Available online on 15.6.2025 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

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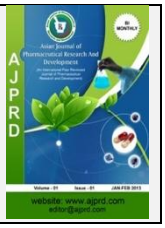

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Review Article

Nanostructured Lipid Carrier: A Review

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A B S T R A C T

Nanostructured Lipid Carriers (NLCs) are nanoscale colloidal systems developed for drug delivery, featuring a core composed of solid and liquid lipids. These lipid-based carriers have emerged as biocompatible, non-toxic, and safer alternatives to polymeric and metallic nanoparticles. Their advantageous properties—such as improved safety, physical stability, and higher drug-loading capacity compared to other lipid-based nanocarriers—have attracted significant interest from researchers aiming to develop efficient and reliable drug delivery systems. NLCs enhance the solubility and permeability of therapeutic agents by encapsulating them within a lipid matrix, making them suitable for administration via challenging biological routes. Furthermore, surface functionalization and the incorporation of specific excipients can enhance targeted delivery and extend systemic circulation. Owing to these features, NLCs hold great potential in the treatment of various conditions, including cancer, infectious diseases, neurodegenerative disorders, hypertension, diabetes, and chronic pain. This review provides a comprehensive analysis of NLCs, focusing on their structural components, fabrication techniques, characterization methods, formulation strategies, and applications in pharmaceutical and therapeutic contexts, particularly in targeted drug delivery systems.

Keywords: Nanostructured Lipid Carrier, Surfactant, Lipids, Targeted drug delivery etc.

A R T I C L E I N F O: Received 11 Jan. 2025; Review Complete 19 March. 2025; Accepted 10 April 2025. ; Available online15 June 2025

Cite this article as:

Ghogare NS, Wankhade VP, Pande SD, Atram SC, Bobade N N, Bhoyar VV, Kokate TS, Nanostructured Lipid Carrier: A Review , Asian Journal of Pharmaceutical Research and Development. 2025; 13(3):88-96, DOI: http://dx.doi.org/10.22270/ajprd.v13i3.1567

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INTRODUCTION:

NANOSTRUCTURED LIPID CARRIER:

In recent years, there has been growing interest in developing topical delivery systems that can enhance drug permeation through the skin. Although chemical permeation enhancers are commonly used for this purpose, their long-term application may pose safety concerns due to potential skin irritation or other adverse effects. This is particularly problematic in chronic treatments. As a result, there is a need for safer and more effective alternatives to improve transdermal drug delivery. Among the emerging strategies, lipid-based nanocarrier have shown significant promise in facilitating drug penetration through the skin, offering a biocompatible and efficient method for enhancing topical drug absorption.

Nanostructured Lipid Carriers (NLCs) were first introduced by Müller in 1999–2000 as an advancement over Solid Lipid Nanoparticles (SLNs). Designed primarily for dermal use in both pharmaceutical and cosmetic formulations, NLCs offer several advantages, including controlled release of active ingredients, targeted drug delivery, enhanced occlusion, improved skin hydration, and increased penetration of active substances. These benefits are largely attributed to their composition, which involves physiological and biodegradable lipids, resulting in excellent skin tolerability and making NLCs a "nanosafe" delivery system. NLCs were specifically developed to address some of the limitations of SLNs, such as low drug loading capacity and the risk of drug expulsion during storage. In contrast, NLCs provide improved drug incorporation, reduced water content in particle suspensions, and greater formulation stability over time, as illustrated in Figures 1.[1-2-3]

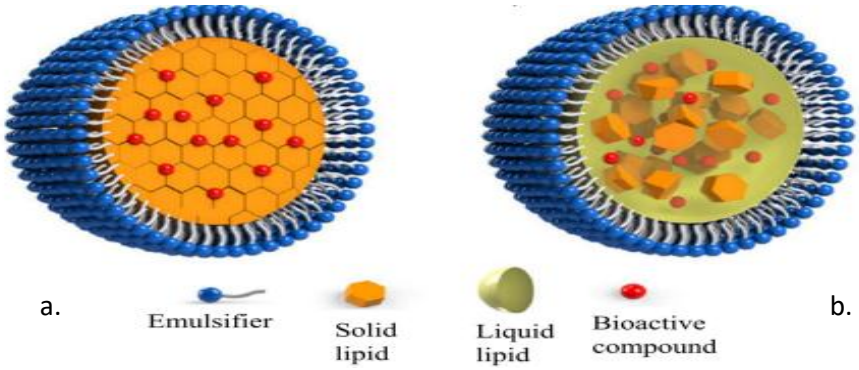


Figure 1: Schematic illustrations of a rigid a. solid lipid nanoparticles (SLNs) with low drug load versus a flexible b. nanostructured lipid carrier(NLCs) with high drug load.

