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Nanostructured Lipid Carrier as a Topical Drug Delivery System: A Review

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ABSTRACT

Nanostructured Lipid Carrier (NLC) represents an advancement in lipid nanoparticle technology, addressing the limitations of Solid Lipid Nanoparticles (SLN). NLC is a delivery system that offers several advantages, such as significantly improved entrapment efficiency, reduced drug expulsion during long-term storage, and increased contact between the drug and the stratum corneum, thereby enhancing drug penetration. The methods used to manufacture NLC include high energy-required such as high-pressure homogenization and high shear homogenization, low energy-required such as microemulsification and phase inversion, and very low or no energy-required such as solvent evaporation and solvent injection. The basic components of an NLC are solid lipids, liquid lipids, and surfactants or mixtures of surfactants. This narrative review refers to several previously published databases on the types, preparation methods, and physical properties of NLC. This review emphasizes explanations pertaining to the role of NLC as a drug delivery system for topical applications.

INTRODUCTION

Drug delivery systems refer to devices that allow the entry of active pharmaceutical ingredients into the body, so that the efficacy and safety of these drugs can be increased by regulating the rate, timing, and location of drug release within the body (Putra *et al*., 2016). From a pharmaceutical perspective, this delivery system offers advantages including increased stability, the potential for drug delivery of different polarities, increased bioavailability, and efficiency of drug absorption (Otarola *et al*., 2015).

Among various drug delivery, the most promising drug delivery is lipid nanoparticles. Originally, Müller and Gasco pioneered the development of Solid Lipid Nanoparticles (SLN) in the 1990s to eliminate the use of organic solvents employed in creating polymeric nanoparticles (Elmowafy and Al-Sanea, 2021). In essence, SLN are lipid formations on a nanoscale that retain solidity under typical body temperatures, upheld by the presence of surfactants (Shanmukhi, 2013). However, SLN have limitations such as limited drug loading capacity, potential gel formation, polymorphism, and during storage drug expulsion (Mukherjee *et al*., 2009; Poonia *et al*., 2016; Chauhan *et al*., 2020).

Nanostructured Lipid Carriers (NLC) appear as the next generation of lipid nanoparticles that overcomes the weaknesses of SLN. The manufacturing of NLC involves the use of biodegradable lipids that seamlessly blend solid and liquid lipids with emulsifiers. The introduction of liquid lipids disrupts the solid lipid structure, creating an irregular crystalline pattern that effectively prevents drug leakage and enables a substantial drug payload (Jain *et al*., 2017). In contrast to SLN, NLC has distinctive epidermal occlusion. They have the ability to inhibit water evaporation, consequently enhancing the permeation of bioactive substances into the stratum corneum. Müller and colleagues describe NLC as an "occlusive plastic foil" that is not visible and augments penetration

(Müller *et al*., 2011). Recently, NLC has emerged as a viable alternative to SLN, polymeric nanoparticles, emulsions, microparticles, liposomes, among others (Jaiswal *et al*., 2016). These versatile nanocarriers are effective for delivering both hydrophilic and lipophilic drugs. NLC appears as talented drug delivery for oral, parenteral, ocular, pulmonary, topical, and transdermal routes (Chauhan *et al*., 2020).

NLC offer significant advantages for both pharmaceutical and cosmetic uses when applied topically or transdermal. They comprise lipid components that are biologically active and biodegradable, resulting in reduced toxicity. NLC possess various beneficial characteristics for topical and transdermal applications, including adhesion, occlusion, hydration, lubrication, smoothness, emollient properties, enhanced skin penetration, and protection of active ingredients from degradation. Additionally, the formulation imparts a whitening effect and maintains the effectiveness of active ingredients (López-García and Ganem-Rondero, 2015).

A pathway through which NLC can penetrate the skin surface when applied topically is the appendageal routes, specifically via hair follicles. Hair follicles serve as effective reservoirs for nanoparticles applied topically, often penetrating deeply into the tissue, reaching up to 2000 μm. The significant storage capacity within hair follicle structures facilitates enhanced permeation and sustained release. Medication particles accumulate within the follicular structure, allowing for drug diffusion from the nanocarrier into the skin (Rancan and Vogt, 2014).

