.** NLC Preparation Methods: High pressure homogenization; High shear homogenization and ultrasonication, Microemulsion, Solvent emulsification/ evaporation, Membrane contractor, Phase inversion temperature, Coacervation.

## NLC Characterization

Physicochemical characterization is required to control and confirm the quality and stability of NLCs produced. Furthermore, information on physical and chemical properties can facilitate the optimization of design for improved efficacy, stability, and safety. Some common techniques used to characterize NLCs are stated below (Chauhan et al. 2020; Nogueira et al. 2022).

1. Particle size analysis.
   Particle size is an essential parameter affecting the stability, bioavailability, and cellular uptake of NLCs. To measure the size distribution, techniques such as dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA) can be used. Generally, NLCs for cutaneous delivery of drugs typically have submicron particle sizes ranging from 40 to 1000 nm based on the lipids composition.
2. Zeta potential analysis.
   The zeta potential (ZP) is a determining factor of the nano dispersion's stability, describing the surface charge and showing long-term stability. Furthermore, ZP is calculated using electrophoretic mobility of the particle in aqueous media. At higher values, particle aggregation due to electrostatic repulsion has a lower probability of occurrence. Meanwhile, at lower ZP, there is a higher possibility for dispersions to coagulate or flocculate, potentially reducing stability. For electrostatically stable NLCs, the ZP of dispersion should be less than -30 mV or above +30 mV. The value of ZP can be measured using electrophoretic light scattering.
3. Morphology analysis.
   Transmission and scanning electron microscopies (TEM, SEM) including atomic force microscopy (AFM) are used to examine the surface morphology of NLCs. These techniques are effective for the dimensional and structural characterization of NLCs. TEM is a strong imaging technology enabling a high-resolution study of the internal structure and morphology of NLCs. It is capable of providing information on lipid nanoparticle's size, shape, and distribution. Meanwhile, SEM is used to investigate the surface morphology including roughness and shape of NLC particles. For this analysis, the sample is prepared by placing it on a gold or copper grid with a known mesh size, followed by staining using a heavy metal salt solution for high contrast in the electron microscope. After drying, the sample is examined under an electron microscope, where nanoparticles are identified against a dark background. Moreover, dehydration during sample preparation can alter the initial shape or structure of nanocarriers.
   AFM is used at the nanoscale to analyze the surface topography and mechanical characteristics of NLC particles, producing data on particle height and roughness. This method is a simple and non-invasive technology used to monitor and control the morphology as well as the size of lipid nanoparticles. The samples used in AFM are prepared by removing water to avoid alteration in the emulsifier phase and polymorphism in lipids. This method does not use beams or radiations but rather a sharp-tipped scanning probe attached to the free end of a spring-like cantilever. The interaction between the tip and surface of the specimen is assessed through deflection, oscillation, or shift in resonance frequency of cantilever motion.
4. Entrapment efficiency
   Entrapment efficiency (EE) is defined as the ratio of entrapped drug weight to total drug weight added to the dispersion. Subsequently, an ultrafiltration-centrifugation method is used to determine the amounts of drugs encapsulated per unit weight of the NLCs. A known NLC dispersion is prepared, and centrifugation is carried out in a centrifuge tube fitted with an ultrafilter. After suitable dilution, an appropriate analysis method is used to determine the amount of free drug supernatant.
5. *In vitro* release studies
   An *in vitro* release study evaluates the kinetics of drug release from NLCs under simulated physiological conditions. In this analysis, NLCs are designed for targeted drug delivery, enabling specific drug localization inside the skin layers. Furthermore, NLCs enable sustained drug release, which is useful for prolonged therapeutic activity. To accomplish this, the lipid matrix is modified for controlling drug release.
6. Crystallinity and polymorphism
   The crystallinity and polymorphism of lipids used in NLCs are essential factors in achieving controlled drug release and improving stability as well as efficiency. Meanwhile, differential scanning calorimetry (DSC) is carried out to obtain information about the lipid state, melting, and crystallization behavior of solid lipids in nanostructures. DSC is also used to analyze pure drugs, lipids, and nanoparticles. By conducting DSC, information about the structure of NLCs can obtained, particularly regarding the mixing behavior of solid and liquid lipids. Increased liquid lipid content also reduces crystallinity and improves imperfections in the highly ordered structure of NLCs. In principle, DSC operates based on varying enthalpy and melting points for different lipid modifications, where lower values result in smaller NLCs with a higher surface area and more surfactants.
   Another important tool for determining polymorphic structural changes in compounds is X-ray diffraction (XRD) analysis. The monochromatic X-ray beam is diffracted at different angles based on the type and arrangement of the atoms as well as the spacing between the planes in the crystals. In this process, lipids can cluster in several arrays, resulting in various polymorphic forms such as micelles, lamellar phases, tubular arrangements, and cubic phases.

