Review Article

Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) for Enhancing Solubility and Stability of Poorly Water-Soluble Drugs: A Comprehensive Review

Hariharan A, Kamaleshwari B, Padma Preetha J, Gayathri R, Sankar C.
Department of Pharmaceutics, KMCH College of Pharmacy, Kalappatti Road, Coimbatore-641048, Tamil Nadu, India.
***Corresponding author's E-mail:** kamaleshwari.b@kmchcop.ac.in

Received: 08-05-2026; **Revised:** 23-07-2026; **Accepted:** 29-07-2026; **Published online:** 20-08-2026.

ABSTRACT

Poor aqueous solubility remains one of the most significant challenges in oral and parenteral drug delivery, affecting the therapeutic efficiency, bioavailability, and clinical success of many modern pharmaceuticals. Lipid-based nanocarriers—particularly Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)—have emerged as promising platforms to overcome these limitations due to their biocompatibility, scalability, and ability to improve solubility and stability. SLNs represent the first-generation solid lipid systems, offering controlled release and protection of labile drugs but suffering from low drug loading and drug expulsion due to crystalline transitions. NLCs, the second-generation improvement, incorporate a mixture of solid and liquid lipids, resulting in less-ordered matrices capable of higher drug loading, minimized drug leakage, and enhanced stability. This review provides an in-depth analysis of the composition, preparation methods, characterization techniques, mechanisms of solubility enhancement, pharmaceutical applications, and limitations of SLNs and NLCs. Representative case studies of clinically relevant poorly water-soluble drugs are discussed. Emerging trends such as targeted lipid nanocarriers, stimuli-responsive systems, and industrial scalability are highlighted as future directions.

Keywords: Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs), Poorly Water-Soluble Drugs, Drug Solubility Enhancement, Lipid Nanotechnology.

INTRODUCTION

The lack of water solubility is an omnipresent problem in pharmaceutical sciences, and 40-70 percent of newly developed chemical entities fit either Biography pharmaceutics Classification System (BCS) Class II or IV. These drugs have the appropriate permeability but have poor aqueous solubility to slow down the dissolution rate, and, consequently, the bioavailability. Traditional methods, including salt formation, micronization, co-solvents, cyclodextrins, and solid dispersions, have provided some advantage, but tend to be ineffective with highly lipophilic, unstable or pH-sensitive molecules[1]

The development of lipid-based nanoparticles has been driven by the need to have a versatile, biocompatible system of nanocarrier that would improve solubility, as well as confer long-term stability. Lipid systems can be compared to biological membranes and enhance the permeability of drugs, as well as dissolve lipophilic compounds. Two of these systems, The Solid Lipid Nanoparticles (SLNs). and Nanostructured Lipid Carriers (NLCs) have received much attention because of their capability to entrap hydrophobic drugs effectively, prevent the degradation of active components and sustained release profiles [2]

SLNs, which came into the limelight of the 1990s, ushered in a platform, based on the physiologically acceptable solid lipids. Despite its benefits in most aspects, the rather weak points of SLNs are leakages of drugs during the crystallization of lipids and the limited loading of drugs. To address these concerns, the second-generation lipid carrier system was created as NLCs. With the additions of solid and liquid lipids, NLCs have an imperfect or amorphous matrix, which improves the accommodation of drugs and prevents their expulsion This review critically addresses the structural, functional and mechanistic dissimilarities in the solubility and stability of poorly water-soluble drugs of SLNs and NLCs. It also addresses methods of preparation, characterization tools, pharmaceutical uses, challenges and future[3].

2. LIPID-BASED NANOCARRIERS: BACKGROUND AND EVOLUTION.

The use of lipid-based drug delivery systems is not a new innovation in pharmaceutics, which started with liposomes in the 1960s. Liposomes, which are made of phospholipid bilayers, were shown to have amazing potential of encapsulating hydrophilic and lipophilic drugs but had high production costs, instability and leaking of the drugs [4] This was followed by the introduction of emulsions and self-emulsifying drug delivery systems (SEDDS) to enhance solubility though they did not have controlled release qualities and high levels of surfactants were needed.The quest to find lipid systems that are safe, scalable and controlled release resulted in the development of Solid Lipid Nanoparticles. Compared to polymeric nanoparticles, SLNs appeared to have several benefits including biodegradability, low toxicity, and no use of organic solvents (entering them as promising alternatives) [5]

Nevertheless, SLNs continued to encounter significant challenges such as:

- Expulsion of drugs during storage.
- Polymorphic lipid transitions.

- Limited drug loading
- Failure to stabilize some hydrophobic molecules.

Nanostructured lipid carriers (NLCs) development was a significant improvement. Combining solid and liquid lipids, the researchers could make the internal structures less-ordered and more flexible to enhance the drug solubility and stability [6]

Nowadays, SLNs and NLCs are the leading lipid-based nanocarriers with enhanced pharmacokinetics, biocompatibility, and the ability to be used in a wide range of dosage forms.

3. SOLID LIPID NANOPARTICLES (SLNs)

3.1 COMPOSITION

Solid lipid nanoparticles (SLNs) are colloidal forms of carriers that are made up of three major constituents: a solid lipid, one or numerous surfactants, and an aqueous medium. The lipid constituent comprises physiologically acceptable materials that includes fatty acids, triglycerides, diglycerides, glyceride mixtures, steroids, or waxes, which are solid at room temperature and physiological temperature. These lipids normally represent a medium level of the formulation and offer structural base that gives the drugs an entrapment and release. Surfactants are added in comparatively low levels in order to stabilize the nanoparticles by reducing surface tension and preventing aggregation, which are found to be among the most commonly used compounds that are known to be safe as pharmaceuticals. Surfactants are often used together in varying formulations in order to achieve a greater colloidal stability and an increase in shelf life.

