

Nanostructured Lipid Carriers: A Novel Approach to Bioavailability Enhancement

Bapurao Ankalgi^{1*} and Malaykumar Chotaliya²

^{1*}Department of Pharmaceutics, School of Pharmacy, RK University, Kasturbadham, Rajkot, Gujarat, 360020, India

²Department of Pharmaceutics, School of Pharmacy, RK University, Kasturbadham, Rajkot, Gujarat, 360020, India
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*Correspondence Author: apuankalgi13@gmail.com

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ABSTRACT

By combining solid & liquid lipids stabilized by surfactants, nanostructured lipid carriers (NLCs) provide a No. of assistances, comprising increased solubility, controlled medicine discharge, increased stability & site-specific targeting, and they have possible to increase bioavailability of drugs that are poorly soluble. Various methods, including ultra-sonication, high-pressure homogenization as well as solvent evaporation is employed for their preparation. Additionally, characterization techniques like particle size examination, zeta potential capacity & in-vitro medicine relief studies provide insights into their stability and efficacy. NLCs have established important possible in oral, transdermal, and ocular & parenteral drug delivery applications, including delivery of BCS Class II & IV drugs as well as herbal formulations. Despite these benefits, challenges related to large-scale production, storage stability as well as regulatory approval remains. Further advancements in formulation techniques, coupled with regulatory harmonization, will facilitate the commercialization of NLC-based therapeutics.

Keywords: Nanostructured Lipid Carriers, Bioavailability Enhancement, Drug Delivery Systems, Lipid-Based Carriers, Controlled Release, Solid Lipids, Regulatory Challenges.

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INTRODUCTION

Bioavailability is portion of a controlled medicine that spreads systemic circulation in its active form relies a major challenge in pharmaceutical growth, specifically for medicines with poor water solubility and permeability. Low aqueous solubility of drugs is responsible for lack of absorption and reduced therapeutic efficacy of nearly 90.00 % of drugs in development and about 40.00 % of promoted drugs¹. Lipid-based drug delivery systems (LBDDS) are novel in order to overcome these bioavailability problems. LBDDS can improve the solubility, increase lymphatic transport and make the absorption through the gastrointestinal tract easier when they contain lipophilic drugs in their lipid matrices². Traditional lipid based carriers such as emulsion and liposomes have been shown to be effective for enhancing the bioavailability of many therapeutic agents. But, they are found to be limited in terms of physical stability, drug loading capacity and scalability³. To address these challenges, NLCs have been introduced as a new generation of lipid nanoparticles. The NLCs consist of a solid & liquid lipid matrix with specific composition that provides enhanced drug loading, controlled release and

stability than the earlier drug delivery systems⁴. The architecture of NLCs is unique, and drugs of difficult physicochemical properties can be accommodated, thus enhancing the range of lipid-based drug delivery systems⁵.

In recent years, NLCs have received a great deal of interest because of the potential to increase the bioavailability of drugs that are poorly water soluble. It has been shown that NLCs have a positive effect on the oral absorption of labile drugs, their protection from degradation and targeted drug delivery, which results in better therapeutic success⁶. NLCs high versatility and efficacy makes it as a promising platform in the development of medicine delivery technologies for overcoming bioavailability problems.

Nanostructured Lipid Carriers

One way to increase a drug's bioavailability is with the use of NLCs, which are nanoparticles made of lipids. They have a stable nanostructured matrix that is composed of a combination of solid and liquid lipids. Unlike SLNs, the addition of liquid lipids in NLCs introduces imperfections in the crystal structure, agreeing for well medicine loading & measured relief⁷.

*Author for Correspondence: apuankalgi13@gmail.com

Table 1: Components of NLCs.

Component	Description	Examples
Solid Lipids	Provide structural stability and control drug release.	Glyceryl behenate, Stearic acid, Cetyl palmitate
Liquid Lipids	Create imperfections in the solid matrix, enhancing drug loading.	Oleic acid, Medium-chain triglycerides, Squalene
Surfactants & Stabilizers	Prevent aggregation of nanoparticles and stabilize the formulation.	Polysorbates, Lecithin, Poloxamers

Types of NLCs

1. Imperfect Crystal Type:

Liquid lipids disrupt the crystal structure, creating imperfections. This increases medicine loading capacity & reduces peril of medicine expulsion throughout storage.