The layer configuration, crystal structure, phase, and polymorphism of lipid and drug molecules are investigated using wide-angle and small-angle X-ray scattering techniques (WAXS, SAXS). WAXS and SAXS patterns also provide information on the length of the short and long spacings of the lipid lattice and the location of the active substance.

## Recent developments in the use of NLCs for natural active ingredient delivery

NLCs are a promising delivery method for hydrophobic drugs (Teeranachaideekul et al. 2008; Soleimanian et al. 2018; Shimojo et al. 2019; Tortorici et al. 2022). In several studies, NLCs show promising results in the delivery of natural products, particularly in improving stability and bioavailability. NLCs also enhance pharmacological activities and provide higher protection from toxicity compared to other nanolipid-based delivery systems (Thakur et al. 2011; Aditya et al. 2014; Krasodomska et al. 2016; Bhise et al. 2017; Huang et al. 2017; Elmowafy et al. 2018). Examples of NLCs are given in this section to highlight their potential as a delivery system for natural medicines, as presented in Table 1.

## NLCs increase the effectivity and bioactivity of natural active ingredients

Several studies have shown that NLCs function as a carrier to enhance the bioactivity and efficacy of natural substances. Quercetin is the flavonoid with the most potent antioxidant activity. In addition to this particular activity, it demonstrates additional pharmacological properties, including anti-inflammatory effects. Chen-Yu et al. (2012) demonstrated that NLC increased the anti-oxidative and anti-inflammatory properties of quercetin, thereby offering potential benefits in the management of inflammatory disorders. Comparatively to the quercetin-containing polyethylene glycol solution, NLC additionally enhanced permeation and increased the quantity of substance retained in the epidermis.

In 2022, de Barros et al. looked into how loading quercetin onto nanostructured lipid carriers made from natural plant oils would work together to fight bacterial skin infections. Five nanostructured lipid carrier systems were designed, each comprising a distinct oil (sunflower, olive, corn, coconut, and castor). The encapsulation of quercetin increased the antioxidant capacity of nanocarriers and decreased their cytotoxicity. Additionally, it was shown that the antibacterial activity of systems containing quercetin against Staphylococcus aureus was enhanced (de Barros et al. 2022).

Sesamol, a phenolic compound with antioxidant activity, was one of the ingredients incorporated into NLC. By incorporating sesamol into an NLC/SLN, Puglia et al. (2017) were able to regulate the rate of sesamol diffusion through the epidermis, thus preserving high concentrations of sesamol in the uppermost layers of skin. Moreover, NLC and SLN extended by 40 hours the antioxidant activity of sesamol.

In Badea et al. (2015), NLCs were developed by combining the active natural ingredient basil oil with the antifungal nystatin. The final products showed high antioxidant activity, 93–96%, while maximum antifungal activity against *Candida albicans* was observed in NLCs with 2% basil oil and 1% nystatin. Karimi et al. (2018) found that turmeric extract had significantly enhanced antioxidant activity when delivered in NLCs. Similarly, antimicrobial activity against all the gram-negative bacilli was observed in microbiological tests by agar dilution.

Furthermore, Chen et al. (2016) through an in vivo study, found that NLC-based curcumin gel showed a significant anti-inflammatory effect when topically administered to rats with auricular edema, without skin irritation. In Shen et al. (2015), GTs showed better therapeutic effects against inflammation when delivered in NLCs than in emulgels.