In the manufacture of NLC systems, it is important to pay attention to the properties and materials used in the formulation, because they really influence the physicochemical properties of the NLC formula such as organoleptic, pH value, particle size, viscosity, and drug entrapment efficiency. Therefore, these physicochemical properties may ultimately influence how effective the NLC system is in transporting bioactive compounds (Shah *et al*., 2016). The main composition that needs to be considered is the selection of the lipid phase to be used, including melting point, crystal morphology, viscosity, and polarity (Listiyana *et al*., 2020).

METHODS

This review focuses on descriptions of NLC, emphasizing their effectiveness as a drug delivery system for topical applications, and provides insights and potential for further research of lipid nanoparticles. The articles were obtained from reputable online databases, such as Google Scholar, PubMed, and GARUDA based on a filtering process using some keywords including "*Lipid Nanoparticles*", "*NLC*", and "*Transdermal Application*".

RESULTS AND DISSCUSSION

Definition of Nanostructured Lipid Carrier

NLC represents the advancement beyond SLN and acts as a carrier system for delivering drugs. It comprises a mixture of solid and liquid lipids that create a lipid framework, stabilized by a surfactant (Khurana *et al*., 2012). NLC has attracted significant research attention as an outstanding drug delivery system, amalgamating the advantages of liposomes, emulsions, and polymer nanoparticles (Martin, 2012).

Advantages and Disadvantages of Nanostructured Lipid Carrier

NLC has several advantages such as improving drug loading capacity by imperfect matrix formation (Vyas *et al*., 2014), solid and liquid lipids used in NLC can stabilize the system physically and chemically (Hendradi *et al*., 2021), liquid lipids improve the dissolvability of active substances with low water solubility (Hendradi and Patimah, 2018), NLC minimizes drug leakage over prolonged storage (Subramaniam *et al*., 2020), and increases the stability of the Active Pharmaceutical Ingredients (API) (Pezeshki *et al*., 2014). NLC is occlusive on the skin because it increases skin hydration so that drugs can easily penetrate the skin, which is due to decreased cell density and wider spacing between cells (Hendradi *et al*., 2021). Besides that, larger surface area results in longer residence time on the skin surface, resulting in longer skin contact time of the drug, enabling sustained release (Bawazeer *et al*., 2020).

Despite its advantages, NLC has limitations. These include potential irritant and sensitizing effects of surfactants (Jaiswal *et al*., 2016), cytotoxicity due to the nature and concentration of the lipid matrix, lipid stability issues (Chauhan et al., 2020), some compounds cannot be formulated in NLC, i.e. antioxidants (Aisiyah *et al*., 2019), and inadequate incorporation of hydrophilic molecules along with the presence of spatially incompatible lipids that lead to greater lipid modification and aggregation, making them difficult to obtain on the market (Sapkota *et al*., 2015).

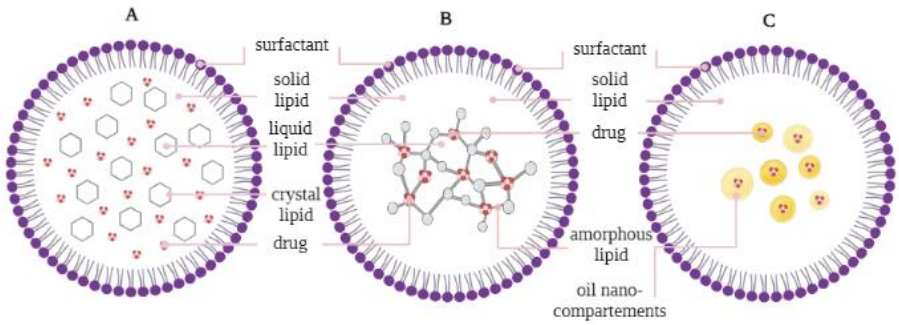

Figure 1. Types of NLC (A) imperfect crystal (B) amorphous (C) multiple (Li *et al*., 2017).

NLC type I (disordered crystal model) (Figure 1)

This type of NLC has poor solid matrix structure (Sharma and Baldi, 2018). The type I NLC can accommodate drugs in the amorphous group because with an irregular matrix, it causes many cavities and spaces (Chauhan *et al*., 2020). This type involves blending spatially differing liquid lipids like glycerides and solid lipids varying in carbon chain saturation and length (Selvamuthukumar and Velmurugan, 2012; Khosa *et al*., 2018). Due to changes in lipid structure, problems such as drug class will arise and cause imperfections in the lipid matrix due to the crystallization method (Shah *et al*., 2015).

