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Review Article

Nanostructured Lipid Carriers (Nlcs): A Comprehensive Review of Formulation Strategies, Preparation Techniques, And Therapeutic Applications

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ABSTRACT

Nanostructured lipid carriers (NLCs) are new lipid-based drug carriers made from a mix of solid and liquid lipids. They were developed to overcome the limits of solid lipid nanoparticles. Their less ordered crystal structure gives more space for drug loading. This leads to better drug encapsulation, less drug leakage during storage, and improved stability. NLCs can also improve drug solubility, give controlled release, and increase bioavailability. They are prepared by methods such as high-pressure homogenization, emulsification, microemulsion, ultrasound, and de novo emulsification. Because they are biocompatible and flexible, NLCs are useful for oral, topical, ocular, and parenteral drug delivery.

INTRODUCTION

Nanostructured Lipid Carriers (NLCs) represent the second generation of lipid-based nanocarriers, developed to overcome the inherent limitations of Solid Lipid Nanoparticles (SLNs), such as low drug loading and drug expulsion during storage(1) . Unlike SLNs, NLCs are composed of a blend of solid and liquid lipids, which creates an imperfect crystalline matrix. This unique structure provides more space for drug molecules, leading to higher encapsulation efficiency and improved stability(2,3). Due to their biocompatibility and ability to enhance the solubility of poorly water-soluble drugs, NLCs are highly versatile (5). They offer controlled drug release and improved bioavailability, making them suitable for various administration routes, including oral, topical, ocular, and parenteral delivery (16,18,19).

1. Nanostructured Lipid Carriers (Nlcs)

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Nanostructured lipid carriers (NLCs) are second-generation lipid-based nanocarriers composed of a mixture of solid and liquid lipids, forming an unstructured lipid matrix. NLCs were developed to overcome the limitations associated with solid lipid nanoparticles (SLNs). Due to their imperfect crystal structure, NLCs provide higher drug loading capacity and reduce drug expulsion during manufacturing and storage by reducing lipid crystallization. They also improve drug solubility within the lipid matrix and provide more controlled drug release profiles compared to SLNs. In addition, NLCs enhance skin permeation, improve formulation stability, and offer better therapeutic efficiency for topical drug delivery(1).

2. Advantages Of Nlc

2.1. Enhanced drug loading capacity
Nanostructured lipid carriers (NLCs) consist of a mixture of solid and liquid lipids that form an imperfect crystalline matrix. Studies have shown increased loading and encapsulation efficiency, leading to better drug retention and improved therapeutic performance.

For example, a study by Eun young yet al prepared curcuma xanthorrhiza extract loaded NLCs with excellent nanoencapsulation efficiency and hydrocolloidal stability, with effectively loading a complex hydrophobic plant derived extract and preserving the bioactivity of its diverse bioactive compounds(2). Another study by Tanvi kadam et al formulated lurasidone hydrochloride loaded NLC with encapsulation efficiency of 94 ± 1.26% w/w. And it showed enhanced bioavailability with improved delivery effectiveness for intranasal administration and there by treating psychosis(3).

2.2. Improved drug stability
The lipid matrix of NLCs protects drugs from oxidation, hydrolysis, and degradation. This helps maintain drug stability and effectiveness over time(4).

2.3. Sustained drug release
NLCs provide sustained and controlled drug release. The release rate can be adjusted by modifying the lipid composition, allowing prolonged therapeutic action.

In a study by Eun young yet al they formulated curcuma xanthorrhiza extract loaded -NLCs and this NLCs achieved sustained release through a biphasic process: an initial rapid release of drug from the surface (~28% in 2 hours) followed by a controlled release from the hydrophobic matrix (~62% over 24 hours)(2).

2.4. Enhanced bioavailability
NLCs improve the solubility and absorption of poorly water-soluble drugs. This leads to increased bioavailability compared to conventional formulations(5).

2.5. Targeted drug delivery
Surface modification or ligand attachment enables NLCs to deliver drugs to specific tissues or cells. This improves therapeutic outcomes and reduces side effects.

An example, Hamong et al successfully developed Curcumin-loaded nanostructured lipid carriers (CUR-NLCs) for lymph targeting with 5.13-fold higher relative bioavailability(5).

2.6. Multiple routes of administration
NLCs can be used for topical, transdermal, oral, and parenteral delivery. This makes them suitable for a wide range of applications(2,3,6).

2.7. Improved permeation
Due to their nanosize and lipid nature, NLCs enhance drug penetration across biological barriers, such as the skin(7).

2.8. Reduced irritation

NLCs enable controlled and localized drug release, which reduces irritation and allergic reactions, improving patient compliance(8).

3. DISADVANTAGES(9)

- Limited Scalability and Manufacturing Challenges
- Stability Issues Under Specific Conditions
- Complex Formulation Design
- Toxicity Concerns of Surfactants and Lipid Components
- Limited Control Over Drug Release in Some Applications

4. TYPES OF NANOSTRUCTURED NLC

There are three types of nanostructured lipid carriers.

a) The imperfect type

b) The amorphous type

c) Multiple type

6.1. Imperfect type NLC

This type is made by mixing structurally different lipids, usually solid lipids with some liquid lipids, which creates irregularities in the crystal lattice. These defects leave more space inside the matrix, so more drug molecules can be incorporated. In this type, drug loading is often improved by using glycerides with different chain lengths and different degrees of saturation, which prevents tight crystal packing(10)

6.2. Amorphous type NLC

In this type, the lipid matrix is designed to remain non-crystalline or amorphous even after storage. Because the particles do not undergo strong crystallization, there is less chance of drug expulsion during storage. This type is useful when long-term physical stability and reduced leakage are important(10).