## NLCs increase the stability of natural active ingredients

NLCs are also appropriate for the delivery of unstable natural active ingredients. Mitri et al. (2011) documented an elevation in the chemical and photostability of the carotenoid lutein and lutein subsequent to their integration into NLC. Additionally, compared to free lutein, the NLC formulation increased penetration rates and sustained the release of the active ingredient. Lycopene is another carotenoid that possesses anti-inflammatory and antioxidant properties. This pigment is one of the most potent antioxidants known and is lipophilic. Okonogi and Riangjanapatee (2015) developed NLC to safeguard lycopene, thereby postponing its chemical degradation due to its extreme instability.

Jiamphun and Chainaya (2023) conduct research on the development of nanostructured lipid carriers (NLCs) and assess their efficacy in increasing the stability and delivery of vanillic and ferulic acid in an aqueous enzymatic extract derived from glutinous rice husk. In contrast to a solution, it was observed that NLCs with high entrapment efficiencies effectively encapsulate and protect both vanillic and ferulic acid.

Zheng et al. (2023) analyze co-loaded nanostructured lipid carriers (NLC) with perilla seed oil (PSO) and formononetin (FMN). The formulation design for enhancing the stability and antioxidant activity of FMN while postponing the oxidation of PSO. FMN-PSO-NLC was synthesized melt-emulsification ultrasonic method. The stability and antioxidant capability of FMN-PSO-NLC were notably enhanced.

Cinnamon essential oil (CEO) possesses a number of advantageous characteristics and exhibits promising po-

tential as a nutraceutical. However, it is important to acknowledge that it may also possess certain drawbacks, including inadequate stability against heat, oxygen, and light during processing and storage, as well as an unpleasant taste. Bashiri et al. (2020) did research in which they made NLC that was loaded with cinnamon essential oil (CEO). They did this by mixing different solid lipids (cocoa butter), liquid consumable oils (sesamol, sweet almond, and black seed oil), and a surfactant (Tween 80). The NLC derived from almond oil exhibited encouraging characteristics in terms of enhancing the stability and protection of CEO across various conditions.

Lacatusu et al. (2018), Tsai et al. (2012), and Ruktanonchai et al. (2009) reported that NLCs can enhance the stability of numerous natural active ingredients, including mangiferin, alpha-lipoic acid, baicalein, and hesperidin.

## NLCs control drug release and deliver natural active ingredients with different polarity

NLCs have the ability to regulate drug release into the systemic circulation and minimize systemic side effects. This lipid-based system provides a controlled release profile for various active components. According to Lasoń et al. (2016), the terpene release pattern from an NLCs matrix is biphasic, indicating that all active components are gradually released after an initial burst effect. Early initial release (burst effect) can be attributed to large amounts of medicinal ingredients such as oils accumulating in the outer shell of nanoparticles.

The release rate of zedoary turmeric oil from SLNs can also be increased through NLCs, adjusted by modifying the oil content in the formula (Zhao et al. 2010). Additionally, genistein is released from NLCs gradually than from SLNs (Andrade et al. 2014). In a study by Jia et al. (2010), silybin-loaded NLCs showed larger areas under the tissue concentration-time curve (AUCs) and were circulated in the bloodstream longer compared to silybin solution. This indicated that NLCs offered a sustained release and a targeting system for the antihepatopathic agent. Ahmad et al. (2018), Huang et al. (2017), and Shi et al. (2016) successfully showed the ability of NLCs to prolong the release of several natural active ingredients, including ursolic acid, baicalin, and quercetin.

## Conclusion

In conclusion, this review showed the effectiveness of NLCs as drug delivery system with high loading capacity and sustained release patterns suitable for treating skin diseases. The results showed that NLCs had been used for delivering antioxidants, gaining much attention in the cosmetic industry due to their potential benefits in improving skin hydration, occlusion, bioavailability, and skin targeting. This lipid-based system could also be prepared using various techniques and characterized through particle size, ZP, morphology analyses, and drug encapsulation efficiency measurement. However, there are still limitations associated with the technology, such as cytotoxic effects, the need for careful selection compatible with lipids, as well as limited preclinical and clinical studies. To overcome these limitations, further research was recommended to explore the applications of NLCs in delivering proteins, peptide drugs, and targeted genes.