STRUCTURE OF NANOSTRUCTURED LIPID CARRIERS:

As the name implies, Nanostructured Lipid Carriers (NLCs) are nanoscale multiparticulate systems, typically ranging from 50 to 500 nanometers in size. Their particle size distribution is influenced by the preparation method and formulation components. Although colloidal in nature and structurally similar to Solid Lipid Nanoparticles (SLNs), NLCs differ primarily in the composition of their lipid core.[3-4]In contrast to Solid Lipid Nanoparticles (SLNs), which have a highly ordered solid lipid core, Nanostructured Lipid Carriers (NLCs) incorporate both liquid and solid lipids, resulting in a less structured, more disordered matrix. This imperfect internal structure allows for greater drug loading capacity and helps overcome common limitations of SLNs, such as crystallization during storage and the subsequent expulsion of the encapsulated drug.[5]The core of Nanostructured Lipid Carriers (NLCs) consists of a combination of solid and liquid lipids. Since lipophilic drugs tend to dissolve more readily in liquid lipids, and the structural imperfections created by blending different lipids introduce additional voids, these carriers offer increased space for effective drug encapsulation. A wide range of lipids approved as GRAS (Generally Recognized As Safe) are available for use in NLC formulations. Selecting appropriate lipids is essential to ensure that the carrier system remains non-toxic and biocompatible.[7]The selection of lipids for NLC formulations should also take into account the compatibility between the drug and the lipid matrix. In addition to the binary mixture of solid and liquid lipids used to form the core, one or more surfactants are incorporated to stabilize the nanocarrier system. These surfactants form a protective layer around the lipid core, preventing aggregation and improving stability. Both the type of lipids and surfactants used significantly influence the particle size, structural integrity, and overall physicochemical characteristics of the NLCs.[8]

Changes in lipid composition and formulation parameters can lead to alterations in the core structure and the arrangement of solid and liquid lipids. Muller et al. classified these variations into three distinct types of NLCs based on the structural differences observed.(Fig. 2)

1. **The first type (Imperfect crystal type):** In this type, a low concentration of liquid lipid is used relative to the solid lipid. The imperfect crystal type features a blend of spatially distinct lipids, such as glycerides, which are incorporated to enhance the overall structure.
2. **The second type (Multiple types or oil-in-fat-in-water O/F/W carrier):** NLC Type II (or Multiple Types), also referred to as the oil-lipid-in-water type, features a higher solubility for the drug compared to solid lipids. This type contains multiple nano-sized compartments dispersed within a solid lipid matrix. It allows for a prolonged drug release, enabling controlled and sustained delivery of the drug.
3. **The third type (Amorphous or non-crystalline type):** An amorphous, structureless matrix is created by blending solid lipids with specific lipids, such as hydroxyl stearate, MCT (Medium Chain Triglycerides), or iso-propyl myristate. Although the lipid matrix remains solid, it is in an amorphous, non-crystalline state, resulting in the formation of NLCs.[8-9-10]