Internal organization of SLNs is not rigid, but depends on a number of factors, such as type of lipid and surfactant employed, drug solubility in lipid phase, drug concentration, and production conditions, especially, the temperature and homogenization. Three main structural models of SLNs have been outlined based on such variables. In homogeneous matrix model (Type I) the drug is distributed homogenously within the solid lipid matrix. This structure is commonly acquired by high-pressure homogenization methods, both hot and cold, and is particularly appropriate when the drug is highly lipophilic such that it allows rather homogenous drug distribution and prolonged release characteristics.

Under the Type II (drug-enriched shell model), the nanoparticles have a lipid-rich core with an outer layer that has increased concentration of drug. This structure is formed when the lipid molecules crystallize initially as the lipid cools thus forming the core and the drug is concentrated in the rest of the molten lipid and crystallizes out as a shell. This structure is not the most appropriate in the case of prolonged drug release as the surface localization of the drug is achieved, but when applied to topical preparations, this structure might be beneficial as the drug is available quickly and the skin is penetrated better, which is further facilitated by occlusive effects of SLNs.

On the other hand, a drug-enriched core model (Type III) is defined by a central area that is enriched with drug that is surrounded by an outer layer that is dominated by lipids. This arrangement takes place upon the drug approaching its solubility limit in the molten lipid and crystallizing prior to the crystallization of the lipid. The resulting make up can provide a better protection of the drug and possibly more sustained release characteristics than shell-enriched systems. All these structural differences together underscore the versatility of SLNs and how the design and conditions of formulation can be strategically adjusted to meet particular pharmaceutical needs in terms of drug loading, release behaviour, and therapeutic performance [7]

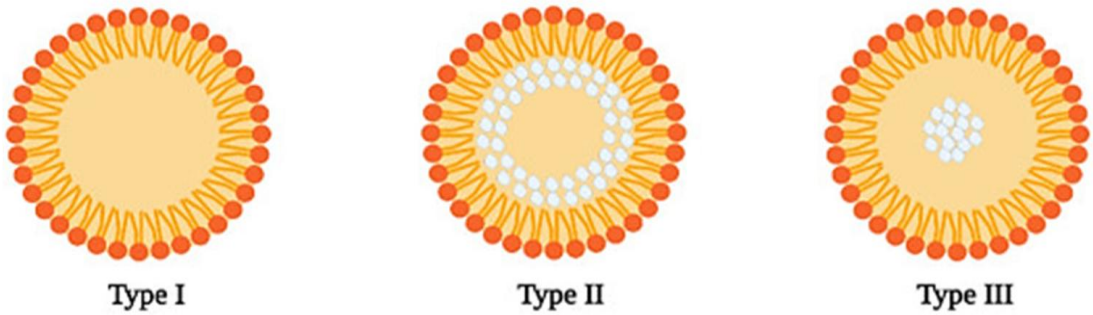

Figure 1: Structure of the different types of SLN: homogenous matrix model (Type I), Drug-enriched shell model (Type II), and Drug-enriched core model (Type III). The drug is represented in white colour.

3.2 METHODS OF PREPARATION

There are several methods of preparation of SLNs developed, each providing some distinct benefits:

High-pressure homogenization (HPH) is employed to achieve homogenization of the food, as it represents a portion of the pasteurization process.

3.2.1 High-Pressure Homogenization (HPH)

This is used in the high-pressure homogenization (HPH) so as to attain homogenization of the food since this is part of the pasteurization process.One of the most popular ways of producing SLNs and NLCs that include phenolic compounds is through high-pressure homogenization. Here, the lipids are melted and blended with aqueous surfactant phase and then the mixture is homogenized under very high pressure

so as to minimize droplet size and generate stable nanoparticles. Some of the compounds that have been encapsulated successfully using this technique include epigallocatechin gallate (EGCG), ferulic acid and quercetin in various lipid matrices [8]

HPH may be done with the hot or cold homogenization processes. The hot technique is above the melting point of lipids and the cold technique is applied on temperature sensitive substances and solidified and then milled and homogenized. These methods have the advantage of being simple, relatively cheap and reproducible. Nevertheless, they demand high energy of operation, special equipment and might not appropriate highly shear-sensitive bioactive molecules. Besides that, mass production is technically challenging.

3.2.2 solvent emulsification-evaporation.

The solvent emulsification/evaporation method involves dissolving the lipids and phenolic compounds in an organic solvent that is water immiscible and emulsification in an aqueous surfactant solution. Lipid nanoparticles are precipitated after the solvent is evaporated after emulsification.This method enables effective lipid solubilization and normally forms small and homogenous particles. It comes in handy especially when heat-reactive substances like curcumin need to be encapsulated, as it does not need high temperatures in its preparation. The process is somewhat simple to take to scale and can be run in an ongoing process. However, there are still apprehensions about using organic solvents, the likelihood of solvent residues in the finished product, and the likelihood of degradation of delicate biomolecules [9]

3.2.3 microemulsion technique

The micro-emulsification process is premised on the fact that at a high temperature, a thermodynamically stable oil-in-water micro-emulsion is formed and then rapidly dispersed in cold water to cause lipid crystallization and the creation of nanoparticles. This method has been used to load the phenolic acids and curcuminoids into SLNs and NLCs. It is said to be appropriate with compounds that are susceptible to mechanical forces since it is based on comparatively gentle working circumstances. The resulting micro-emulsion systems can however be volatile to dilution, temperature variations, and changes in composition which can result in reproducibility and robustness of formulations during the long term [10]

3.2.4 ultrasonication

Ultrasonication: There is a combination of heated lipid and aqueous surfactant phases, and then subjected to high-frequency ultrasound in order to minimize the size of the droplets and create nanoparticles. The technique is easy, fast, and needs simple laboratory equipments. Even though it is convenient in the initial formulation development, ultrasonication tends to cause less efficient dispersion of lipids and relatively large particles especially when loading hydrophilic or poorly lipid-soluble phenolic compounds [11]

