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# Nanostructured lipid Carriers: An Advanced Drug Delivery Approach

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**ABSTRACT**
Nanoparticulate systems have become promising platforms for drug therapy, providing solutions to improve drug efficacy and address its inherent limitations. Among these systems, lipid nanoparticles show significant potential in drug delivery. Nanostructured lipid carriers, which represent the second generation of lipid nanoparticles, have emerged as a promising alternative carrier system compared to other carrier systems. NLCs are colloidal drug delivery systems characterized by a solid matrix made up of spatially incompatible lipids, leading to an imperfect crystal structure. This unique composition allows for the accommodation of higher drug payloads and offers improved drug loading capacity compared to first-generation lipid nanoparticles. These nanocarriers' lipid-based structure offers several benefits, such as improved drug solubility, controlled release, targeted delivery, and increased bioavailability. This article aims to provide a comprehensive overview of NLCs, covering their various types, formulation techniques, characterization methods, and applications. The versatility and efficacy of NLCs make them a promising avenue for addressing challenges in drug therapy, ranging from enhancing drug efficacy to improving patient compliance.



## INTRODUCTION:

In recent years, nanotechnology has seen significant advancements and widespread applications across various fields[1]. In pharmaceutical nanotechnology has revolutionized drug delivery,[2] allowing for targeted and controlled release of drugs. Nanocarriers, in their diverse forms , hold immense potential to offer innumerable opportunities for drug delivery in various fields[3]. Nanodrug delivery techniques are categorized into two types: lipid-based systems, such as liposomes, ethosomes, solid lipid nanoparticles and nanostructured lipid carriers, and polymeric systems, including nanospheres, nanocapsules, and nanofibers[4].The level of interest in lipid based carrier system remains high due to the use of biocompatible and biodegradable lipids[5]. Lipid based system preferred over polymeric systems because the lipid nanocarriers overcome the problems which is arises with polymeric systems such as cytotoxicity, lack of suitable large scale production method and high cost[6] The interest in lipid-based carrier systems remains strong due to the use of biocompatible and biodegradable lipids[5]. Lipid-based systems are favored over polymeric ones because they address issues associated with polymeric systems, such as cytotoxicity, lack of suitable large-scale production methods, and high costs[6]. The advent of solid lipid nanoparticles marked the start of research into innovative lipid nanoparticulate drug delivery methods. Introduced in 1990, solid lipid nanoparticles are an alternative to conventional colloidal carriers such as polymeric nanoparticles, emulsions, and liposomes.[7]. However, SLNs have limitations, including drug expulsion and limited drug loading capacity. To overcome these challenges, Muller developed a new lipid carrier called Nanostructured Lipid

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Carrier in 1999/2000[8]. NLCs, a colloidal drug delivery system, consist of a solid lipid matrix and a spatially incompatible liquid lipid. This unique NLC structure offers numerous advantages, such as enhanced drug loading capacity and support for larger drug payloads[9]. Nanostructured lipid carriers represent the next generation lipid nanoparticles, offering several benefits over conventional drug delivery systems, such as increased solubility, improved bioavailability, and enhanced therapeutic efficacy. NLCs exhibit superior physical stability, minimizing drug expulsion and extending the drug's shelf life[10]. The inclusion of liquid lipid allows for higher drug loading capacity, facilitating the delivery of a larger quantity of the active pharmaceutical ingredient while maintaining the carrier system's structural integrity[8].

**Types of NLCs:**
NLC systems should effectively convert inputs in order to save vital data while using the least amount of energy possible. In addition to meeting stringent output standards, they must be resilient and flexible to a range of inputs. As functionality grows, it is critical to manage complexity through simplifications, and iterative development is necessary to refine designs. Based on the various production techniques and composition of the lipid blends, nature and concentration of surfactants, the drug solubility in melted lipids there are three categories exist for NLCs.