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Iveta Nedeva, Vlayko Vodenicharov, Vera Karamfilova, Yavor Assyov

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Research Article

## Association study between $D_2$ receptor A-241G, rs1799978 genetic variation and olanzapine efficacy in Iraqi schizophrenic patients

Zahra Jawd Mohammed Ali Al-Musawi, Atheer Majid Rashid Al-Juhaishi

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Review Article

## Malaria in Indonesia: current treatment approaches, future strategies, and potential herbal interventions

Tina Christina L. Tobing, Wahrianto, Eka Saputri, Nasywa Inayah Wafa, Putri Daffa Zulfianti, Lidwina Iswari Sihaloho, Annisa Rabbiatul Husna, Devia Salsabila, Fito Hansen Hotasi Silalahi, Alex Insandus Sitohang, Aysiah Sabrina, Atika Darayani Hasyati Harianja, Silvyani Agustilova Barus, Salwa Sabina, Annisa Aulia Rahma, Adrian Joshua Velaro, Khairunnisa Khairunnnisa, Emil Salim, Fahrul Nurkolis, Rony Abdi Syahputra

10.3897/pharmacia.71.e116095

15-02-2024



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Research Article

## Adherence to disease-modifying therapies among patients with multiple sclerosis in Bulgaria – A real world study

Yoana Seitaridou, Teodora Chamova, Maria Kamusheva

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Research Article

## Phytoconstituents, antioxidant, and cholinesterase inhibitory activities of the leaves and stem extracts of *Artocarpus sericicarpus*

Suciati Suciati, Erlinda Rhohmatul Laili, Hamizah Haula, Lidya Tumewu, Nitra Nuengchamnong, Nungruthai Suphrom, Aty Widyawaruyanti

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Tanya Zlatanova, Jeliazko Arabadjiev

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Research Article

## Fenugreek galactomannan: High-Performance Thin-Layer Chromatography (HPTLC) method for identification and quantification of galactose and mannose

Vanya Nalbantova, Velislava Todorova, Niko Benbassat, Cedric Delattre

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## Gallates – toxicological data and a pilot study on the prevalence of contact sensitization

Maya G. Lyapina, Silvia P. Tsanova-Savova, Maria G. Nikolova, Maia L. Vizeva, Georgi Ts. Momekov

10.3897/pharmacia.71.e120507

23-02-2024



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Research Article

## HPLC method for the determination of nifedipine in rat plasma: development, validation, and application to pharmacokinetic drug-herb interaction study

Devy N. A. Hasanuddin, Afrillia Nuryanti Garmana, Lucy Sasongko

10.3897/pharmacia.71.e119198

26-02-2024



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# Pharmacia

**COUNTRY**

Bulgaria

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Media Ranking in Bulgaria

**SUBJECT AREA AND CATEGORY**

Health Professions
- Pharmacy

Medicine
- Pharmacology (medical)

Pharmacology, Toxicology and Pharmaceutics
- Pharmaceutical Science

**PUBLISHER**

Pensoft Publishers

**H-INDEX**

18

**PUBLICATION TYPE**

Journals

**ISSN**

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**COVERAGE**

1945, 1954-1955, 1987-1991, 1997-2023

**INFORMATION**

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phdptp@gmail.com

SCOPE

The journal Pharmacia publishes original research papers, preliminary communications, short communications (notes) and review articles, in the pharmaceutical and related sciences. The Journal also publishes announcements, reports of conferences, biographies (anniversaries, awards, etc.) as well as book reviews. Pharmacia is a multidisciplinary journal devoted to pharmaceutical and allied sciences. Topics covered are: analytics, biochemistry, biopharmaceutics, biotechnology, cell cultures, clinical pharmacy, drug delivery, drug design, drug disposition, drug stability, medicinal chemistry, metabolism, molecular modeling, basic and clinical pharmacology, pharmacognosy, pharmacoepidemiology, pharmacoeconomics, pharmacodynamics and pharmacokinetics, social pharmacy, radiopharmaceuticals, toxicology.