3.2.5 double-emulsion method

The technique of the double-emulsion (water-oil-water, w/o/w) is primarily applied when highly hydrophilic phenolic compounds, which have low affinities to lipid matrices, are to be entrapped. This process follows a two-step procedure in which the first step involves dissolving the phenolic compound in water and then the emulsions into an organic phase that has dissolved lipids to create a primary w/o emulsion. This is then emulsified into second aqueous phase and the organic solvent is extracted to attain nanoparticles. This has been utilized to entrap anthocyanins and other polar phenolics to enhance their thermal and PH stability. Nevertheless, it is a fairly complicated procedure and includes several steps and usually the partial deposition of the active compound to the external aqueous phase that can reduce encapsulation efficiency [12]

3.3. MECHANISM OF SOLUBILITY ENHANCEMENT BY SOLID LIPID NANOPARTICLES

3.3.1. Nanoscale Particle Size and Increased Surface Area

The solid lipid nanoparticles (SLNs) are generally on the range of 50-1000 nm. At this size, the particle size is very small and hence offers a very high surface to volume ratio, thereby enhancing interaction with the surrounding aqueous media and thereby elevating the apparent solubility of poorly water-soluble drugs. Predominantly, smaller particles have a higher rate of dissolution because they have a lower diffusion layer thickness and higher surface free energy which means that they dissolve more quickly than coarse drug particles.

3.3.2. Lipid Matrix Incorporation and Drug Partitioning

In SLNs, the drug of poor water solubility is impregnated into a lipid core made of lipids that are biocompatible (e.g., glyceryl behenate, stearic acid). The drug can be either dispersed in a molecular form, or it can be parted in lipid domains. In such lipid matrices, the drug is in a less crystalline or amorphous form as compared to the bulk crystalline form, which has inherently greater apparent solubility. By converting crystalline drugs to a disordered a state in SLNs, one eliminates energy barriers to lattice energy, which encourages the release of drugs into the aqueous phase.

3.3.3. Surfactant-Mediated Wetting and Dispersion

Surfactants (e.g. poloxamers, lecithin) usually stabilise SLNs, adsorbing onto the surface of the nanoparticles. These surfactants enhance wetting of hydrophobic drug particles and aid in particle dispersion in water. High wettability slows aggregation and improves the contact between the drug-loaded lipid particles and the dissolution medium, in effect, increasing drug molecule solubilization.

3.3.4. Nanocarrier-Driven Solubilization

A fundamental process that drives the solubility increase of SLN is that solubilization of hydrophobic drug molecules occurs in the lipid medium of the particle and on the particle-water interface. During the formulation, drug

molecules are partitioned into the lipid core but when they interact with aqueous media (such as gastrointestinal fluids), they are desorb gradually, which essentially exposes them to a pseudo-solubilized form, which increases their apparent solubility compared to when they are in free drug crystals. This is different to the normal dissolution due to the fact that the lipid carrier will serve as a reservoir of solubilization which will enable the availability of drugs in the dissolution media.

3.3.5. Controlled Drug Release and Maintenance of Supersaturation

The kinetics of release can be used to encourage and maintain longer periods of time of a supersaturated solution of the drug by SLNs. On desorption of the drug into gastrointestinal fluids, in the locality of the lipid matrix, there can be brief local concentrations that are above equilibrium solubility, increasing absorption. Stabilizing surfactants and lipid materials are available to slow down the precipitation of drugs and help in the maintenance of high concentrations of the drug in the aqueous phase [13]

4. NANOSTRUCTURED LIPID CARRIERS (NLCS).

Nanostructured Lipid Carriers (NLCs) are a second-generation lipid-based nanocarrier system, which was developed on the basis of Solid Lipid Nanoparticles (SLNs) to address the inherent limitations of the former. Even though SLNs are made completely of solid lipids that are solid at room temperature and at the body temperature, NLCs comprise hybrid lipid matrix made of solid and liquid lipids combined with appropriate surfactants. This distinctive combination results in the less ordered and flexible internal structure in contrast with the highly crystalline matrix of SLNs, which is a strongly affecting factor in drug loading and stability. The NLCs are prepared by mixing solid lipids biocompatible with liquid lipids or oils in certain proportions (usually not more than 70:30 solid to liquid lipid). The introduction of liquid lipids causes defects in the structure of solid lipid matrix, which provide an increase in space and unordered areas where drug molecules can be accommodated. These carriers are solid at physiological and ambient temperatures, although the intermolecular organization of lipids is less organized and rigid compared to SLNs.

NLCs in formulation are usually made of:

Solid lipids (e.g., stearic acid, glycerol behenate, etc.)

Solid lipids/oils (e.g., coconut oil, tallow, beef tallow, lard, beef tallow, palm oil, coconut oil), medium-chain triglyceride, oleic acid, trans-fat, or: Liquid lipids/oils (e.g., coconut oil, olive oil, sunflower oil, flax oil, nut oil, walnut oil, vegan waffles, coconut waffles, soy waffles, gluten-free waffles, gluten

- Surfactants/ emulsifiers (e.g. poloxamers, lecithin) to stabilize the dispersion.
- Continuous medium of aqueous.

Such composition framework enables NLCs to be well-preserved in terms of external morphology yet, inside of them, they possess a lipid matrix containing a micro- and nanodomain of different molecular order and mobility to incorporate drugs.[14-16]

4.1. TYPES OF NLC STRUCTURES

4.1.1. Imperfect type NLCs

Type I (imperfect crystal type) is acquired by combination of lipids of various lengths or by adding mono-, di-, or triglycerides. This leaves a lipid matrix that has a huge number of imperfections and void spaces that give better environment to load drug [17]

4.1.2. Amorphous type NLCs

Medium-chain triglycerides together with solid lipids are mixed to form the amorphous type (Type II). In this system, the solid lipids do not recrystallize following the cooling of the process of NLC preparation to produce an amorphous structure particle. Since recrystallization is not used when cooling or storing, the release of unwanted drugs is reduced resulting in stability and increase in shelf life [18]

4.1.3. Multiple type NLCs

There are several types of type NLCs (Type III) that are making solid lipids mix with oils like oleic acid and/or long- and medium-chain triacyl glycerides. To form successfully, the oil should be added at a concentration which is greater than the solubility of the oil in the solid lipid. The high levels of excess oil are fractionated into very small droplets during the cooling process of the nano emulsion, to create nanocompartments that are scattered throughout the solid lipid matrix [19]