**The imperfect type:**
It is also known as imperfect type. When a portion of solid lipid is replaced with liquid lipid or oil, an irregular crystal lattice or matrix is formed. This occurrence demonstrates the availability of additional space for drug accommodation, hence enabling increased drug loading. By creating an imperfect crystal core, extra space is available for the inclusion of drugs rather than a well ordered or structured matrix that would have forced the drug out of the core.

**The amorphous type:**
Amorphous types are created by blending lipids in a manner that inhibits their crystallization. This approach is used to prevent crystallization within the matrix and to avoid drug leakage, as crystallization often leads to drug expulsion. Specific lipids that resist crystallization during the homogenization and cooling of nanoemulsion, such as hydroxy octacosanyl hydroxystearate, isopropyl myristate, and dibutyl adipate, are utilized in the formulation of amorphous type NLC [15].

**The multiple type:**
Lipophilic drugs are more soluble in liquid lipids than in solid lipids. In this type, high concentrations of oils are combined with solid lipids, causing the oil to disperse into the solid matrix at low concentrations[16]. Adding more oil than its solubility allows can lead to phase separation, resulting in the creation of small, oily nanocompartments encased in a solid lipid matrix[17].

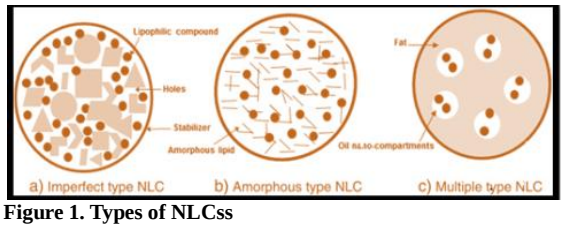

**Figure 1. Types of NLCss**

**Advantages of NLCs [5-9]**
Nanostructured lipid carriers offer several advantages over other conventional lipid-based carrier system such as solid lipid nanoparticle

1. NLCs exhibit good dispersibility in an aqueous medium.
2. High drug loading capacity.
3. Better physical and chemical stability.
4. Ease of production
5. Encapsulation of both hydrophobic and hydrophilic drugs

**Disadvantages of NLCs [18-20]**
Recently very few disadvantages for the NLC were reported in literatures and they can be described as following

1. cytotoxic consequences associated with the concentration and nature of lipid matrix.
2. Stability of lipids.
3. Irritation and sensitizing action of surfactant.
4. Gene delivery technologies, as well as the use and effectiveness of protein and peptide therapies, still require improvement.

**Components of NLCs:**
Generally, nanostructured lipid carriers consist of solid lipids, liquid lipids, an emulsifying agent, and water.

**5.1 Lipids:**
The primary component in the preparation of NLCs are lipids, influencing drug loading capacity and formulation stability. Selecting the appropriate lipid is essential before using them in the preparation of lipid nanoparticle dispersion [22]. The standard ratio for solid and liquid lipids in the formulation ranges from 70:30 to 99.9:0.1[23]. Various types of solid lipids are used in NLC preparation, including fatty acids (myristic , stearic and palmitic acid), glycerides (glyceryl monostearate, glyceryl palmitostearate, tripalmitin, tristearin), and waxes. These lipids with the exception of cetyl palmitate are generally recognized as safe [24]. To lower the crystallinity of the solid lipid core and integrate it,

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liquid lipids are added to NLCs. Compared to solid lipids, drugs are more soluble in liquid lipids [25]. The two most often utilized liquid lipids are oleic acid and MCT. e It is crucial to use biocompatible and health-promoting oils in the formulation [26].

| Lipids | Examples |
|---|---|
| Waxes | Beeswax, Carnauba wax and cetyl palmitate |
| Fatty acids | Palmitic acid, stearic acid, Myristic acid |
| Monoglycrides | Glyceryl Monostearate |
| Diglycerides | Glyceryl palmitostearate |
| Triglycerides | Caprylate triglyceride,glyceryl tribehenate |
| Liquid lipids | Oleic acid, soyabean oil, medium chain triglycerides(MCT)/ caprylic triglycerides, alpha-tocopherol/Vitamin E, Squalene Hydroxyoctacosanyl hydrostearate and Isopropyl myristate |
| Cationic lipids | Cetyl pyridinium chloride (hexadecyl pyridinium chloride, CPC), Cetrimide (tetradecyl trimethyl ammonium bromide, CTAB. |