2. Amorphous Type:

Formed lipids will use for solidify in an amorphous state instead of a crystalline one. This prevents drug expulsion and ensures uniform drug distribution.

3. Multiple Type:

It contains small liquid lipid compartments within solid matrix, resembling a “water-in-oil-in-water” structure. This type is appropriate for both hydrophilic & lipophilic drugs⁸.

PREPARATION TECHNIQUES OF NLCs

NLCs are formulated using various techniques to achieve desired particle size, stability, and drug loading capacity.

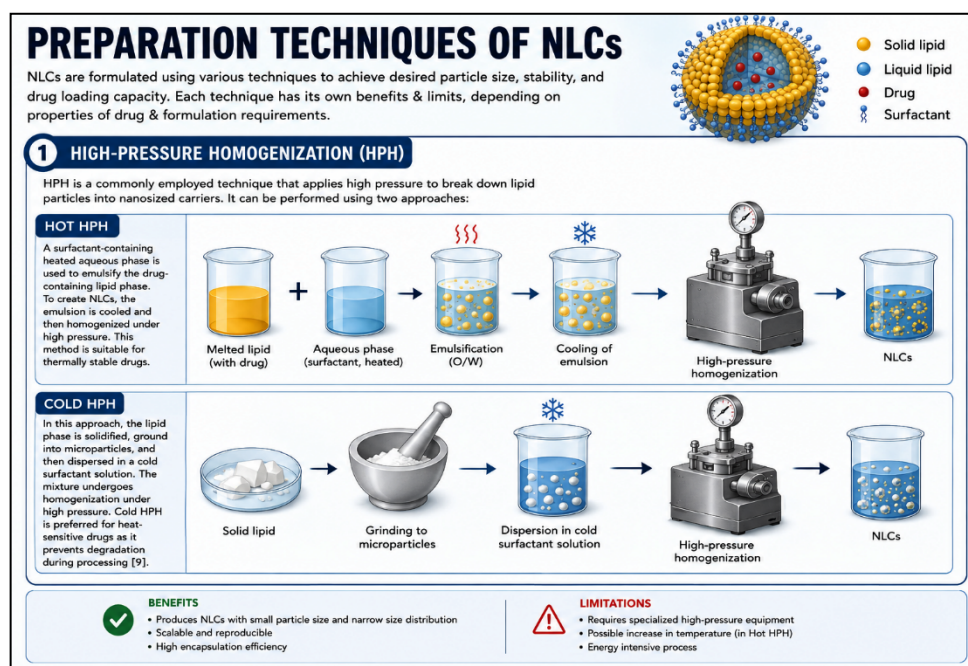
Each technique has its own benefits & limits, depending on properties of drug & formulation requirements.

1. High-Pressure Homogenization (HPH): HPH is a commonly employed technique that applies high pressure to break down lipid particles into nanosized carriers.

It can be performed using two approaches:

Hot HPH: A surfactant-containing heated aqueous phase is used to emulsify the drug-containing lipid phase. To create NLCs, the emulsion is cooled and then homogenized under high pressure. This method is suitable for thermally stable drugs.

Cold HPH: In this approach, the lipid phase is solidified, ground into microparticles, and then dispersed in a cold surfactant solution. The mixture undergoes homogenization under high pressure. Cold HPH is preferred for heat-sensitive drugs as it prevents degradation during processing (Fig. 1)⁹.


Fig. 1: Preparation Techniques of NLCs by High-Pressure Homogenization.