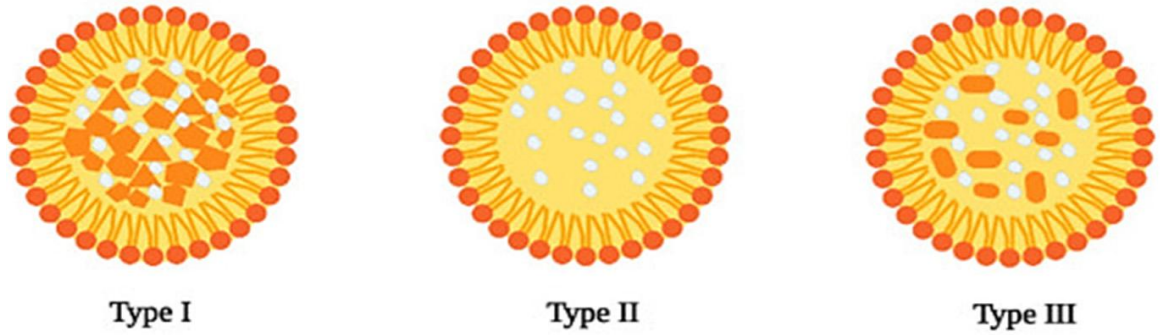

Figure 2: The structure of various types of NLCS imperfect crystal (Type I), Amorphous (Type II), Multiple type (Type III). The drug is depicted in white.

4.2. PREPARATION METHODS

The process of NLCs preparation is similar to that of SLNs, but the lipid mixtures are different. Techniques include:

- Homogenization under a high pressure.
- Microemulsions
- Solvent-based methods
- Ultrasonication
- Double-Emulsion Method [20]

5. CHARACTERIZATION TECHNIQUES FOR SLNs AND NLCs

5.1. particle size, polydispersity index (PDI) and size distribution.

Technique Dynamic Light Scattering (DLS), Photon Correlation Spectroscopy (PCS). These are the most common methods of measuring the average size and size distribution of lipid nanoparticles. The size of the particles affects the most important behaviors through cell uptake, drug release and biodistribution. Low PDI means that there is a homogenous population of nanoparticles and it is preferable in predicting performance.

DLS/PCS is used to quantify changes in scattered light of suspended particles to determine hydrodynamic diameter. Significant to both SLNs and NLCs since the size of the particle determines the rate of dissolution and bioavailability [21]

5.2. Zeta potential (surface charge).

Technique: electrophoretic light scattering, Zeta potential measures the electrical charge of surfaces of nanoparticles and is a important measure of colloidal stability. The large absolute values mean that the electrostatic repulsions between particles are large, and the particles are less likely to be aggregated, which leads to high long-term stability. This parameter also shows the effect of surfactants or coating material on surface properties of nanoparticles [22]

5.3. Morphology and surface structure.

Techniques Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), Atomic Force Microscopy (AFM) and Microscopy offers the direct visual evidence of particle morphology, surface texture and structural homogeneity. The SLNs and NLCs are usually seen as spherical or closer to spherical with particle sizes in agreement with those seen in DLS. TEM is typically prevalent in internal and external detailed morphology.

- SEM provides the topography and structure of the surface.
- AFM is capable of measuring surface images at nanometre scale in near-physiological conditions [23]

5.4. crystallinity and thermal behaviour.

Methods: X- Ray Diffraction (XRD), Differential Scanning Calorimetry (DSC). These techniques determine the physical properties of lipids (crystalline and amorphous), transitional polymorphism, and drug-lipid matrix interaction. Since SLNs are characterised by a high degree of crystallinity, DSC and XRD assist in the determination of the modifications of the lipid order involved in the drug loading and expulsion throughout storage. Mix solid and liquid lipids NLCs are less crystalline, and in many cases associated with an increased drug loading capacity.

DSC measures melting and recrystallization.

Many crystal phase and molecular packings can be seen using XRD [24]

5.5. drug loading and encapsulation effectiveness.

Methods: High-Performance Liquid Chromatography (HPLC), UV -Visible Spectroscopy.

These methods of analysis determine the degree to which drugs are absorbed and held in the lipid carrier when compared to free drugs.

- The encapsulation Efficiency (EE%) is the percentage of drug that is entrapped.
- Drug Loading (DL) is the ratio of the drug within the mass of the nanoparticle.

Proper quantification of these parameters is necessary to be able to correlate the variables of formulation with the results of performance [25]

5.6. in-vitro drug release experiments.

Techniques: Dialysis Bag Method, Franz Diffusion Cell, Drug release studies are simulated by the technique by applying controlled conditions in the diffusion of the drug out of the nanoparticle matrix. The data are useful in predicting the release kinetics, which determine the therapeutic effect. The kinetic models (most commonly Higuchi or Korsmeyer-Peppas are commonly used to analyze release profiles [26]

5.7. stability testing

Parameters Measured: Size variation of the particles, zeta potential variation, retention of the drug content. The stability tests are also conducted under conditioned conditions (e.g. ICH guidelines) to determine the change in physical and chemical properties with time. This assists in making sure that there are no problems with shelf-life or performance of formulations [27]

6. Mechanisms of Solubility Enhancement by NLCs

6.1. Nanoscale Particle Size and Increased Surface Area

The size range of NLCs is usually 50300 nm. The particular area of surface is drastically augmented at this scale which boosts interaction amid the nanoparticles and the aqueous dissolution medium. Principle of dissolution kinetics states that smaller particles dissolve faster because they have less diffusion layer thickness and high surface energy. This leads to greater apparent solubility and dissolution rate in drugs in comparison to rough drugs.

6.2. Lipid Matrix Solubilization of Hydrophobic Drugs

Insoluble drugs that are poor in water have strong affinity to lipophilic surroundings. Drugs dissolved in the lipid matrix made of solid and liquid lipids are found in NLCs. This lipid stage serves as a solubilizing reservoir, in which the drug is kept in a dissolved or molecularly dispersed form and not as crystalline particles.