**Surfactants:**
Surfactants have a significant impact on the drug dissolution and permeability. The choice of surfactant is determined by aspects such as delivery method, hydrophilic-lipophilic balance (HLB) value, lipid modification, and impact on particle size[27]. Their primary function is to rapidly adhere to interfaces and significantly lower surface tension, thereby enhancing solubility[28]. An ionic surfactant sodium deoxycholate have low emulsification efficiency, can increase the charge of nanoparticles, which enhances electrostatic repulsion and improves the physical stability of colloidal systems. Polaxamer 188, a non-ionic surfactant, provides enhanced steric stability by reducing fine particle aggregation in colloidal systems [29].

| Surfactants | Examples |
|---|---|
| Ionic Surfactant | Sodium oleate, Sodium dodecyl sulphure |
| Non-ionic Surfactant | Span 20,80,85, Tween 20,80, Tyloxapol, Polaxamer 188, Polaxamer 407 |
| Amphoteric Surfactant | Egg Phospholipid (Lipoid E 80, Lipoid E80 S) |
| Co-Surfactant | Butanol,Butyric acid |

**Method of preparation:**
Various methods are employed to prepare nanostructured lipid carriers. These include high-pressure homogenization, solvent emulsification evaporation, solvent injection, solvent emulsification diffusion, and microemulsion methods, among others.

**High Pressure Homogenization:**
High-pressure homogenization is the most widely used technique for producing NLCs, especially for large-scale nanoparticle production, due to its advantages like easy scalability and reduced production time[30]. This method applies high pressure (100-2000 bar) to the lipid, using high shear stress to break particles down to submicrometer or nanometer sizes[31].

**Hot Homogenization:**
In this technique, the active pharmaceutical ingredient is dissolved in melted lipids and then rapidly dispersed in an aqueous emulsifier while stirring at high speed. This process is maintained at a constant temperature. The resulting emulsion is homogenized under high pressure and ultrasonic intensity, forming a nano-range emulsion. After cooling, nanoparticles precipitate, which can be collected using a heat exchanger or cold water[32].

**Cold Homogenization:**
The cold homogenization method involve melting and mixing the lipid blend to create lipid microparticle dispersion, which is then combined with a cold surfactant solution to form a pre-suspension. Homogenization at up to 5-10 cycles at 1500 bar at room temperature yields NlCs as the final product.

**Solvent Emulsification Evaporation Method:**
This method involves dissolving the lipid matrix in a water-immiscible organic solvent, followed by emulsification in the aqueous phase before solvent evaporation. The pre-emulsion is then evaporated under reduced pressure, leading to the formation of NLCs[34].

**Solvent injection method:**
This approach is sometimes referred to as the solvent displacement method. This approach provides a high level of efficiency and a faster rate of production. Through the use of an injection needle, lipids are rapidly injected into an aqueous solution of surfactants after being dissolved in a water-miscible solvent. This method's main flaw is that it uses organic solvents[35].

**6.6 Solvent diffusion method:**
This process involves adding the drug and lipid to a mixture of organic solvents that are miscible with water. To obtain a clear liquid phase, the solution is sonicated at a high temperature. An aqueous phase is prepare using surfactants and water, and mixing is done at the same temperature as the liquid phase. Then, using a high temperature and continuous mixing, the lipid phases are introduced to the aqueous phase. Under constant mixing, the finished

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dispersion is cooled to ambient temperature, allowing the organic solvent to evaporate and produce NLCs[36].