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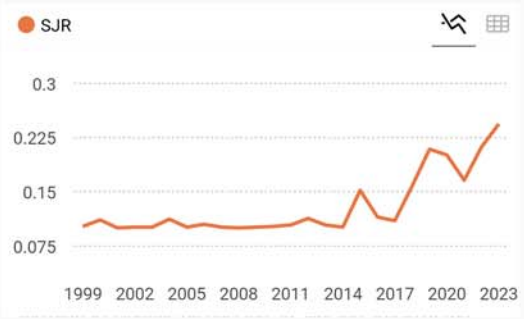


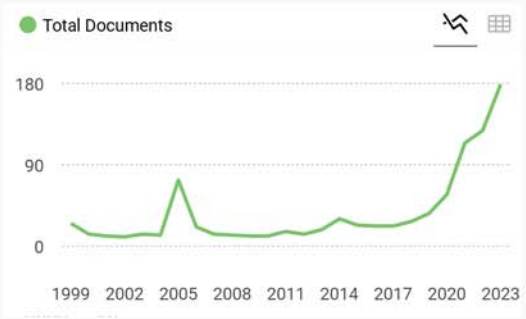


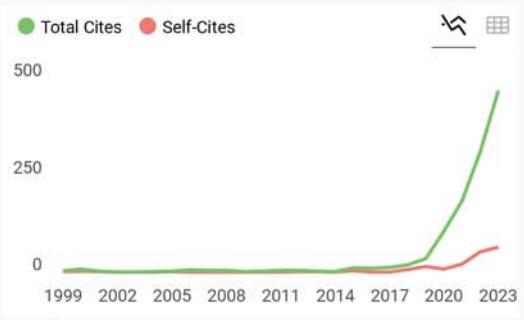


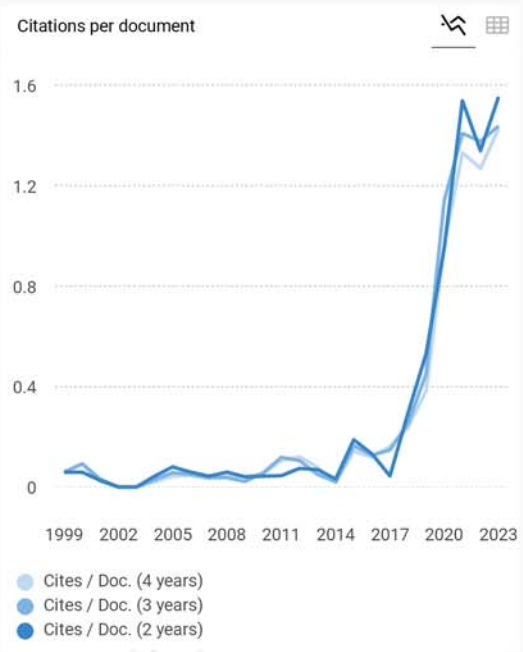


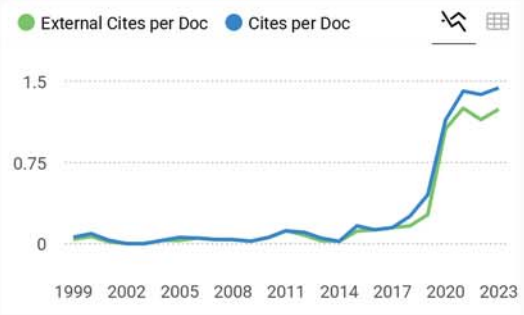


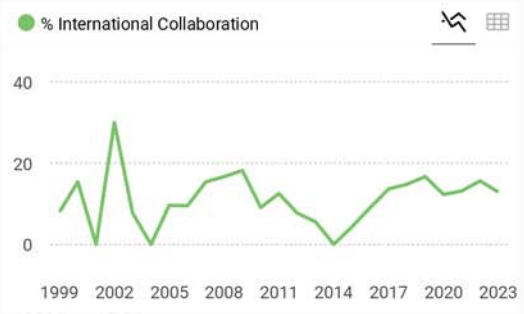


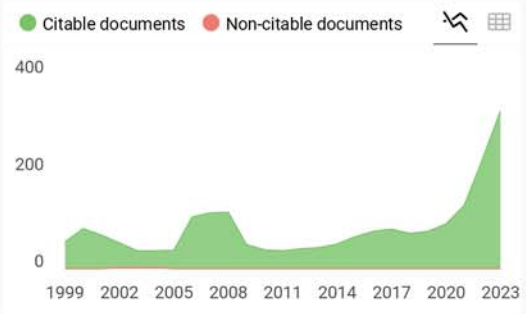


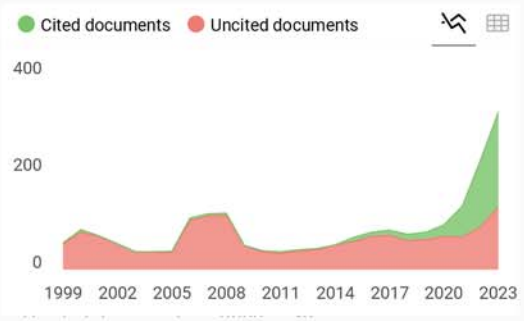



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I can see on the site of this journal showing it is impact factor 1.1 , but when I search in Web of science website it doesn't show those information, how can I confirm?

reply

SCImago Team

**Melanie Ortiz** 8 months ago

Dear Delveen, thank you very much for your comment. SCImago Journal and Country Rank uses Scopus data, our impact indicator is the SJR (Check it above). We suggest you consult the Journal Citation Report for other indicators (like Impact Factor) with a Web of Science data source. Best Regards, SCImago Team

N **Naelaz Zukhruf** 1 year ago

Hello...Could you tell me about this journal, Is still indexed in Scopus 2021.
If I search in Scopus, this journal Scopus coverage from 1997-present. I Have already read your explanation that the SJR indicators for 2020 will be available in June 2021. And now March 2023 so how about this indicator?

Hopefully I will find the answer soon
Thank you

reply

SCImago Team

**Melanie Ortiz** 1 year ago

Dear Naelaz,
Thank you for contacting us. Our data come from Scopus, they annually send us an update of the data. This update is sent to us around April / May every year. The SJR for 2021 was released on 11 May 2022. Therefore, the indicators for 2022 will be available in May/June 2023 and before that date we can´t know what will happen with this journal. Best Regards, SCImago Team