- 2. Ultra-sonication:** Ultra-sonication uses ultrasonic waves to break down lipid droplets into nanoparticles. The lipid phase is melted, emulsified with an aqueous surfactant solution as well as subjected to ultra-sonication to decrease particle size. It is a simple and effective method for lab-scale production. However, there is a risk of metal contamination from the probe, and it is unsuitable for large-scale applications¹⁰.
- 3. Solvent Evaporation Method:** This method was comprising dissolving medication and lipid in a volatile organic solvent as well as emulsifying them into a water-based phase with surfactants. Under lower pressure, the organic solvent evaporates, causing NLCs (lipids) to precipitate. This technique is useful for hydrophobic drugs, though the complete removal of solvents is essential to ensure safety¹¹.
- 4. Micro emulsion Technique:** The micro emulsion method involves forming a clear micro emulsion using a mixture of molten lipids, surfactants, co-surfactants & water. The micro emulsion is then rapidly spread in cold water, resulting in NLC formation through lipid precipitation. This method offers excellent particle size control but often requires high surfactant concentrations, which may lead to toxicity concerns¹¹.
- 5. Double Emulsion Method:** Encapsulating hydrophilic medications is best accomplished using the double emulsion technique. The process includes making a W/O/W double emulsion, which stands for water in oil in water. A primary water-in-oil emulsion is formed by dissolving the medication in aqueous phase & then emulsifying it into lipid phase. The last step in making a double emulsion is to emulsify this emulsion even further into an outside water phase. NLCs are formed upon solvent evaporation or cooling. While effective for hydrophilic drugs, this method may suffer from low encapsulation efficiency and particle instability (Fig. 2)¹⁰.

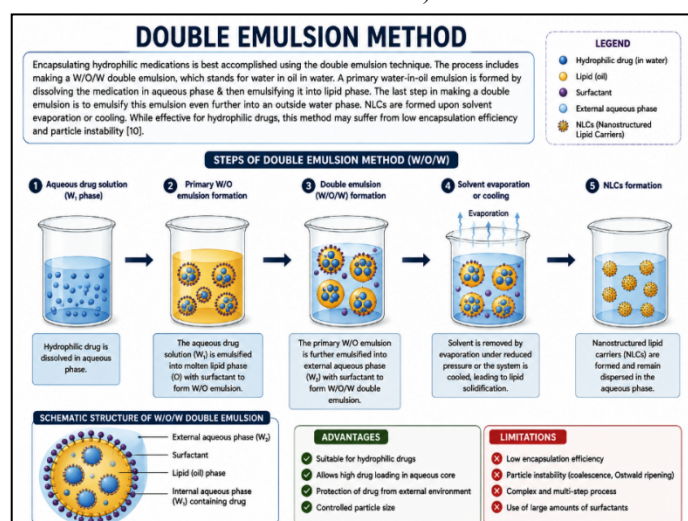


Fig. 2: Preparation Techniques of NLCs by Double Emulsion Method.

CHARACTERIZATION OF NLCS

NLCs are extensively characterized to ensure their efficacy, stability, and safety. The major parameters that are used in the characterization of NLCs are Particle size, Surface charge, Drug encapsulation efficiency, Thermal behavior; Morphology, Crystallinity & medicine relief outline

1. Particle Size & Zeta Potential: Particle Size:

The size ranges of NLCs are generally between 50nm and 500nm. The particle size and PDI (polydispersity index) reflecting size distribution is typically determined by DLS (Dynamic Light Scattering). To maintain the drug stability and controlled release, the smaller particles with low PDI are necessary¹².

Zeta Potential: Zeta potential is a measure of the surface charge of nanoparticles, which is related to their colloidal stability. The higher the zeta potential (positive or

negative) the greater the electrostatic repulsion and therefore the more stable the particle will be in the long term¹³.

2. Drug Encapsulation Efficiency: The efficiency of drug incorporation into lipid matrix is referred as drug encapsulation efficiency. The EE% represents the efficiency of the drug loading process, a crucial factor for effective therapeutic delivery. The type of lipids, the solubility of the drugs, and the preparation technique are all factors that will affect the EE¹⁴.

3. Morphological Analysis: The shape and surface characteristics of NLCs are assessed using:

TEM: Give higher resolution pictures, for internal structure of nanoparticles.

SEM: It offers exhaustive surface morphology pictures, accent particle consistency and aggregation tendencies.

These techniques validate the spherical shape, smoothness of particles and overall integrity of NLCs¹⁵.

4. Thermal Behavior: DSC is used to determine the thermal characteristics of NLCs:

It consists of estimation of the melting point. Melting point changes can be a sign of drug incorporation or lipid alterations.