**6.7 Microemulsion method:**
SLN and NLC have been produced using microemulsion formation since the early 90s. This method the microemulsion formed by mixing of melted lipids with a hydrophilic aqueous phase containing a surfactant and co surfactant with a gentle stirring. In second step the hot microemulsions distributed in cold water under moderate stirring. This results in solidification of lipid droplets. The NLC produced using this method have a narrow size distribution and spherical in shape.

**6.8 Phase inversion technique:**
In this method lipid, drug, water and surfactant are mixed under stirring and applying three temperature cycles to reach the inversion process after which the shock is applied by diluting the mixture in cold water resulting in NLC preparation [38].

**6.9 Ultrasonicaton or high speed homogenization:**
This method is among the least studied. Lipid and medication are mixed above their melting points in this approach. In order to form an emulsion, this melted solution was added to an aqueous mixture that contained surfactant and had been heated to the same temperature using a high-speed stirrer. After that, it is sonicated to minimize droplet size and cooled gradually in order to produce the dispersion of nanoparticles [39].

**7. Characterization of NLCs**
The physicochemical parameters of NLC must be characterized using the right methods to ensure their stability, performance, and product quality. Particle morphology, drug entrapment efficiency, crystallinity studies, and other evaluation factors shed light on how feasible NLCs are as drug delivery systems.

**7.1 Particle size analysis**
Dynamic light scattering, also referred to as photo correlation spectroscopy (PCS), was utilized for particle size analysis using the Malvern Zetasizer Nano ZS (Malvern Instruments, UK). Prior to measurement, all samples were diluted with distilled water to ensure suitable scattering intensity. Measurements were conducted at 25°C, with each one performed three times. The hydrodynamic diameter Rd (intensity-weighted mean diameter) is determined through DLS[40].

**7.2 Zeta potential and polydispersity index:**
A zeta potential analyser used to assess the surface charge and PDI of nanoparticles examined by dynamic light scattering using the Zeta PALS particle sizing software. To prevent particle agglomeration, electrostatic stabilization requires a zeta potential either above or below 30 mV[41]. The formulation of NLCs can be significantly impacted by the surface charge since it offers vital information on the long-term stability and aggregation and dispersion of the particles[42].

**7.3 Morphology of NLCs:**
The shape of particles is a critical factor that can influence various properties of nanoparticles, including their physical and chemical stability, entrapment and loading efficiency, the location of active ingredients within lipid particles, and the rate and release of drugs. The morphology of nanostructures is typically assessed using various microscopic techniques, such as atomic force microscopy, scanning electron microscopy, and transmission electron microscopy (TEM). TEM is the most frequently used tool for examining the morphology of NLCs. Scanning electron microscopy (SEM) generates images of components by scanning the surface with a focused electron beam, while transmission electron microscopy (TEM) produces images after an electron beam passes through the material[43].

**7.4 Crystallinity:**
The efficacy of NLC formulations as controlled release systems is contingent upon the physical condition of the bioactive ingredient in both aqueous and lipid phases. Additionally, factors such as polymorphic changes and melting behavior of the dispersed phase influence crystal form, particle morphology, release rate, drug loading, crystallinity index, and the maximum solid-state temperature of nanoparticles. Additionally, factors including polymorphic alterations and the melting characteristics of the dispersed phase affect crystal structure, particle shape, release kinetics, drug loading capacity, crystallinity index, and the peak solid-state temperature of nanoparticles. Proper emulsifier selection and understanding of the melting point are crucial during heat treatment of NLC-enhanced foods. The lipid composition of NLC particles generally demonstrates a reduced melting point compared to the original solid lipid while maintaining a solid state at body temperature[45]. Techniques such as X-ray spectroscopy, DSC, and NMR analysis are commonly used to investigate the drug's status, polymorphism, and melting behavior in lipid nanoparticles within NLC formulations. The polymorphic variations and melting behavior of lipid nanoparticles in NLC, as well as the drug's

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state, are frequently studied using X-ray spectroscopy and DSC.