NLC type II (amorphous model) (Figure 1)

This type of NLC can increase drug loading by solid and liquid lipids, resulting in an amorphous matrix (Gomaa *et al*., 2022). In the type II method, the lipid matrix is consistently amorphous while remaining in a solid state (Iglic *et al*., 2019). Crystallization techniques and methods often result in drug expulsion, so NLC can be formulated using a mixture of solid lipids such as hydroxyoctacosanyl hydroxyl stearate, isopropyl palmitate or medium-chain triglyceride (MCT). Noncrystalline NLC are formed solid (Sharma and Baldi, 2018).

NLC type III (multiple type) (Figure 1)

In this type, the lipid matrix is formed from more liquid lipids so that it is distributed throughout the solid matrix, and causes more drug solubility in the liquid lipid compartments, thus allowing higher drug loading. In addition, the solid lipid functions as a barrier, inhibiting drug leakage and enabling sustained release (Khosa *et al*., 2018). Specifically, for lipophilic drugs, dissolution in the oil phase can occur, followed by the cooling step of the high-temperature homogenization process after the type II process (Sharma and Baldi, 2018).

Components of Nanostructured Lipid Carrier

Lipid

The NLC matrix is composed of solid and liquid lipids, with ratios ranging from 70:30 to 99.9:0.1 (Souto *et al*., 2020). The overall lipid content of NLC can vary between 5% to 40% (Souto *et al*., 2020). It is crucial to carefully select an appropriate lipid before proceeding with nanoparticle preparation. The properties of the nanocarriers can be affected by the type and structure of the lipid used (Chauhan *et al*., 2020). In general, lipid selection is based on physiological tolerability, physicochemical structure, drug solubility, and compatibility of solid or liquid lipid (Elmowafy and Al-Sanea, 2021). The degree of crystallization in the different lipids utilized also affects drug encapsulation and loading, as well as size, charge, and effectiveness (Noor *et al*., 2017). Research has demonstrated that increasing the lipid quantity by 5-10% leads to a rise in particle size (Imran *et al*., 2017).

Widely used solid lipids are glyceryl behenate, soy phosphatidylcholine, glyceryl monostearate, cetyl alcohol, and stearyl alcohol. The solid lipids used must be acceptable and biodegradable (Chen *et al*., 2013). Frequently employed liquid lipids include carnauba wax, oleic acid, caprylic acid, soybean lipid, and olive oil (Tamjidi *et al*., 2013).

Surfactant

NLC can be stabilized by surfactants or mixtures of surfactant at 1.5 to 5% (w/v) (Elmowafy and Al-Sanea, 2021). These surfactants play a crucial role in maintaining stability by reducing the interfacial tension between the lipid and aqueous phases due to their amphiphilic nature, ideally positioned at

the interface (Souto *et al*., 2020). Therefore, surfactants are necessary to enhance the nanoparticle interface quality for achieving stability (Han *et al*., 2008). Surfactant type and concentrations affect the quality and efficacy of NLC. Besides that, the selection of surfactants can affect the toxicity, structural robustness, and crystalline arrangement of NLC (Karn-Orachai *et al*., 2014). The surfactant systems also affect the degree of drug solubility and permeability. Surfactants selection is based on the administration route, its impact is on the size of particles, modification of lipid, and the value of Hydrophilic-Lipophilic Balance (HLB) (Chauhan *et al*., 2020). The HLB of both the lipid and the lipid matrix is assessed to determine the necessary quantity of emulsifier to incorporate into the formulation (Keck *et al*., 2014).

Ionic surfactants can increase the surface charge of nanoparticles, induced electrostatic repulsion, and physical stability can be improved (Souto *et al*., 2020). Through the steric stabilizing effect of nonionic surfactants, nanoparticle aggregation can be avoided (Souto *et al*., 2020).