On contact with the biological fluids, the drug molecules gradually partition off the lipid phase and into the aqueous phase, which effectively presents the drug in a pre-solubilized form, and elevates the apparent solubility of the drug.

6.3. Reduction in Drug Crystallinity

Introduction of the liquid lipids into the solid lipid structure interferes with the standard organization of lipid molecules and produces defects of structures. This disorderly surrounding does not allow the drug to recrystallize into a highly orderly lattice. The drugs that are in amorphous or partially disordered forms have a lower lattice energy and need less energy to dissolve, which enhances the solubility and rate of dissolution.

6.4. Surfactant-Induced Wetting and Micellar Assistance

The surface of the nanoparticles is adsorbed by surfactants present in NLC formulations and increases the wettability of lipid particles. Enhanced wetting also enhances quick penetration of water into the nanoparticle surface and facilitation of diffusion of drugs into the surrounding medium. Also, surfactants can be present in the aqueous phase as micellar structures, further solubilizing released drug molecules and preventing precipitation and retaining supersaturation.

6.5. Surfactant-Induced Wetting and Micellar Assistance

NLCs are capable of holding large amounts of drugs at greater equilibrium solubility. Nucleation and crystallization in the solution is slowed by the slow diffusion of the drug molecules out of the lipid matrix and stabilization of the molecules by surfactants. This prolonged supersaturation has a major effect of increasing drug absorption in vivo and increases bioavailability [28]

7. Advantage of Nanostructured Lipid Carriers Over Solid Lipid Nanoparticles.

Despite the numerous researches that suggest SLNs as efficient lipid-soluble vectors of poorly water-soluble drugs based on facilitating bioavailability and preserving labile drugs, they also pose a number of challenges that have led to the evolution and utilization of NLCs

7.1. Enhanced Drug Loading Capacity

SLNs have a low drug loading capacity especially in cases where the drug molecules are highly lipophilic or large. The highly ordered crystalline structure can exclude drug molecules during the cooling and recrystallization of the solid lipid matrix resulting in low payloads. Conversely, NLCs, owing to the existence of liquid lipid, are a less perfect matrix, which includes more space and less firmly packed lipid chains. This flexibility of structure gives extra space to accommodate drugs and hence the drug loading capacities of such are much higher than SLNs.

7.2. Reduced Drug Expulsion and Enhanced Stability

Polymorphic transitions of the crystalline nature of SLNs can take place during the storage and result in crushed drug molecules being forced out of the matrix (drug expulsion). Due to less ordered internal structure with mixed lipid states, NLCs are less crystalline and have reduced polymorphic transitions, which reduces expulsion of the drug during storage and enhances long-term stability.

7.3. Improved Controlled Release Behaviour

Drug release profiles can be tailored by the disordered and heterogeneous lipid matrix in NLCs and give longer and predictable release than SLNs. Variations in lipid domain environments (solid liquid) cause the diffusion of the incorporated drug to be affected and form a more controlled way of controlling the kinetics of therapeutic release [29,30]

7.4. Better Physical Performance & Formulation Flexibility

The liquid lipid content of NLCs assists in attaining smaller particle sizes, lesser gelation as well as enhanced physical stability in aqueous dispersion because of steric stabilization and less lattice packing. This also allows easier manufacturing of scale-up and sometimes better performance in the biological system

Table 1: Correlation of SLNS and NLCS.

Feature	SLNs	NLCs
Lipid Matrix	Pure solid lipid (highly crystalline)	Solid + liquid lipids (less ordered matrix)
Drug Loading	Moderate/limited	Higher (due to structural imperfections)
Drug Expulsion	Higher risk	Lower risk during storage
Stability	Good but can change with polymorphism	Enhanced due to disordered matrix
Controlled Release	Possible	Often improved and tunable
Structural Perfection	High	Intentionally imperfect

8. Applications of Nanoparticles of Solid Lipid Nanoparticles (SLNS) and Nanostructured Lipid Carriers (NLCS).

The lipid-based Nanotubes, Solid Lipid Nanoparticle (SLNs) and Nanostructured Lipid Carrier (NLCs) have been extensively researched as delivery systems because they have immense potential over conventional delivery systems. Both carriers consist of physiological lipids, which makes them biocompatible and bio degradable with lower toxicity than the polymeric nanoparticles or standard

emulsions. Their properties have allowed them to be used in a wide variety of therapeutic and cosmetic uses.

8.1. Oral drug delivery systems

Among the most studied uses of SLNs and NLCs is the use of improving the oral delivery of highly insoluble drugs. Limitations in the aqueous solubility and intestinal absorption are significant in the process of attaining therapeutic plasma concentrations of most active pharmaceutical products. Lipid nanoparticles enhance oral absorption, which is due to the enhancement of apparent solubility, intestinal lymphatic delivery and gastric degradation protection. SLNs and NLCs were demonstrated to enhance bioavailability of hydrophobic drugs delivered orally because of enhanced dissolution, gastrointestinal-protection and intestinal barrier-permeation[31,32]

8.2. Topical and dermal delivery

Topical and dermal formulations have made use of lipid nanocarriers because of their capacity to enhance penetration in the stratum corneum, skin hydration, and controlled delivery once the formulation is applied. The lipid matrix assists in creating the occlusive film on the skin that decreases the transepidermal water loss and increases the drug permeation. Both SLNs and NLCs have been applied in cosmetics and dermatotherapeutics to deliver anti-inflammatory agents, antioxidants and other skin-acting compounds with better efficacy and less irritation than traditional creams or gels can do [33]

8.3. Ocular drug delivery

There are physiological barriers to ocular drug delivery that are difficult to overcome because of rapid tear clearance and various physiological factors that reduce drug accessibility into intraocular tissue. SLNs and NLCs have been considered, which can be used as a carrier that can increase bioavailability of drugs in the ocular tissues by increasing corneal contact time, and controlled release. Their lipid structure is biocompatible, which reduces irritation at the same time as the drug residence on the surface of the eye is enhanced. Anti-inflammatory, antifungal and glaucoma drugs have been tested to be delivered by these systems in order to improve the therapeutic results [34]