**7.5 Drug Entrapment efficiency:**
Determining drug loading efficiency is essential for NLCs as it affects their release characteristics[46]. The entrapment efficiency, which measures the perentage of drug encapsulated within NLCs, reflects the nanosystem's ability to contain the drug [2]. This can be calculated as the difference between the total amount of drug added and the free, non-entrapped drug relative to the total amount of drug added. The ultrafiltration-centrifugation method is used to determine how much medication is encapsulated per unit weight of the NLC. In a centrifuge tube fitted with an ultrafilter, a known dispersion of NLCs is made and centrifugation is carried out. A spectrophotometer is used to measure the amount of free medication in the supernatant following the proper dilution. The concentration gradient and rate of drug release are altered by higher encapsulation, which significantly affects EE% and the drug's release from NLCs[47].

**7.6 Drug-lipid (excipients) interaction:**
The FTIR technique is frequently employed to ascertain how drug interact with lipids or excipients. The shifting or weakening of drug functional group peaks or the appearance of previously unidentified peaks in the physical combination are signs of the drug-excipient interaction. Peaks of lipid functional groups are visible in NLCs when a medication is inserted into the matrix. In Fourier Transform Infrared Spectroscopy (FTIR), peaks indicate the wave number at which particular molecular functional groups emit infrared radiations. It is possible to measure the transmission between 4000 and 400 cm-1[48].

**7.7 Drug Release:**
Controlled or sustained drug release from nanostructured lipid carriers (NLCs) can lead to an extended half-life and reduced enzymatic degradation within systemic circulation. The proportion of oil in the lipid matrix, the composition of the emulsifier, and the production temperature are all factors that affect drug release from NLCs. The dialysis method is frequently employed to investigate drug release from NLCs. In this method, drug-loaded NLCs are placed in a dialysis tube, soaked in distilled water overnight, sealed at both ends, immersed in a dissolution medium, and positioned on a magnetic stirrer at 37°C. Samples are collected at regular intervals and replaced with an equivalent volume of fresh medium. The drug concentration is then determined spectrophotometrically at an appropriate wavelength[49].

**Applications of NLCs:**
Nanostructured lipid carriers have become important in drug delivery. NLCs have emerged as effective delivery systems for administering pharmaceuticals via oral, parenteral, ophthalmic, topical, pulmonary, and transdermal routes.

Oral drug administration is the most preferred route due to advantages like patient compliance and non-invasiveness. Nonetheless oral administration has a number of drawbacks including poor bioavailability, short retention period in the gastrointestinal (GI) tract and limited targeting ability. NLCs offers some special characteristics to get beyond the drawbacks of oral administration, such as ph protection, enzyme activity, improve bioavailability and enhancing the absorption from the gastrointestinal tract via intestinal lymphatic system transportation[50].

Nanostructured lipid carriers offer promising prospects for ocular drug delivery due to their unique properties. Topical drug administration to the anterior segment of the eyes is challenging because of the following factors such as conjunctival absorption of the drug, precorneal drug loss, nasolachrimal drainage and the cornea which is a primary barrier to the passage of the most drugs. Drug penetration into the posterior ocular segment is limited by the presence tough blood ocular barriers. For posterior segment drug delivery, intravitreal and subconjunctivital injections are used; however, these can cause tissue damage and result in worst patient compliance[51].

Pulmonary drug delivery represents a one of the possible drug delivery route for the treatment of a number of lung conditions by an inhalation. Respiratory airways systems have biological barriers including mucus, ciliated cell NLCs are more stable than polymeric nanoparticles, liposomes and emulsions against the shear forces produced during nebulization. NLCs appear to be a viable technique for treating pulmonary problems since they can directly reach the lung epithelium, resulting in a faster onset of action, desired dose, avoidance of undesired side effects and dosing frequency[52]. The topical route has been extensively utilized to deliver drugs to dermal areas through the use of lipid-based nanoparticles. The topical use of NLCs has been the subject of numerous investigations and experiments in recent years due to its unique properties[53]. Drug permeation can be facilitated by NLCs by increasing the apparent solubility of encapsulated medicines, which can generate a large concentration gradient on the skin. The drug release is better controlled since the nanoparticles cling firmly to the skin's surface. NLCs are therefore utilized topically to apply a