Crystallinity Assessment: DSC thermograms indicated that a decrease in crystallinity may indicate better drug loading and better sustained release¹⁶.

5. Crystallinity and Polymorphism: A XRD analysis is used to determine the crystalline or amorphous state of the NLCs: The crystalline state is indicated by sharp XRD peaks and a decreased crystallinity is shown by wider peaks.

Polymorphism: Lipids can exist in a variety of polymorphic forms and this may affect the drug release rate and physical stability of the formulation¹⁷.

6. *In-vitro* Medicine Relief Studies: *In-vitro* medicine relief studies evaluate the release of medicine as NLCs are placed under simulated physiological conditions. Key parameters include:

Release Kinetics: Models like first-order, Higuchi models as well as zero-order are useful to evaluate release mechanism.

Mechanism of Release: *In-vitro* testing helps to gain insights from sustained drug release behavior of NLCs, which is necessary for better therapeutic efficacy¹⁸.

Mechanism of Bioavailability Enhancement: Advanced medicine delivery system, NLCs increase bioavailability of healing substances in a variety of ways. The mechanisms are: increased solubility and permeability, increased drug stability, controlled and sustained release, and lymphatic transport⁵⁰⁻⁵⁶.

IMPROVED SOLUBILITY AND PERMEABILITY: NLCs are useful in enhancing the solubility of poorly water-soluble medicines by incorporating them in a lipid matrix that enhances their dissolution rate in the gastrointestinal tract. The lipid formulation helps to disperse and absorb the drug. Further, the small size of the NLCs makes them permeable and allows crossing intestinal barriers, enhancing the permeability across biological membranes¹⁹.

2. Enhanced Drug Stability: Oxygen, light and digestive enzymes are examples of environmental factors that cause the encapsulated drugs to degrade in NLCs. In NLCs, the solid lipid matrix protects the encapsulated drugs from degradation by these environmental factors. This protection helps continue chemical integrity of drug, preventing degradation & spreading its shelf life. The enhanced stability of NLCs has been proven, which guarantees stable therapeutic activity with time²⁰.

3. Controlled and Sustained Release: NLCs are intended to relief their medicine payload in a skillful way. Soluble and insoluble lipids in the NLCs are in agreement for their effect on the release profile of the drug, promoting a prolonged therapeutic action in the blood. This controlled release allows for lower dosing frequency and less fluctuation of drug level, improving therapeutic response and adherence²¹.

4. Lymphatic Transport Mechanism: NLCs have the ability to transport the drug through the intestinal lymphatic pathway, thus avoiding the hepatic "first-pass" effect. This is especially beneficial for lipophilic drugs, because the lipid part of NLCs increase chylomicron production, which is absorbed into the lymphatic system. Avoiding the first pass metabolism results was in a greater amount of medicine reaching systemic circulation, thus increasing availability²².

APPLICATIONS OF NLCS IN BIOAVAILABILITY ENHANCEMENT

NLCs are innovative medicine distribution approaches, which recover the bioavailability of medicines in different modes of administration. NLCs have emerged as an effective platform to overcome the shortcomings of traditional formulations, such as poor solubility, low permeability, and instability of the drugs⁵⁷⁻⁶¹.

Oral Drug Delivery: Oral route is the most commonly preferred route due to the convenience. But a lot of drugs are poorly soluble in water and have low permeability which has reduced bioavailability. NLCs are made of a lipid matrix that is used to encase hydrophobic drugs, enhancing their solubility and absorption in the gastrointestinal tract. It has been demonstrated that NLCs^{23, 24} can lead to significant enhancements in bioavailability of drugs such as cannabidiol and ranolazine.

Transdermal and Topical Delivery: Transdermal and topical delivery systems are beneficial for local treatment and systemic absorption of drugs without invasive methods. The stratum corneum is a formidable barrier, however. The NLCs improve permeation of skin, increase hydration levels and create a lipid layer which promotes drug diffusion. For skin diseases, formulations with the help of NLCs for drugs such as roflumilast have proven to have better drug retention and therapeutic efficacy^{25, 26}.