8.4. Targeted and Controlled Drug Delivery

SLNs and NLCs have found use in targeted drug delivery especially in cancer therapy and in central nervous system (CNS) targeting. Their small nanoscale size allows them to be targeted passively by the enhanced permeability and retention (EPR) effect on tumor tissues and owing to surface modification, they can be targeted actively to different cell types. NLCs are especially helpful in the delivery of chemotherapeutic agents where the therapeutic index of the drug is increased because of their increased loading and minimized leakage. Newer research also examines the use of lipid carriers in the targeted delivery across the blood-brain barrier [35]

8.5. Parenteral and pulmonary delivery.

SLNs and NLCs have been explored as a method of delivering parenterally to obtain prolonged release and enhance drug pharmacokinetics. They are applicable to the intravenous and intramuscular administration of different drugs based on their capacity to entrap drugs with varying physicochemical properties. In addition, another emerging field is inhalation delivery to pulmonary ailments whereby the lipid nanoparticle aerosol has been engineered to accumulate in the lungs to provide localized treatment [36]

8.6. Cosmetic and Personal Care Products

In addition to pharmaceuticals, SLNs and NLCs have also become popular in cosmetic and personal care preparations. Their capacity to entrap lipophilic active ingredients such as vitamins, sunscreens and antioxidants increases stability, targeted release, and skin penetration and does not alter safety profiles. Their application as anti-aging creams, sunscreen formulations and moisturizers reflects the efficiency of lipid nanocarriers in non-drug applications [37]

9. Case Studies Demonstrating the Potential of SLNs and NLCs for Poorly Water-Soluble Drugs

9.1. Curcumin

Curcumin is a polyphenolic substance having fully characterized anti-inflammatory, antioxidant, and anticancer effects with highly detrimental effects on clinical translation due to very low aqueous solubility, rapid degradation at physiological pH, and oral bioavailability. Formulations based on lipid nanoparticles have been greatly considered in order to address such limitations. NLC formulations have been shown to increase oral bioavailability many-fold over curcumin suspensions in in vivo studies which report both a long systemic circulation time and an increase in tissue distribution. The net effect of these enhancements is an increase in the therapeutic efficacy of lipid nanocarriers in inflammation and tumor models, which reinforces the appropriateness of using lipid nanocarriers in the delivery of phytochemicals [38]

9.2. Quercetin

Quercetin is an antioxidant, anti-cancer and cardioprotective flavonoid with extensive research on its practical applications, but its high insolubility and high first-pass metabolism limit its usefulness. Its dissolution behavior and physicochemical stability have been found to be significantly enhanced upon incorporation into SLNs and NLCs. The lipid matrix improves wetting of the quercetin and keeps it in a molecularly dispersed form as well as the size of the nanoscale how the particle size increases the effective surface area of absorption. Quercetin-loaded NLCs are associated with increases in intestinal permeability and longer half-life, which is better than conventional formulations. Also, oxidative degradation is minimized by encapsulation, which further defines lipid nanoparticles as an ideal choice in long-term storage of quercetin-based products [39]

9.3. Paclitaxel

Paclitaxel is an extremely powerful anti-cancer agent with very low solubility in water and this requires solubilizing agents that are toxic in treatment that are used in commercial preparations. Alternatives proposed have been lipid nanoparticle systems which are safer and more efficient. Paclitaxel-loaded SLN and NLC have a high solubilization of the drug to the lipid core and do not require tough solvents. Besides increasing apparent solubility, the systems also offer controlled release as well as increased tumour accumulation due to augmented permeability and retention effects. Among others, NLCs exhibit increased loading of drugs and less expulsion of drugs than SLNs. Preclinical research shows that paclitaxel-loaded NLCs cause increased cytotoxicity in tumour cells and reduced systemic toxicity indicating that they are likely to increase the safety and efficacy of the treatment [40]

9.4. Itraconazole

Itraconazole is a broad-spectrum antifungal agent that has extremely low aqueous solubility and has an unpredictable oral absorption with variable bioavailability. To overcome these challenges, delivery systems that are based on lipid nanoparticles have been designed. The formulations of SLN and NLC are found to increase the rate of dissolution by a large amount by dispersing itraconazole in a lipid environment and decrease drug crystallinity. The NLC systems also promote the high level of encapsulation and stop the precipitation during storage because of imperfect lipid structure. According to pharmacokinetic studies, which are reported in open-access sources, the maximum plasma concentration and area under the curve of itraconazole were significantly higher-in itraconazole-loaded NLCs than in conventional capsules. These advances enable to facilitate more predictable responses to therapy and less variability of doses [41]

9.5. Levosulpiride

Levosulpiride is a dopamine D 2 receptor blocker applied in gastrointestinal diseases and depression, which is less soluble in water and has low permeability, which limits the oral bioavailability. It has been formulated into SLNs and NLCs to improve its biopharmaceutical performance. The encapsulation of lipid nanoparticles enhances the dissolution of the drug and prevents degradation of the drug molecule in the gastrointestinal tract. Formulations of NLC have been shown to be more drug loaded, release over an extended period and intestinal absorption is increased over SLNs. It is shown that animal experiments demonstrate better systemic exposure and longer pharmacological action, which means that lipid nanocarriers will effectively overcome the solubility-limited absorption of levosulpiride.[42]

10. DIFFICULTIES AND DRAWBACKS OF SOLID LIPID NANOPARTICLES AND NANOSTRUCTURED LIPID CARRIERS.

10.1. Limited Drug Loading Capacity

The limited drug loading capacity is one of the biggest formulation issues that are linked to the use of solid lipid nanoparticles (SLNs). This is because the crystalline configuration of solids lipids is very organized and leaves minimal space where the drug molecules can be carried. The molecules of drug can be removed out of the lipid matrix during solidification leading to low encapsulation efficiency and non-uniform distribution of drugs. Even though liquid lipids are used to form structural defects in nanostructured lipid carriers (NLCs) to improve drug accommodation, drug loading is still limited by physicochemical properties of the drug and lipid constituents and may not be sufficient in high dosage therapeutics [43]