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variety of medication classes for better penetration and prolonged release. The brief time needed to market these medicines is another advantage of using NLCs for topical delivery of active chemicals[54]

NLCs are an effective method for delivering nutraceuticals due to their high drug loading stability and encapsulation efficiency. Besides providing controlled release of encapsulated components, they can improve the bioavailability and stability of bioactive compounds, as well as the shelf life, consumer acceptability, nutritional value, and safety of food systems[24]. NLCs have garnered significant interest as carriers for chemotherapeutic agents because they can enhance the chemical and physical stability of incorporated drugs and significantly boost the potential of therapeutically effective agents that were previously limited by poor pharmacokinetic properties[2].

**Recent Advancements**

| Sr No. | Drug | Therapeuticarea | Route of drug delivery | Formulation Innovation | Outcomes | Ref. |
|---|---|---|---|---|---|---|
| 1. | methotrexate (MTX), docetaxel (DTX), and doxorubicin (DOX) | Anticancer | Oral drug delivery | Co- delivery of three anti cancer agents | enhanced cytotoxicity and apoptosis induction, along with reduced cell migration and colony formation capabilities. | [55] |
| 2. | Baicalin and Quercetin | Antibiotic | Ocular drug delivery | Thermosensitive insitu Nlc gel | improved transcorneal penetration, longer drug release, and longer precorneal residence time | [56] |
| 3. | Levosulpride | Antipsychotic | Oral drug delivery | pegylated | Increased permeation across Caco-2 cell culture monolayes and intestinal tissue | [57] |
| 4. | Rivastigmine | Alzheimer | Nose to brain drug delivery | Double optimization of drug delivery | Enhanced bioavailability | [58] |
| 5. | Hesperidin | Psoriasis | Topical drug delivery | Qbd approach | Sustained release | [59] |
| 6. | Paclitaxel | Anticancer | Parenteral drug delivery | NLCs formulated with MF59 adjuvant components; also explored co-loading with cannabidiol | Provided safer formulation with reduced toxicity, synergistic anticancer effect, and improved circulation time. | [60] |
| 7. | Amphotericin B | Antifungal | Pulmonary drug delivery | Prepared NLC dry powder inhalers (spray-dried) optimized for aerodynamic performance. | High lung deposition, enhanced dissolution, and effective antifungal action for ABPA. | [61] |
| 8. | Triamcinoloneacetonide | Anti-inflammatory | Buccal drug delivery | NLCs incorporated into mucoadhesive buccal films using Box–Behnken design. | Prolonged buccal retention, stable and controlled local release. | [62] |

## CONCLUSION:

In conclusion, Nanostructured Lipid Carriers (NLCs) represent the most recent and advanced formulations within the lipid nanoparticle category, offering versatility in drug loading, modulation of release profiles, and enhanced pharmaceutical performance. These distinctive attributes of NLCs arise from their unique composition, which incorporates a blend of solid and liquid lipids. NLCs have diverse applications in medical science for the treatment of various diseases, efficiently delivering both hydrophilic and hydrophobic drugs through multiple routes, including oral, parenteral, topical, ocular, pulmonary, and brain-targeted drug delivery. The design and development of multifunctional NLCs, loaded with combinations of drugs and biological actives targeted to specific sites, will open new avenues for research in the cosmetic and pharmaceutical industries. This development signifies a significant step toward a new technological era in human clinical trials. The key advantages of NLCs, such as reduced drug payload, decreased drug toxicity, cost-effective large-scale production, biocompatibility, biodegradability, ease of manufacturing, and improved chemical stabilization of active ingredients, position them as highly promising and nearly ideal nanocarriers, addressing various challenges in drug delivery with potential transformative impacts on healthcare and medical treatments.

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