Ocular and Nasal Delivery: Medicines delivery to eye & nasal cavity is stimulating due to rapid clearance and low permeability. In eye delivery, NLCs provide extended drug residence time, better corneal penetration and controlled delivery of drugs. For nasal delivery, the NLCs can help transport the drugs into the brain, bypassing blood brain barrier. Intranasal NLC formulations have been studied with drugs such as lurasidone hydrochloride, which have demonstrated better brain bioavailability^{27, 28}.

Parenteral Administration: Medicines that are used for a quick start of action or when taken by mouth are not effective may be given by parentage (intravenous and intramuscular injections). NLCs enhance solubility and stability of hydrophobic drugs, which avoids dose dumping and helps reduce drug toxicity. NLC formulations of drugs like remdesivir have shown better therapeutic properties & decreased side effects likened to predictable formulations²⁹.

Recent Advances and Case Studies: NLCs have created large potential for improved bioavailability and therapeutic effect of medicines. Their applications have been showcased in the field of delivering BCS Class II & IV medicines, herbal medicines & through co-encapsulation strategies, respectively, in the recent times.

NLCs in Delivery of BCS Class II & IV Drugs: Class IV medications have lower solubility and lower permeability as opposed to BCS Class II pharmaceuticals, which have high permeability and low solubility. These properties are detrimental to the absorption of drugs and therefore to their bioavailability. NLCs have the potential to provide a solution by loading the drug into lipid molecules, increasing the bioavailability, stability and solubility of these drugs. For instance, a study was developed BCS Class IV drug (furosemide) using Box–Behnken design approach. The optimized NLCs exhibited greater drug loading capacity, improved release profile and therapeutic efficacy as compared to the conventional formulations³⁰.

NLCs in Herbal Drug Delivery: Poor solubility and instability of herbal medicines is one of the limiting factor associated with the bioavailability of the medicines. The bioactive herbs compounds are more stable and have therapeutic effect in NLCs. In a recent study, the antioxidant activity of oleuropein, a polyphenolic compound, was increased by encapsulating it in NLCs. The results proved that NLCs were suitable for the delivery of herbal drugs as they showed enhanced stability and bioactivity of oleuropein. This is an interesting strategy for enhancing the bioavailability of plant-based therapeutics.

Co-Encapsulation Approaches: Co-encapsulation involves loading multiple drugs or therapeutic agents in a single NLC system to achieve synergistic properties, decrease side effects as well as increase patient compliance. This strategy is particularly beneficial in conditions requiring combination therapies. For instance, a dual NLC/hydrogel system was developed for the co-encapsulation and delivery of curcumin and quercetin. This formulation showed greater skin penetration and prolonged drug release, with a better therapeutic efficacy in skin disorders^{31, 32}. Therefore, co-encapsulation with NLCs has taken place as an active targeted and controlled medicine delivery approach.

Safety & Toxicity Considerations: NLCs are explored widely as effective medicine delivery systems but safety and toxicity are quite important features to be ensured for clinical applications. It is crucial to assess biocompatibility

of lipid components, toxicity tests and following all regulatory guidelines to determine the safety profile.

Biocompatibility of Lipid Components: Biocompatibility is an important parameter determining the safety of lipid components for NLCs. Many of the lipids and surfactants used in NLC formulations have a Generally Recognized as Safe (GRAS) status, indicating that they are non-toxic and safe for pharmaceutical use. Many solid and liquid lipids are used such as glyceryl monostearate (GMS), oleic acid, stearic acid (SA) which is biocompatible and biodegradable³³.

NLCs, formed from solid & liquid lipids, provide a disordered lipid matrix which prevents crystallization, improves drug loading and decreases the level of cytotoxicity. Moreover, to enhance the formulation stability and reduce the negative effects, the surfactant such as Tween 80 and poloxamers are often used as stabilizers³⁴. The biocompatibility of these components renders NLCs safe to use in drug delivery applications.

Toxicity Assessment Methods: Toxicity is measured in both in-vitro & in-vivo models. The in-vitro investigations are mostly cytotoxicity tests, where cell lines are used to determine whether there is any damage to the cells caused by the products or whether any changes to the cells have occurred during their metabolism. Cell viability and membrane integrity can be assessed using many methods such as the MTT assay and LDH assay [35]. To assess the systemic and organ-specific effects of NLCs *in-vivo* toxicity investigations are conducted on animal models. Any adverse effects are detected using parameters like body weight, biochemical markers and histopathological analysis. A study of the NLCs containing thymoquinone showed that it was safe in rats as the formulation was biocompatible³⁶. The studies are crucial to determine the safe dosage levels for human use.