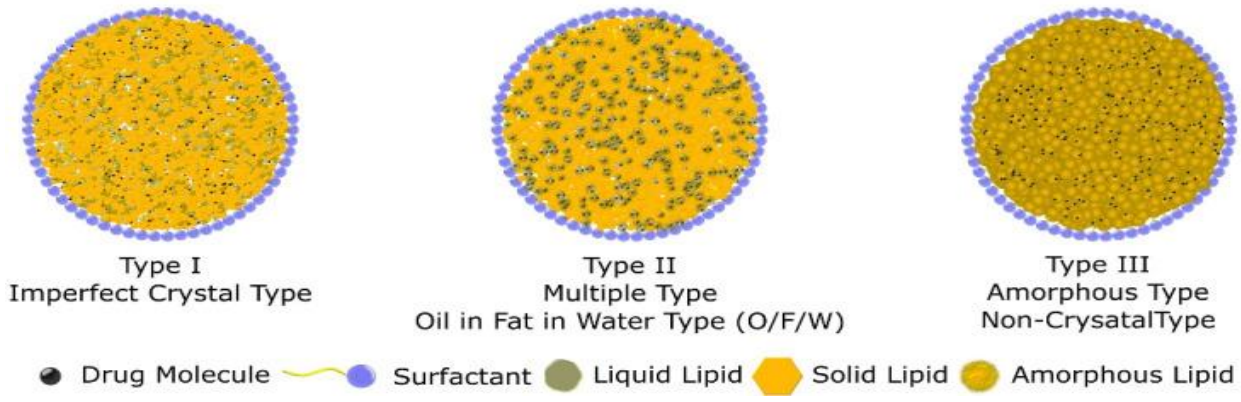


Figure 2: Types of NLCs

Surfactant and Lipid Functions in Formulation Development: The properties and effectiveness of nano-lipid carriers and lipid nanoparticles are significantly affected by the type and concentration of surfactants used. Due to their amphiphilic nature, surfactants tend to accumulate at the interface between lipid and aqueous phases, where they reduce the interfacial tension. Ionic surfactants, such as sodium deoxycholate, can enhance the nanoparticle charge, which increases electrostatic repulsion and contributes to the physical stability of the colloidal system. Non-ionic surfactants, particularly Poloxamer 188, provide additional steric stabilization, helping to prevent aggregation of the nanoparticles in colloidal formulations.[9]

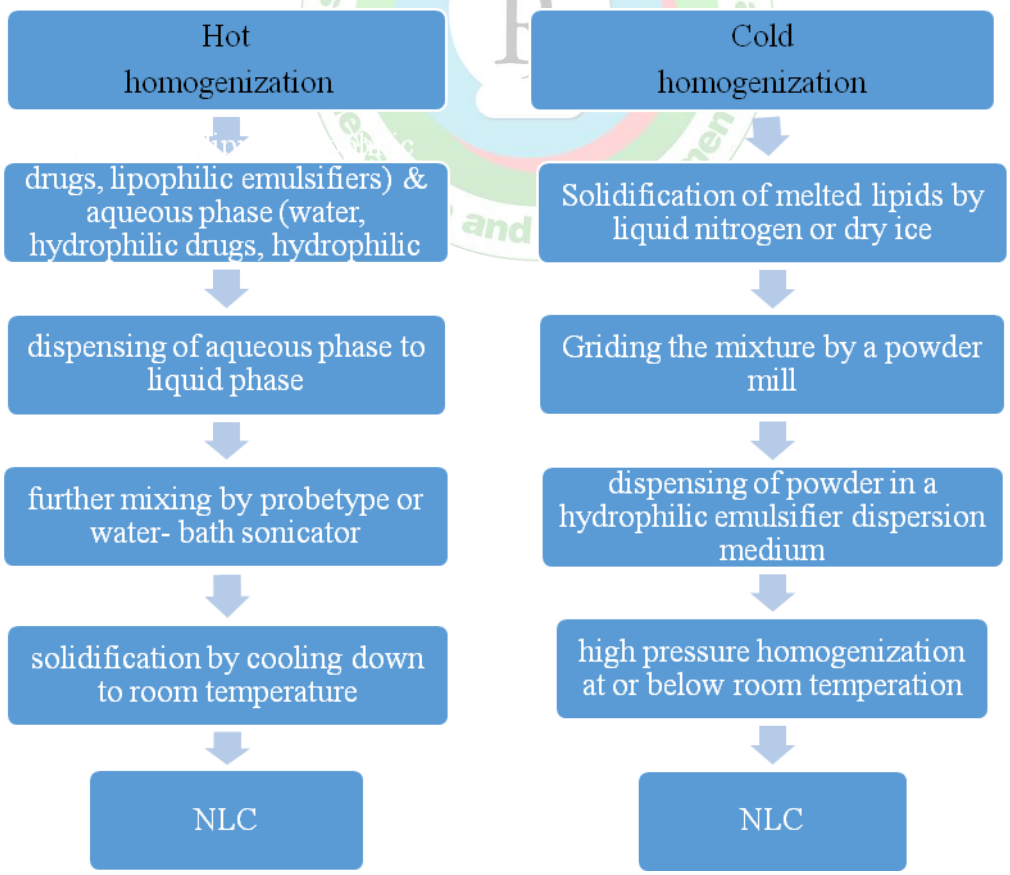
Table 1: List of different lipids and surfactant used in NLCs:

LIPIDS	EXAMPLES
Solid Lipids	Stearic acid, Glyceryl monostearate, Glyceryl behenate, Glyceryl palmitostearate, Palmitic acid, Beeswax , Carnauba wax etc.
Liquid Lipids	Oleic acid, Isopropyl myristate, Paraffin oil, Vitamin E, Coconut oil, Olive oil, Almond oil, Capryol 90 etc.
Surfactants	Pluronic® F-68(poloxamer 188), Pluronic® F-127 (poloxamer 407), Tween 20, Tween 40, Tween 80, Polyvinyl alcohol, Soya lecithin, Span20, Span40, Span60, Sodium deoxycholate, etc.

METHODS OF MANUFACTURING OF NANOSTRUCTURED LIPID CARRIER (NLCs):

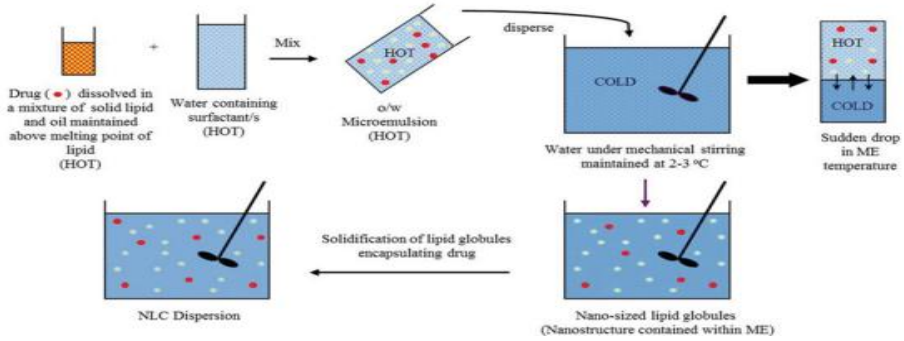
1. **Homogenization techniques**[11-12]

- **Hot high pressure homogenization technique:** In this method, the lipid phase is first heated to 90°C. The hot lipid phase is then mixed with the aqueous phase containing surfactants, also at the same temperature. The resulting pre-emulsion is subjected to three cycles of high-pressure homogenization at 90°C. Finally, the oil-in-water emulsion is cooled to room temperature, allowing the SLNs or NLCs to solidify.
- **Cold High-Pressure Homogenization Technique**: The lipid phase is melted and then cooled to solidify, after which it is ground to form lipid micro particles. These micro particles are dispersed in a cooled aqueous phase containing surfactants to create a pre-suspension. The suspension is then homogenized using a high-pressure homogenizer at room temperature and pressure.

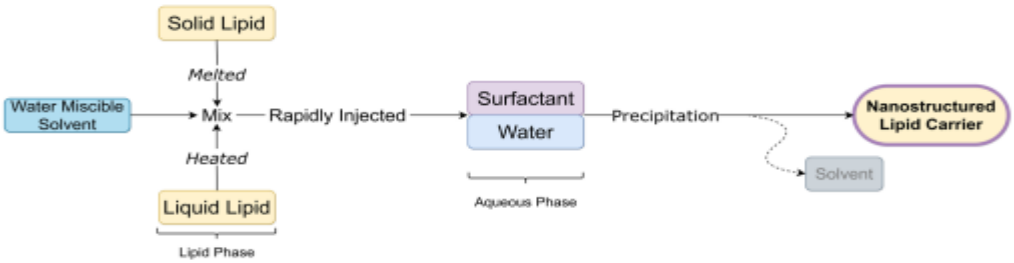


2. **Micro-emulsion:** The melted lipids are combined with a hydrophilic aqueous phase containing a surfactant and co-surfactant to form an emulsion, which can be either water-in-oil (w/o) or oil-in-water (o/w), depending on the proportions of the components used. The emulsion is then mixed vigorously to break the particles down into the micron size

range. A clear, thermodynamically stable micro-emulsion is formed and subsequently dispersed into a chilled hydrophilic phase for further particle size reduction and the production of NLCs.[11]