N **Naela** 1 year ago

Hello...
Could you tell me about this journal, Is still indexed in Scopus 2021.
If I search in Scopus, this journal Scopus coverage from 1997-present. I Have already read your explanation that the SJR indicators for 2020 will be available in June 2021. And now March 2023 so how about this indicator

Hopefully I will find the answer soon
Thank you

reply

SCImago Team

**Melanie Ortiz** 1 year ago

Dear Naela,
Thank you for contacting us. Our data come from Scopus, they annually send us an update of the data. This update is sent to us around April / May every year. The SJR for 2021 was released on 11 May 2022. Therefore, the indicators for 2022 will be available in May/June 2023.
We suggest you consult the Scopus database directly to see the current index status as SJR is a static image of Scopus, which is changing every day.
The Scopus' update list can also be consulted here:
https://www.elsevier.com/solutions/scopus/how-scopus-works/content
Best Regards, SCImago Team

A

**Angel T. Alvarado** 2 years ago

Sirs
Scimago
Good afternoon
I verified until March 2022 that Pharmacia was in Q2; Today I am surprised that it is in quartile 3.
Please, could you tell me the exact date of the evaluation of the magazine and its fall to Q3.
Thanks for your attention.
Angel Alvarado

reply

SCImago Team

**Melanie Ortiz** 2 years ago

Dear Angel,
Thank you for contacting us. Our data come from Scopus, they annually send us an update of the data. This update is sent to us around April / May every year. The SJR for 2021 was released on 11 May 2022.
Best Regards, SCImago Team