REGULATORY PERSPECTIVES: The regulatory bodies such as U.S. Food & Drug Administration (F.D.A.) & European Medicines Agency (E.M.A.) have emphasized on detailed safety assessment & adherence to guidelines for the NLC formulations. Most NLCs used the biodegradable lipids which are GRAS, so they are generally easier to pass regulatory procedures³³. But detailed information about physicochemical properties, toxicity profile and in vivo pharmacokinetics is required for regulatory approval. Consistency and stability testing are also essential for commercialization, and the batch-to-batch consistency must be taken into account. On-going research and uniform guideline for lipid-based nanoparticles will further simplify regulatory process for NLC-based therapeutics³⁴.

FUTURE PROSPECTS AND CHALLENGES: What lies ahead and what needs to be improved. What's to come and what can be better. NLCs are becoming more interesting as drug delivery systems. But the large scale production, stability and compliance with regulatory standards are tough or difficult challenges. Addressing

these issues will be crucial for the successful commercialization of NLC-based products.

Scale-Up and Industrial Production: Laboratory to industrial scale scale-up of NLC manufacture is a complex process. Common methods used are more-pressure homogenization & microfluidics etc.; however maintaining product quality in large scale production is a challenge. The encapsulation efficiency of the drugs, particle size and formulation uniformity have to be monitored and optimized. Adopting a Quality by Design (QbD) approach to the process can aid identification of critical process constraints & product consistency in scale-up. In addition, the production method directly influences the cost-effectiveness, which demands more improvement in the cost-effective and scalable production methods to achieve commercialization³⁸.

Stability and Storage Issues: The physical as well as chemical stability of NLCs during storage is an important concern. These issues may arise, such as particle aggregation, leakage of the drug, lipid crystallization, etc., which can diminish the drug's efficacy. The use of both solid and liquid lipids in the formulation leads to an ordered lipid matrix which helps prevent the expulsion of drugs from the lipid matrix and can help to minimize crystallization. Further, with an appropriate surfactant and optimization of the storage conditions (such as temperature and pH), NLC stability is further enhanced³⁹. Such advanced analytical tools as DSC & XRD can be used to monitor the behavior of lipids during storage to ensure the stability of the product⁴⁰⁻⁴³.

Overcoming Regulatory Hurdles: NLCs have to be regulated rigorously because of their nanoscale characteristics. Inclusive biocompatibility, toxicity and stability assessments are required by regulatory agencies such as the USFDA & EMA. While there are various components of lipids that have accepted safety data (Generally Recognized as Safe (GRAS)), extra safety data are often required. The regulatory requirements are also the ability to show batch-to-batch consistency, to carry out thoroughly designed *in-vivo* studies and to exclude unwanted nanoparticles. A set of common procedures for the evaluation and testing of NLCs could facilitate the regulatory evaluation process⁴⁴⁻⁴⁶.

CONCLUSION

The NLCs represent the revolutionary way of medicine delivery systems, providing substantial improvements in the bioavailability & therapeutic efficiency of poorly soluble medicines. They present a unique lipid matrix with solid & liquid lipids which enable better medicine loading capacity, long duration of effect & stability. Different formulations have been used with success to create NLCs that have an optimized physicochemical property. Their healing properties have been confirmed by *in-vivo* and *in-vitro* studies and characterization methods help to control quality. Versatility of NLCs has been proven in various routes of administration, such as oral, transdermal, ocular and parenteral. Further, they are found to be widely

applicable in the area of delivery of BCS Class II & IV medicines, herbal formulations & Co-encapsulated medicines. But issues such as scale up, stability and regulatory approval are yet to be overcome. The use of advanced manufacture and stability enhancement strategies of regulations will speed up clinical translation of NLC-based formulation. Overall, as research and technology progresses, NLCs offer tremendous promise in the field of modern pharmaceutical therapy, offering safer & more additional real treatment options for many medical conditions.

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