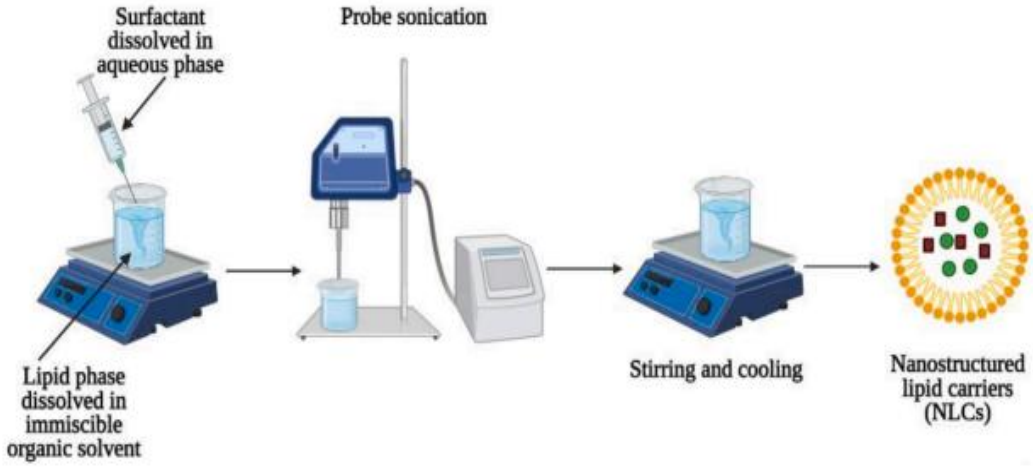
3. Solvent injection method: The solvent injection method is a straightforward and rapid production technique. It involves dissolving lipids in a water-miscible solvent, which is then quickly injected into an aqueous surfactant solution through an injection needle. This method is advantageous due to its simple preparation process and the avoidance of high temperatures, shear stress, and complex equipment. However, its main drawbacks include the use of organic solvents and the production of low particle concentrations.[11]



4. Phase inversion method: In this technique, the drug, lipid, water, and surfactant are gently mixed and heated to a temperature above the phase inversion temperature of the surfactant. During the heating process, the surfactant undergoes dehydration, altering its hydrophilic-lipophilic balance and changing its affinity for each phase, leading to the inversion of the emulsion. When rapidly cooled (using an ice bath), the surfactant regains its hydrophilic properties, facilitating the formation of small NLC particles.[11]

5. Solvent emulsification-evaporation technique: In this method, lipids and drugs are dissolved in a water-immiscible organic solvent along with a surfactant, before the solvent is evaporated. The resulting pre-emulsion is then subjected to sonication. Afterward, the dispersion is cooled to room temperature to produce aqueous NLC dispersions. This approach is known for its rapid and straightforward production process.[11]

6. Solvent emulsification-diffusion technique: This technique can be applied to both aqueous and oily phases, with the solvent used being partially miscible with water. The lipid and drug are dissolved in a water-saturated solvent, and the organic phase is then stirred using a mechanical stirrer. Once an oil-in-water (o/w) emulsion is formed, water is added to the system in a typical ratio of 1:5 to 1:10. This addition allows the solvent to diffuse into the continuous phase, leading to the aggregation of the lipid into nanoparticles.[13]



7. Solvent displacement or injection technique: In this method, the lipid is dissolved in a solvent such as dimethyl sulfoxide or ethanol, which is then quickly injected into a surfactant solution. The resulting precipitates are filtered to obtain nanoparticles. To achieve smaller particle sizes, a high solvent migration velocity is preferred, which makes less lipophilic solvents more suitable. While this technique avoids the use of high heat, shear stress, and complex equipment, the presence of the organic solvent remains a disadvantage.[13]

8. Melt emulsification and ultra-sonication: The drug-lipid mixture is melted and mixed with a pre-heated surfactant solution, followed by sonication using a probe sonicator. The resulting solution is then rapidly cooled to form nanoparticles. It is crucial to optimize the sonication duration to achieve the desired particle size and entrapment efficiency. A probe sonicator is preferred over a bath sonicator due to its higher intensity, though it may introduce metal contamination depending on the sonication time, probe condition, and mixing procedure.[12]