6.3. Multiple type NLC

This type contains tiny oil compartments dispersed within a solid lipid matrix, often described as an oil-in-fat-in-water structure. The oil nanodomains act as internal reservoirs for lipophilic drugs, which can improve entrapment and control drug release. It is especially helpful when the drug dissolves better in liquid lipids than in solid lipids(10).

5. Preperation Of Nanostructured Lipid Carrier (Nlc)

5.1. Hot High-Pressure Homogenization (HPH)

Solid and liquid lipids were heated at until melted. Then drug was added to the melted lipid phase. The aqueous phase, which contained surfactant or emulsifier like tween 80 in double-distilled water, was prepared at the same temperature. Then aqueous phase was dispersed into the lipid phase at same temperature under continuous mixing. The resulting pre-emulsion was then immediately passed through a high-pressure homogenizer. NLCs were obtained by solidification in an ice bath(11).

5.2. Cold high-pressure homogenization method

Solid lipid liquid lipid and drug were dissolved in ethanol in 70±2°C. Surfactant was dissolved in deionized water or various buffer solutions to prepare the aqueous phase. The aqueous phase was maintained at 4±2°C. The lipid phase was

transferred to the aqueous phase under magnetic stirring at 1,000 rpm. The mixture was continuously stirred at 4±2℃ for 2 h to obtain the coarse NLCs suspension. It was then subjected to high-pressure homogenization at 0-4℃. The homogenization condition (pressure and cycle number) was varied(12).

5.3. Emulsification–homogenization technique

The solid lipid was melted at above 5 °C of its melting point and the liquid lipid and was added with continuous stirring to make the homogeneous mixture. The aqueous surfactant solution was prepared in distilled water and heated at the same temperature. The hot aqueous surfactant solution was added to the melted lipid mixture at 15,000 rpm for 15 min to form a coarse primary emulsion. The primary \ coarse emulsion was further subjected to a homogenizer for 5 min. The prepared emulsion was cooled to room temperature to form and further stored for evaluation(13).

5.4. Solvent emulsification method

The lipid phase, consisting of a solid lipid and liquid lipid, was melted and maintained at an elevated temperature. A surfactant solution was prepared separately in water and heated to the same temperature. The aqueous phase was then added to the molten lipid phase under continuous stirring to form an emulsion, which was further stirred to obtain nanostructured lipid carriers upon cooling(14).

5.5. Ultrasound dispersion method

Melt solid lipid and liquid lipid above melting point temperature. Then add drug to melted lipids to prepare lipid phase. Make aqueous phase by dissolving required amount of tween 80 in water. Then add aqueous phase to the lipid phase to form coarse emulsion. The coarse emulsion was sonicated using probe sonicator for 4 min(15)**.**

5.6. De novo emulsification method.

The oil phase contains mixture of liquid lipid and solid lipid and the aqueous phase was composed of surfactant and distilled water. After separately preheating the oil phase and aqueous phase to 70°C, the aqueous phase was transferred to the oil phase and stirred with a magnetic stirrer at 1,400 rpm for 1 min. To reduce the droplet size to the nanometer range, these mixtures were placed in 25°C bath- sonicator and sonicated five times for 5 min with an interval of 10 s at 40% amplitude by a probe-type ultrasonicator(16).

5.7. Microemulsion template strategy

The oil phase consist of melted solid lipid and liquid lipid. Drug was dissolved in this mixture. The aqueous phase consisted of surfactant, solublizer, and water. Temperatures for both phases were maintained above the melting point of the lipid. The oil phase was added to the aqueous phase, and both phases were mixed using a cyclomixer at this temperature to form a microemulsion. This warm microemulsion was diluted in cold water (2–3°C) under mechanical stirring to form NLC dispersion(17).

6. Application Of Nlc

6.1. Oral delivery:

NLCs help improve bioavailability of poorly soluble drugs and protect them from gastrointestinal degradation. They may also improve intestinal absorption through transcellular, paracellular, and M-cell uptake pathways, which can increase bioavailability and reduce first-pass metabolism. This makes them valuable for medicines that need better

absorption without changing the active ingredient.(18)

6.2. Topical delivery

In topical and dermal formulations, NLCs are used to increase drug penetration into the skin with keeping the drug localized at the site of application. They can also support prolonged release, which is helpful for inflammatory skin conditions, antifungal therapy, alopecia, and local wound-related treatments. Their lipid composition improves compatibility with the skin barrier and can reduce irritation compared with some conventional carriers(19).

6.3. Ocular delivery

NLCs are widely studied for eye delivery because the eye has strong barriers that limit drug penetration. Researchers showed that NLC formulations can increase corneal permeability, extend precorneal residence time, and improve ocular bioavailability compared with simple suspensions. They are therefore useful for conditions requiring sustained ophthalmic delivery, such as corneal inflammation or neovascularization(20).

6.4. Parenteral delivery

Nanostructured lipid carriers (NLC) are excellent for injectable drug delivery because they combine several important advantages in this system. Their small nanometer-sized particles can circulate safely through the bloodstream without blocking blood vessels. And their unique lipid composition allows them to carry high amounts of drug while remaining stable during storage. NLC effectively prevent drugs from breaking down due to chemical damage or oxidative stress during circulation. And they offer flexibility in controlling how quickly the drug is released into the body. These properties like small size, high drug capacity, stability, and protective function, make NLC a superior choice for parenteral administration(16).

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