Other components

Organic salts and ionic polymers can act as opposing ions when creating nanostructured carriers to tackle the task of encapsulating water-soluble drug compounds. Another type of additives used in NLC formulation is surface modifiers, designed to reduce their absorption by macrophages in the Reticuloendothelial System (RES). Hydrophilic polymers like PEG, poloxamines, or poloxamers are utilized to envelop the lipid particles, prolonging the presence of drug molecules in the systemic circulation. Surface modification can provide additional benefits such as improved physical stability, biocompatibility, drug targeting, and enhanced circulation across epithelial barriers (Shah *et al*., 2015; Üner and Yener, 2007).

Requirements of Nanostructured Lipid Carrier

NLC is expected to have characteristics including a particle size ranging from 10 to 1000 nm (Kovács *et al*., 2017). In general, topical formulations have a particle size of 200 to 300 nm (Nayak *et al*., 2018), a homogeneous size of particle distribution (PDI < 1), pH is expected to enter the skin range of 4.0 to 6.8 to prevent skin irritation (Kon *et al*., 2017), viscosity 32.5 to 2499.5 cPs, zeta potential value ± 30 mV in order to obtain high electrostatic stabilization of nanoparticles and avoid aggregation, spherical particle morphology, has entrapment efficiency of 80 to 99%, and is stable during storage (Annisa *et al*., 2016; Tamjidi *et al*., 2013; Salvi and Pawar, 2019).

Preparation methods of Nanostructured Lipid Carrier

Categorization of methods can be done into three types based on the energy they require:

High energy-required methods

High-Pressure homogenization

The advantages of High-Pressure Homogenization (HPH) are not only short production times, but it also allows easy transfer from laboratory to large-scale production (Beloqui *et al*., 2016). Furthermore, this technique is simple to upscale and is an appealing method employed in the production of drugs and topical cosmetics (Leonida and Kumar, 2016). The high-pressure used in the homogenization process also avoids the use of organic solvents in the formulations, making it environmentally friendly (Chauhan *et al*., 2020). In this method, a high-pressure sample is forced through a narrow slit of about a few microns. Particle sizes can be reduced to the submicron range due to the presence of high shear stresses and cavitation forces (Souto *et al*., 2020). This method can be done with both high and low temperatures by being dissolved or dispersed about 5°C above the melting point (Souto *et al*., 2020).

a. Hot HPH

The pre-emulsion formed from the lipid mixture dispersed in the surfactant and heated to a suitable temperature is fed into an Ultra-Turax homogenizer, maintaining a controlled temperature for a duration of 3 to 5 cycles at pressure levels ranging from 500 to 1500 bar, then followed by cooling the nanoemulsion so that it can form nanoparticles (Chauhan *et al*., 2020). Since the high-temperature causes the viscosity to decrease, it can reduce the particle size to become smaller (Naseri *et al*., 2015). The limitation of this method is that the compounds are very sensitive to temperature which can be partitioned from the lipid to the aqueous phase at high-temperatures (Grumezescu, 2016; Souto *et al*., 2020).

b. Cold HPH

This method, as outlined by Chutoprapat *et al.* (2022), proves effective in addressing challenges such as drug degradation during the pre-emulsion stage and crystallization of nanoemulsions leading to inefficient drug loading. This method is used for compounds that are sensitive to temperature and hydrophilic (Souto *et al*., 2020). Although this method minimizes heat stress, it cannot entirely

eliminate it, given that the pharmaceutical active ingredient needs to be dissolved in the liquid lipid phase (Souto *et al*., 2020). Subsequently, this liquid is cooled to a solid state using dry ice or liquid nitrogen, so that it is then milled to become fine powder particles and to form lipid nanoparticles; then, dispersion is done using a homogenizer at room temperature at 500 bar for 5 cycles (Ganesan and Narayanasamy, 2017). This method is not an energy efficient method, because the homogenization stage requires high energy (Ganesan and Narayanasamy, 2017). In addition, the cold HPH showed larger and more polydisperse particles compared to the hot HPH (Hernández-Sánchez and Gutiérrez-López, 2015; Souto *et al*., 2020).