10.2. Drug Expulsion During Storage

Drug expulsion during storage is especially a problem with SLNs because they are susceptible to lipid polymorphism between metastable and thermodynamically stable crystalline forms. These changes may result in the reorganization of the lipid matrix and the displacement of the encapsulated drug to the surface of the particle or to the surrounding medium, resulting in the reduction of the drug content and the change in the release behaviors. NLCs are better able to absorb this phenomenon though full prevention of any drug leakage during extended storage is hard to achieve [44]

10.3. Physical Instability of Nanoparticle Dispersions

SLNs as well as NLCs are prone to physical instability, such as aggregation, particle growth, gelation, and phase separation. This can be caused by a lack of steric or electrostatic stabilization, variations in temperature or long-term storage. Modifications in the size and surface characteristics are able to play a significant role in drug release kinetics, bioavailability, and reproducibility of therapeutic performance [45]

10.4. Manufacturing and Scale-Up Challenges

Formulation and processing parameters, including the temperature, homogenization pressure, and cooling rate, need to be tightly regulated in order to achieve lipid nanoparticles production. The energies used in most of the preparation techniques such as in high-pressure homogenization and ultrasonication are energy-consuming and sensitive to small deviations, and often result in batch-to-batch variability. These make it more difficult to manufacture in large scale and make production more expensive, making it less commercially viable [46]

10.5. Drug–Excipient Compatibility Issues

The solubility and retention of the drug in the lipid matrix is important to the successful formulation of SLNs and NLCs. Other drugs with poor solubility in water have low affinity with lipid excipients or they are chemically degraded by high temperatures during the formulation. Hydrophilic drugs are

even more problematic because they have low partitioning into lipid phases, and sometimes complicated formulation strategies are required.

10.6. Surfactant-Related Toxicity Concerns

Despite lipids being considered safe and biocompatible, the surfactants involved in the stabilization of SLN and NLC dispersions can cause cellular toxicity, membrane irritation or hemolysis especially when used in high doses or when the systems are administered systemically. Thus, the choice and optimization of surfactants should be done with care in order to be safe and acceptable to the regulatory authorities.

10.7. Biological and In Vivo Performance Variability

After its administration, SLNs and NLCs can be exposed to the biological constituents, i.e. plasma proteins and enzymes, and develop a protein corona or be enzymatically broken down into lipid components. These interactions may change the biodistribution, clearance and drug release behaviour leading to unpredictable in vivo behaviour. The physiological variation of patients also helps to attain poor and inconsistent therapy results [47]

11. FUTURE PERSPECTIVES

11.1. Advanced Lipid Matrix Engineering

The rational design of lipid matrices is likely to be the subject of future studies in order to enhance drug loading capacity and long term stability further. Innovations in lipid blends, such as structured lipids, functionalized lipids, etc., could enable the more effective and efficient accommodation of drug molecules and reduce crystallinity-driven expulsion of drugs. In the case of NLCs, the ratio and molecular compatibility between solid and liquid lipids will be an important factor in determining reproducible performance and improved shelf stability.

11.2. Surface Functionalization and Targeted Delivery

The surface modification with the help of ligands, antibodies, peptides, or polysaccharides is likely to be a significant part of the future development. Functionalized SLNs and NLCs may maximize cellular uptake, tissue specificity and cross biological barriers including the blood brain barrier and the intestinal epithelium. Further advancement of receptor-mediated targeting systems can make lipid nanoparticles precision drug delivery platforms in more complex diseases.

11.3. Expansion into Biologics and Gene Delivery

Even though currently applying it to small lipophilic drugs, current studies indicate the potential continues to increase in the application of SLNs and NLCs in the delivery of peptides, proteins, and nucleic acids. Further development of formulation strategies and surface chemistry would help to counterbalance current limitations in regards to instability and poor encapsulation efficiency of biomacromolecules and thus increase the clinical application of lipid nanoparticles.

11.4. Improvement in Manufacturing and Scale-Up Technologies

Further work on scaling, cost-efficient, and reproducible manufacturing methods will be prioritized in efforts to help make the clinical translation. The conventional batch processes will be substituted by continuous production systems, microfluidic platforms and low energy emulsification processes. Such innovations may help minimize variation, enhance quality management and facilitate mass trade production.

11.5. Regulatory Harmonization and Standardization

It will be essential to develop standardized procedures to characterize, test stability, and safety to be accepted by the regulation. An international development of specific harmonized guidelines unique to lipid nanoparticle systems can enhance the rapid approval rates and lead to investments in industries. High levels of availability of clinical data will also enhance regulatory confidence of SLN- and NLC-based therapeutics.

11.6. Personalized and Precision Medicine Applications

As pharmacogenomics and disease profiling advances, SLNs and NLCs can be designed according to the needs of the individual patient. Tailored preparations that are variable in drug loading and release characteristics would maximize the therapeutic effects and reduce the side effects, especially in the case of chronic and multifactorial diseases [48]