9. Double-emulsion technique: In double emulsion technique the drug (mainly hydrophilic drugs) is dissolved in aqueous solution, and further emulsified in melted lipid. The primary emulsion is stabilized by adding stabilizer that is dispersed in aqueous phase containing hydrophilic emulsifier, which is followed by stirring and filtration. Double emulsion technique avoids the necessity to melt the lipid for the preparation of peptide-loaded lipidnanoparticles and the surface of the nanoparticles could be modified in order to sterically stabilize them by means of the incorporation of lipid-PEG derivatives.[13]

CHARACTERIZATION OF NLCS:

1. **Particle size and particle size distribution measurement:**The particle size of NLC systems was determined using photon correlation spectroscopy (PCS) with a Malvern Rasterizer 2000MU. To measure the particle size, the undiluted sample was placed into a disposable plastic cuvette, which was then gently shaken for 5–10 seconds before being positioned on the sample holder. The average particle size and polydispersity index were recorded using photon correlation spectroscopy at a 90° angle and at a temperature of 25°C.[14]
2. **Zeta potential analysis:**The surface charge of the nanoparticles was assessed by measuring the zeta potential using a Zetasizer. Before analysis, the NLC suspensions were diluted with double-distilled water (1:100) to achieve uniform dispersions. The conductivity was then measured at 25°C. All values reported are the average of three separate measurements.[14]
3. **Morphology Shape and surface morphology:**NLCs were observed using a scanning electron microscope (SEM). A single drop of the sample was placed on a slide, and any excess water was allowed to evaporate at room temperature. The slide was then attached to an aluminum stub using double-coated adhesive tape. The stubs were coated with gold to a thickness of 200 to 500 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. Photomicrographs were captured at various magnifications.[14]
4. **Drug entrapment efficiency (DEE) and drug loading (DL**A 2.0 ml volume of drug-loaded sample was centrifuged (SIGMA F-18 K, Sartorius) at 12,000 rpm for 30 minutes at 20°C to separate the lipid and aqueous phases. The supernatant was then filtered through 40 µm filter paper (Hi-media, Mumbai), and the absorbance of the sample was measured using a UV-VIS spectrophotometer (UV-1800, Shimadzu, Japan).The entrapment efficacy of NLC was calculated as follows:Drug Entrapment Efficiency (%w/w)=Total amount of drug Amount of drug in supernatant×100/Total amount of drug
5. DrugLoading (%w/w)=Initial drug–free drug/Mixed lipid ×100[14]
6. **In vitro release study of drug loaded NLC:** In vitro release studies were conducted using a Keshary Chien (K-C) cell to assess the drug release profile from each formulation. The diffusion cells were maintained at 37±2°C using a water jacket. A dialysis membrane (70, Hi-Media, Mumbai, India) with a pore size of 2.4 nm and a molecular weight cutoff between 12,000–14,000 Da was used and mounted on the K-C cells. The release membrane's surface area was 3.14 cm^2. Phosphate buffer saline (PBS; pH 7.4) served as the receptor medium (10 ml), which was stirred at 100 rpm. NLC dispersion was placed in the donor compartment. During the experiment, the solution in the receptor compartment was kept at 37±0.5°C. At specified time intervals, the sample was withdrawn from the receiver compartment and replaced with an equal volume of freshly prepared PBS (pH 7.4). The withdrawn samples were analyzed using a UV-Visible spectrophotometer.[14]

ADVANTAGES:[4-15-16]

- **Enhanced Drug Solubility**: NLCs improve the solubility of poorly water-soluble drugs, facilitating better absorption.
- **Controlled Release:** They provide a sustained and controlled release profile, allowing for reduce dosing frequencies and maintain therapeutic levels over an extended period.
- **Improved Stability:** NLCs are more stable than traditional lipid-based systems, reducing drug degradation and improving shelf life.
- **Biocompatibility and safety:** Made from natural lipids, NLCs are generally biocompatible and safe for use in pharmaceutical applications.
- **Targeted Delivery**: NLCs can be modified to target specific tissues or cells, enhancing the precision of drug delivery.
- **Reduced Toxicity**: By controlling the release and targeting specific sites, NLCs can help minimize systemic toxicity.