High shear homogenization

This method is faster and simpler to do when compared to the HPH method. The aqueous phase containing molten lipid loaded with the drug and surfactant is heated independently to a temperature above the lipids melting point. Subsequently, the aqueous and lipid phases are combined using a high shear ultrasonic probe sonicator or homogenizer (Üner *et al*., 2014; Pinheiro *et al*., 2016). With the appropriate amount and type of surfactant, lipid nanoparticles can be formed using simple ultrasonic or high shear homogenization methods (Chutoprapat *et al*., 2022). When using an ultrasonic probe sonicator, one must consider metal contamination (Oláh *et al*., 2014). However, ultrasonication using a specific probe type achieves favorable outcomes, including homogenization, dispersion, deagglomeration, grinding, and emulsification (Ultrasonics, 2020).

Low energy-required methods

Microemulsification

In this method, both the lipid and the aqueous phase are warmed to the uniform temperature with gentle stirring to form a microemulsion. Then, it is dispersed with cold water (2 to 10°C) with stirring to form nanoparticles. Finally, larger particles can be removed by rinsing the system with distilled water and lyophilizing it to remove excess water (Souto *et al*., 2020). At low temperature conditions, it is possible to form nanoparticles in this method (Gasco, 1993). The optimal duration of stirring, lipid concentration, and drug amount are carefully adjusted in this approach to attain the desired size and improved entrapment efficiency. Moreover, this technique for producing NLC does not necessitate specialized equipment or energy, making it easily scalable for commercial use (Qidwai *et al*., 2016; Joshi *et al*., 2019). However, this method has limitations such as higher surfactant concentrations are required and very low particle concentrations in the suspension (Souto *et al*., 2020).

Phase inversion

In this approach, the mixing of the lipid phase, water phase and active ingredient pharmaceutical is carried out using magnetic stirring at (85-60-85-60-85°C). It is a solvent-free method to achieve a mixture. The mixture is dissolved with cold distilled water and subjected to thermal shock to form lipid nanoparticles (Souto *et al*., 2020). This method requires a long preparation time because the process is complicated even though organic solvents are not needed for this method and the heating process is short (Souto *et al*., 2020), and the NLC formed may be less stable (Duong *et al*., 2020).

Very low or no energy-required methods

Solvent evaporation

Solvent evaporation involves the deposition of particles within an oil/water (O/W) emulsion. Initially, the lipid phase is dissolved along with the drug substance, and then the aqueous phase is introduced to create an O/W emulsion. Furthermore, to form nanoparticles is done by evaporating organic solvents (Iqbal *et al*., 2012). This method can avoid thermal effects, and the utilization of organic solvents is a disadvantage of solvent evaporation (Oláh *et al*., 2014).

Solvent injection

This method is a simple and rapid manufacturing method in which lipids are dissolved in an appropriate solvent, followed by the swift injection of surfactant using a syringe into an aqueous solution (Khosa *et al*., 2018). The resulting mixture is filtered to eliminate surplus lipids (Schubert and Müller-Goymann, 2003). The effectiveness of this method relies on the rapid diffusion of the solvent across the interface between the solvent and lipid in an aqueous phase (Anuradha and Kumar, 2014). The benefits of this technique include ease of manufacturing without the need for high heat, shear stress and complex equipment, as well as the utilization of organic solvents and low concentration of particles is a disadvantage of this method (Subramaniam *et al*., 2020).

Characterization of Nanostructured Lipid Carrier

Particle size and polydispersity index (PDI)

For particle size characterization, we can use Dynamic Light Scattering (DLS) and laser diffraction, which can measure particle sizes ranging from 0.1 to 10 µm or 0.01 to 3500 µm by exploiting the intensity of light scattering due to particle movement as the laser beam passed through the dispersion. Small particles exhibit faster variations in scattered light than large particles. Measuring particle size is particularly crucial in nanostructured formulations, as smaller particle sizes result in a greater interfacial area. This, in turn, can enhance drug distribution and absorption on the skin surface (Esposito *et al*., 2015; Rajinikanth and Chellian, 2016). To find out the distribution of a particle size, the PDI value can be shown, where if the PDI value of 0.3 or less is considered acceptable to represent the monodispersity of the nanoparticles (Oláh *et al*., 2014). Hence, PDI measurements are crucial to verify a limited range of particle sizes (Das *et al*., 2012).