N

**Nur Alam Abdullah** 2 years ago

Dear editorial team of the pharmacia, I would like to ask how long it will take us as authors to get confirmation of the rejection or acceptance of our manuscript.
tx regards.

reply

SCImago Team

**Melanie Ortiz** 2 years ago

Dear Nur,
Thank you for contacting us.
We are sorry to tell you that SCImago Journal & Country Rank is not a journal. SJR is a portal with scientometric indicators of journals indexed in Elsevier/Scopus.
We suggest you visit the journal's homepage or contact the journal's editorial staff , so they could inform you more deeply.
Best Regards, SCImago Team

L

**Linda Laksmiani** 3 years ago

Hello...Could you tell me about this journal, Is still indexed in Scopus 2021.
If I search in Scopus, this journal Scopus coverage from 1997-present. I Have already read your explanation that the SJR indicators for 2020 will be available in June 2021. And now August 2021 so how about this indicator?

Hopefully I will find the answer soon
Thank you

reply

SCImago Team

**Melanie Ortiz** 3 years ago

Dear Linda,
Thank you for contacting us. Our data come from Scopus, they annually send us an update of the data. This update is sent to us around April / May every year. The SJR for 2020 has been released on 17 May 2021 (check it above). Therefore, the indicators for 2021 will be available in May/June 2022.
Best Regards, SCImago Team

D

**Dr.Alex** 3 years ago

Dears,

Kindly can you tell me is this journal still ranked in sjr during 2020-2021?

Regards

reply

SCImago Team

**Melanie Ortiz** 3 years ago

Dear Dr.Alex,
Thank you for contacting us. Our data come from Scopus, they annually send us an update of the data. This update is sent to us around April / May every year. The SJR for 2019 was released on 11 June 2020. Therefore, the indicators for 2020 will be available in June 2021.
Best Regards, SCImago Team

M

**Ms.pharmadi** 3 years ago

Dear

Kindly could you tell me does this journal still indexed in web of science and scopus in 2021

Many thanks!

reply

SCImago Team

**Melanie Ortiz** 3 years ago

Dear Ms. Pharmadi,
Thank you for contacting us.
SJR is a portal with scientometric indicators of journals indexed in Elsevier/Scopus. Unfortunately, we cannot help you with your request referring to the index status. We suggest you consult Scopus database (see the current status of the journal) or the mentioned database for further information.
Best Regards, SCImago Team

T

**Tamara** 3 years ago

Could you please tell me, is this magazine re-indexed in the Scopus database in 2021?

reply

SCImago Team

**Melanie Ortiz** 3 years ago

Dear Tamara,
Thank you very much for your comment.
All the metadata have been provided by Scopus /Elsevier in their last update sent to SCImago, including the Coverage's period data. The SJR for 2019 was released on 11 June 2020. We suggest you consult the Scopus database directly to see the current index status as SJR is a static image of Scopus, which is changing every day.
For further information, please contact Scopus support: https://service.elsevier.com/app/answers/detail/a_id/14883/kw/scimago/supporthub/scopus/
Best Regards, SCImago Team

H

**Haider F. Shamikh Al-Saedi** 4 years ago

Hello
i hope to get submission in ypour journal how to get it ?

reply

SCImago Team

**Melanie Ortiz** 4 years ago

Dear Haider,
thank you for contacting us.
We are sorry to tell you that SCImago Journal & Country Rank is not a journal. SJR is a portal with scientometric indicators of journals indexed in Elsevier/Scopus.

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Best Regards, SCImago Team

T **taras** 6 years ago

Good day. I would like to publish an article on pharmacological research in your journal.
I would like to know if you are printing an article and what requirements to the article, and what price article?
Thank you.
Good day for you.

reply

SCImago Team

**Elena Corera** 6 years ago

Dear Taras, in the link below you will find the information corresponding to the author's instructions of this journal. Best regards, SCImago Team
http://ores.su/en/authors/

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Publisher: Pensoft Publishers

ISSN: 0428-0296

Subject area: Health Professions: Pharmacy | Pharmacology, Toxicology and Pharmaceutics: Pharmaceutical Science | Medicine: Pharmacology (medical)

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