VARIOUS ROUTES OF ADMINISTRATION OF NLCS:

1. **NLC FOR TOPICAL ADMINISTRATION:** The smaller size of NLCs enhances their interaction with the stratum corneum, leading to an increased amount of active compound penetrating the skin. Additionally, nano-sized particles can firmly adhere to the skin surface, enabling more controlled drug delivery. Since NLCs offer higher drug loading capacity compared to SLNs, they can create a higher drug concentration gradient on the skin surface, which aids in

drug permeation. NLCs have proven to be effective for delivering drugs through the topical route, enhancing drug permeation, skin hydration, controlled drug release, and drug stability.[12-17]

Table 2:

Active ingredients	Method of preparation	Research highlights	References
Aceclofenac	Melt-emulsification	NLC gel showed a rapid onset of action and prolongedduration of action as compared with the marketed gel.	24
Clotrimazole	High -pressure homogenization	NLC showed a faster release.	25
Diacerein	Hot homogenization-ultrasonication	NLC-based gel showed quicker start and sustained operation for up to 24 hours.	26
Terbinafine hydrochloride	High- pressure homogenization	NLC formulation showed better permeation into the skin and reduced fungal burden in a shorter duration of time as compared to marketed gel preparation.	27
Apremilast	Cold homogenization ultrasonication	Nanostructured lipid form of poorly water-soluble drug increased drug deposition in the skin.	28

2. **NLC FOR ORAL ADMINISTRATION:** Oral drug delivery systems dominate the drug delivery market, but ongoing research focuses on enhancing these systems due to challenges such as low drug solubility, limited absorption, rapid metabolism, fluctuating plasma levels, and food-related variability. Over the past few years, colloidal drug carriers like micelles, liposomes, nano-emulsions, nano-suspensions, and polymeric nanoparticles have addressed many of these issues. However, these systems still face challenges including limited stability, aggregation, drug leakage during storage, low production yield, residual organic solvents in the final product, and potential cytotoxicity. As a result, researchers have explored lipid-based carrier systems as an alternative, particularly for improving the absorption of poorly water-soluble drugs. Numerous in vivo studies have demonstrated that lipid carriers can enhance the absorption of these drugs, with the effectiveness often depending on the specific chemical properties of the lipid used.[16]

Table no.3

Active ingredients	Method of preparation	Research highlights	References
Quercetin	High- pressure homogenization	The optimized QT-NLC, the average particle size, the zeta potential and the average entrapment efficiency were 129 ± 12.13 nm, −26 ± 4mV and 93.50±0.35% respectively.	29
Simvastation	Emulsification-solvent evaporation technique	A single dose of SIM-NLC, 4-fold increase in bioavailability was observed,as compared to theSIM suspension	30
Carvedilol	Emulsification-ultrasonication	NLC formulation remarkably improved the oral bioavailability of CAR. The promising findings in this investigation suggest the practicability of these systems for the enhancement of bioavailability of CAR	31
Nimodipinae	High- pressure homogenization	NMP-NLC shared a spherical shape of ~70nm.High encapsulation efficiency of 86.8%±2.1%	32
Docetaxel	Emulsification-ultrasonication	The DNLCs achieved excellent drug entrapment, a satisfactory particle size and good GI stability. Results indicate that the NLCs are very promising method forenhancing the oral absorption of anticancer drugs	33

3. **NLC AS A DELIVERY TO THE BRAIN**: The brain is well protected by the blood-brain barrier (BBB), which significantly restricts the diffusion of substances, making drug delivery to the brain particularly challenging. In fact, around 98% of newly developed drugs fail to effectively cross the BBB. Among the promising approaches for overcoming this challenge are nanostructured lipid carriers (NLCs), which enable drug delivery to the brain without requiring chemical modification of the drug itself. These carriers are known for their efficient brain uptake, biocompatibility, and biodegradability. Key benefits of using this route include:

- Bypassing hepatic first-pass metabolism
- Achieving a faster onset of action compared to oral administration
- Lowering the frequency of dosing

For example, NLCs formulated with Asenapine (ANS) maleate have demonstrated improved delivery to the brain and enhanced bioavailability of the drug.[18]

Table no. 4:

Active ingredients	Method of preparation	Research highlights	References
Flibanserin	Hot-Emulsification- ultrasonication	To improve the drug bioavailability.	34
Rivastigmine	High- pressure homogenization, ultrasonication	HPH was selected as the most suitable production method, Although the ultrasound technique has also shown effectivenes.	35
Temozolomide	High- pressure homogenization	Improved delivery of chemotherapeutic agent to the brain with potential of lesser side effects	36
Artemisinin	Solvent evaporation method	ART-loaded NLCs can be successfully achieved high entrapment efficiency and controlled drug release profile suitable for brain administration	37
Atazanavir	Melt- emulsification	Greater Cmax in the brain and 4- fold improvement in brain bioavailability	38

4. **NLC AS A OCULAR DELIVERY:** Topical administration is a noninvasive and widely preferred method for delivering drugs to the anterior segment of the eye. However, one of its major limitations is the low ocular bioavailability, primarily due to the short residence time of the drug at the site of action. While alternative methods such as intravitreal or subconjunctival injections can improve drug delivery, they carry significant risks including bleeding, infections, and potential vision loss.

Nanostructured lipid carriers (NLCs) offer a promising solution to these challenges through several mechanisms:

- They extend the release duration and increase the retention time of the drug on the ocular surface.
- NLCs enhance ocular bioavailability by facilitating drug transport through both transcellular and paracellular pathways.
- They help bypass ocular blood barriers that typically limit drug penetration.
- These carriers protect the encapsulated drug from degradation by enzymes present in the tear film.
- By maintaining therapeutic levels for longer periods, NLCs can reduce the frequency of drug administration, thereby improving patient compliance.[9]

Table 5:

Active ingredients	Method of preparation	Research highlights	References
Celecoxib	Micro emulsion template technique	Study showed faster onset and elicited prolonged activity until 24 h.	39
Ciprofloxacin	Hot homogenization	It prolongs the residence time on the ocular surface after topical administration, improves ocular bioavailability	40
Curcumin	Hot- melt emulsification and ultrasonication	The formulation enhanced curcumin permeation across excised corneas	41
Lactoferrin	Double Emulsion/ solvent evaporation	High EE and LC values were obtained (up to 75%	42
Dexamethasone	Ultrasonication	For the stability and the entrapment efficacy of NLCs; lower surfactant and lipid concentrations could be Beneficial.	43

5. **NLC AS GENE DELIVERY SYSTEM**: Advancements in medicine, biotechnology, and genetic engineering have significantly improved our understanding of complex diseases and opened new avenues for their treatment, which are often beyond the capabilities of traditional therapies. One such advancement is the use of RNA and DNA delivery for the treatment and prevention of both genetic and acquired conditions. However, delivering genetic material directly into cells presents major challenges due to its large size, hydrophilic nature, negative charge, and vulnerability to degradation. To address these obstacles, vectors are commonly employed to facilitate the efficient and safe transport of genetic material into target cells.[20]Lipid-based nanoparticles have proven to be a better alternative due to their enhanced biocompatibility. NLCs (Nanostructured Lipid Carriers) can be integrated into a variety of formulations for delivering genetic material through multiple routes, thanks to their greater stability compared to other nano-vectors.[21]In addition to systemic gene delivery, the inhalation and transdermal routes are being investigated for targeted delivery, offering the potential for site-specific treatment and reduced toxicity, as seen in conditions like lung cancer.[22-23]

CONCLUSION:

Nanostructured Lipid Carriers (NLCs) represent a novel and advanced generation of lipid-based nanocarriers, engineered through the integration of nanotechnology with biocompatible lipid matrices. These systems offer a versatile and efficient platform for drug delivery across multiple administration routes. NLCs exhibit superior characteristics, including enhanced physicochemical stability, high drug loading capacity, and the ability to achieve controlled and sustained drug release. Their unique capability to encapsulate both hydrophilic and lipophilic therapeutic agents further broadens their application spectrum. The favorable

biocompatibility, scalability for industrial production, and potential for targeted delivery position NLCs as promising candidates for clinical applications in diverse therapeutic domains such as oncology, dermatology, and neurodegenerative diseases. Ongoing research and technological innovation are imperative to address existing limitations and to fully exploit the potential of NLCs in advancing precision medicine and patient-specific drug delivery

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