Zeta potential

Zeta Potential (ZP) indicates surface charge and information on long-term stability as indicated by a high ZP value which means the system is stable, conversely a low ZP value indicates agglomeration or flocculation and makes the system less stable (Lu and Gao, 2010). In general, for electrostatic stabilization of NLC, the ZP of the dispersion should be ±30 mV (Thatipamula *et al*., 2011; Chauhan *et al*., 2020).

Morphology

Various techniques can be employed to analyze the morphology of nanostructures. Transmission Electron Microscopy (TEM) is the most widely utilized, and other techniques include Scanning Electron Microscopy (SEM), and Atomic Force Microscopy (AFM). In TEM, NLC is diluted and placed on a carbon-coated copper lattice, which is then stained (such as with uranyl acetate or phosphotungstic acid), dried, and then imaged (Gomaa *et al*., 2022).

Drug loading (DL) and entrapment efficiency (EE)

Drug Loading (DL) represents the proportion of the drug mass trapped within the nanoparticles relative to the mass of the nanoparticles. DL is calculated using the formula:

%DL = (Weight of drug entrapped/Weight of nanoparticles) x 100%

The Entrapment Efficiency (EE) measures the percentage of nanoparticles that successfully encapsulate drugs. EE refers to the proportion of the drug being trapped and the drug added during nanoparticles fabrication (Scalia *et al*., 2015). EE can also be calculated using the following formulas:

%EE = (Weight of entrapped drug/Weight of drug added) x 100%

%EE = [(Weight of drug added Weight of free drug)/Weight of drug added] x 100%

Free drug in a matrix can be separated using one of the techniques such as ultracentrifugation by analyzing the supernatant using a Uv-Visible spectrophotometer or High-Performance Liquid Chromatography (HPLC) (Opatha *et al*., 2020).

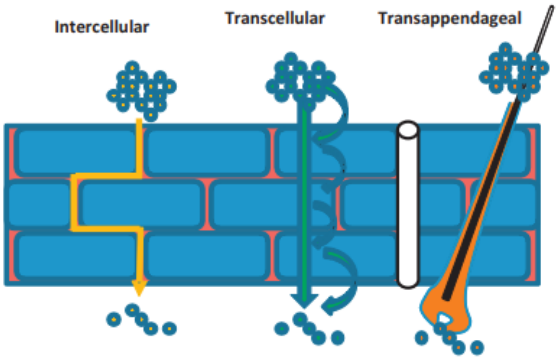

Figure 2. Pathway of drug penetration through the skin (Lane, 2013).

Table 1. Examples of NLC topical formulations

API	Components	Findings	References
Meloxicam	Monostearin, α-tocopherol, Kolliphor P 188, Tween 80	The particle size result was found to be about 445.8 to 545.9 nm, the PDI result was about 0.028 to 0.045, and all of patch formulas loaded NLC had meloxicam concentrations above 95%.	Hendradi *et al*., 2018
Diethylammonium diclofenac (DETA)	Stearic acid, oleic acid, Tween 80	The particle size result was about 351.9 to 1370.0 nm, the PDI result was about 0.373 to 0.489, the pH of the all formula was found about 6.157 to 6.326, the viscosity of the all formula was found to be about 323.7 to 288.8 cPs, morphology showed that spherical shapes corresponding to NLC particles were observed, and all of formula DETA loaded NLC had entrapment efficiency above 73%.	Hendradi *et al*., 2017
Meloxicam	Monostearin, Miglyol 808, Tween 80	The particle size result was about 421.9 to 518.9 nm, the pH of the all formula was found about 5.72 to 5.87, the viscosity of the all formula was found to be about 32.0 to 123.7 cPs, the morphology showed that there were spherical forms, and all of formula meloxicam loaded NLC had entrapment efficiency above 87%.	Annisa *et al*., 2016
Diclofenac diethylammonium (DETA)	Glyceryl monostearate, caprylic acid, Tween 80	The particle size result was about 134.467 to 2252.233 nm, the PDI result was about 0.260 to 11.776, the pH of the all formula was found to be about 5.45 to 5.71, the viscosity of the all formula was found about 441.3 to 1266.3 cPs, the morphology showed that there were spherical forms, and all of formula DETA loaded NLC had entrapment efficiency above 70%.	Hendradi *et al*., 2021
Meloxicam	Monostearin, α-tocopherol, Kolliphor P 188, Tween 80	The particle size result was about 431.1 to 515.3 nm, the zeta potential result was about 10.4 to -16.5 mV, the pH of the all formula was found to be about 5.98 to 6.07, the viscosity of the all formula was found about 57.87 to 162.67 cPs, the morphology showed that there were spherical forms, and all of formula meloxicam loaded NLC had entrapment efficiency above 74%.	Anggraeni *et al*., 2017
Meloxicam	Cetyl palmitate, caprylic acid, Tween 80, propylene glycol	The particle size result was about 210.66 nm, the PDI result was about 0.213, the zeta potential result was about -27.33 mV, the pH was found to be about 6.0, the morphology showed that there were spherical forms, and meloxicam loaded NLC had entrapment efficiency 85.61%.	Khurana *et al*., 2013
Diclofenac sodium	Glyceryl monostearate, lanolin PEG-75, phospholipon 90G, precirol ATO 5, Tween 80, cremophor RH 40	The particle size result was about 54.38 to 126.67 nm, the PDI result was about 0.250 to 0.3305, and all of formula diclofenac sodium loaded NLC had entrapment efficiency above 60%.	Nguyen *et al*., 2017
Piroxicam	Soy lecithin, ethyl oleate, Tween 80, n-butanol	Particle size result started at ~40 nm in diameter and reached a mean value of approximately 160 nm after a 20-days period, the PDI result was a mean value of 0.215, the zeta potential result was about -40 mV, formula piroxicam loaded NLC had entrapment efficiency above 80%, and a release rate above 60%, and the results of the skin irritation test indicated that no reaction was observed on the skin.	Otarola *et al*., 2020

Route of penetration Nanostructured Lipid Carrier

Numerous scientific references have confirmed that NLC have the potential to control the penetration of drugs into the skin, thereby reducing the absorption of undesired substances into the bloodstream (Puglia and Bonina, 2012). The small and dense structure of NLC ensures close contact with the stratum corneum, potentially augmenting the penetration of active compounds into the skin. Consensus has been reached among researchers regarding the pathways through which nanoparticles traverse the skin, as depicted in Figure 2.

The suggested mechanism for enhancing particle permeation through the stratum corneum, facilitated by drug diffusion, includes the following:

1. Unadulterated vesicles loaded with drugs that penetrate into various skin layers.
2. Lipid vesicles. Due to its fluidity and skin lipid-modifying properties, it acts as an entry enhancer.
3. The creation of NLC and an exchange of drugs with the skin subsequent to the amalgamation of carrier lipids and skin cell lipids.
4. Another pathway involves utilizing hair follicles, pilosebaceous units, and sweat gland pores (Wang *et al*., 2012).

This is due to the hair follicles represents an invagination of the epidermis and extends deep into the dermis, providing a larger surface area for drug absorption. Among the appendageal routes, hair follicles have emerged as the paramount pathway for nanoparticle penetration. Furthermore, hair follicles act as efficient repositories for nanoparticles administered topically, typically distributed up to 2000 µm deep within the tissue. Due to the large storage volume because of the shape of the hair follicle, it achieves both improved permeability and sustained release. Drug particles accumulate in the follicular mold, followed by the diffusion of the drug from the nanocarrier into the skin (Rancan and Vogt, 2014). Skin penetration of NLC depends on a variety of factors, including their composition as well as physicochemical properties such as size, aggregation, surface charge of the particles, hydrophobicity, solubility of the particles in the skin, solubilizing properties of the particles against skin lipids, and the particles' capacity to form a film (Chauhan *et al*., 2020).

Applications of Nanostructured Lipid Carrier for topical

Concise information regarding different formulations and their respective results is presented in Table 1.

CONCLUSIONS

NLC is a remarkable and encouraging lipid nanocarrier for topical administration, offering more flexibility of drug loading, increased penetration into the skin, and promising occlusive effects. It also enables modulation of drug release kinetics and flexibility of hydrophilic and lipophilic active drugs. It offers both carrier compatibility and reduced side effects. Lipid nanocarriers have attracted the attention of the industry because of their increasingly qualified and validated technology upscaling, the Generally Accepted As Safe (GRAS) status along with excipient biocompatibility, and the ease of large-scale manufacturing.

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