CONCLUSION

Nanostructured lipid carriers and solid lipid nanoparticles are a good example of lipid-based nanocarrier systems to overcome poor solubility and instability of hydrophobic drugs. Although SLNs offer better drug protection and controlled release, their usability is hampered by low drug loading, and the drugs may leak out of the systems during storage. As an improved form of these, NLCs have an improved drug incorporation, physical stability and release behavior because they have a structurally imperfect lipid matrix. These systems collectively have a great potential to enhancing oral and non-oral drugs delivery performance. This will require further optimization of formulation design, mass-producing technologies, and regulatory standardization in order to enable their successful clinical translation and further pharmaceutical use.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Viegas C, Patrício AB, Prata JM, Nadhman A, Chintamaneni PK, Fonte P. Solid Lipid Nanoparticles vs. Nanostructured Lipid Carriers: A Comparative Review. *Pharmaceutics*. 2023;15(6):1593. doi:10.3390/pharmaceutics15061593.
2. Lin C-H, Chen C-H, Lin Z-C, Fang J-Y. Recent advances in oral delivery of drugs and bioactive natural products using solid lipid nanoparticles as the carriers. *J Food Drug Anal*. 2017;25(2):219–234. doi: 10.1016/j.jfda.2017.02.001.
3. "A Review of Formulation Strategies for Cyclodextrin-Enhanced SLNs and NLCs." *Int J Mol Sci*. 2025;26(13):6509.
4. "Optimized Nanoparticles for Enhanced Oral Bioavailability of a Poorly Soluble Drug: SLNs vs. NLCs." *Bentham Science*. 2025.
5. Patil D, Pattewar S, Palival S, Patil G, Sharma S. Nanostructured lipid carriers: A platform to enhance oral bioavailability of lipophilic drugs. *J Drug Deliv Ther*. 2024;9(3-S):2750.
6. Gangavarapu A, Tapia-Lopez L, Sarkar B, et al. Lipid nanoparticles for enhancing oral bioavailability. *Nanoscale*. 2024; 16:18319–18338. doi:10.1039/D4NR01487A.
7. "Nanostructured Lipid Carriers (NLCs) as a Novel Nanotechnological Strategy for Improving Oral Drug Bioavailability." House of Wisdom J. 2025.
8. "Nanostructured Lipid Carriers: A Next-Generation Lipid-Based Delivery System." J Popul Therm Clin Pharmacol. 2024.
9. "Nanostructured Lipid Carriers for Delivery of Chemotherapeutics: A Review." *PubMed*. 2020.
10. Jacob S, Rao R, Gorain B, Boddu SHS, Nair AB. SLNs and NLCs for Anticancer Phytochemical Delivery. Pharmaceutics. 2025;17(8): 1079.doi:10.3390/pharmaceutics 17081079
11. Madane RG, et al. Curcumin-loaded nanostructured lipid carriers as a drug delivery system. *PubMed*. 2016; (NLC with enhanced brain delivery).
12. Kamel AE. Curcumin-loaded NLCs: Enhanced release and cytotoxicity in breast cancer cells. *PubMed*. 2019.
13. Selvaraj K, et al. Curcumin-Loaded NLC-PG with improved solubility and release kinetics. *PubMed*. 2019.
14. Rapalli VK, et al. Curcumin-loaded NLCs: Improved skin penetration and efficacy. *PubMed*. 2020.
15. Lin C-H, et al. Review article on SLNs for oral administration and bioavailability enhancement. *PMC*. 2017.
16. Patil D, Pattewar S, Palival S, et al. NLCs enhance drug loading and bioavailability. *J Drug Deliv Ther*. 2024;9(3-S):2750.
17. "Solid Lipid Nanoparticles: Preparation Methods and Therapeutic Potential in Oral Cancer." *Bentham Science*. 2025.
18. Das S, Ng WK, Tan RBH. Are nanostructured lipid carriers better than SLNs? Evidence from clotrimazole study. *Eur J Pharm Sci*. 2012; 47:139–145.
19. Dudhipala N, Janga KY, Gorre T. Comparative SLN vs NLC evaluation: nisoldipine study. *Artif. Cells Nanomed Biotechnol*. 2018; 46:616–625.
20. Belloqui A, Solinís MA, Rodríguez-Gascón A, Almeida AJ, Praet V. Nanostructured lipid carriers: Promising drug delivery systems. *Nanomed Nanotechnol Biol Med*. 2016; 12:143–161.
21. Naseri N, Valizadeh H, Zakeri-Milani P. SLNs/NLCs: Structure, Preparation and Application. *Adv Pharm Bull*. 2015; 5:305–313.
22. Üner M, Yener G. Importance of SLNs in various administration routes. *Int J Nanomed*. 2007; 2:289–300.
23. Müller RH, Shegokar R, M Keck C. 20 years of lipid nanoparticles: Present state & industrial applications. *Curr Drug Discov Technol*. 2011; 8:207–227.
24. Doktorovova S, Kovacevic AB, Garcia ML, Souto EB. Preclinical safety of SLNs and NLCs: in vitro & in vivo. *Eur J Pharm Biopharm*. 2016; 108:235–252.
25. Doktorovova S, Souto EB, Silva AM. Nanotoxicology applied to SLNs/NLCs—A systematic review of in vitro data. *Eur J Pharm Biopharm*. 2014; 87:1–18.
26. Scholer N, Hahn H, Müller RH, Liesenfeld O. Influence of lipid matrix & size on macrophage response. *Int J Pharm*. 2002; 231:167–176.
27. Dudhipala N, Janga KY, Gorre T. NLC vs SLN: Permeation & pharmacokinetic evaluation. *Artif Cells Nanomed Biotechnol*. 2018; 46:616–625.
28. Chen C-C, Tsai T-H, Huang Z-R, Fang J-Y. Effects of lipophilic emulsifiers on oral administration from NLCs: Pharmacol examples. *Eur J Pharm Biopharm*. 2010; 74:474–482.
29. Zhuang C-Y, Li N, Wang M, et al. Vinpocetine loaded NLCs for improved bioavailability. *Int J Pharm*. 2010; 394:179–185.
30. Gaba B, Fazil M, Ali A, et al. NLCs as a bioavailability enhancement tool. *Drug Deliv*. 2015; 22:691–700.
31. Mehnert W, Mader K. SLN production, characterization & applications. *Adv Drug Deliv Rev*. 2001; 47:165–196.
32. Müller RH, Mader K, Gohla S. SLN for controlled drug delivery—State of the art. *Eur J Pharm Biopharm*. 2000;50(1):161–177.
33. Pouton CW. Formulation of poorly water-soluble drugs for oral administration. *Eur J Pharm Sci*. 2006;29(3–4):278–287.
34. Radtke M, Souto EB, Müller RH. NLC: A novel generation of solid lipid carriers. *Pharm Technol Eur*. 2005;17(4):45–50.
35. Schäfer-Korting M, Korting HC, Roberts MS. Topical drug delivery: Lipid nanoparticles. *Eur J Pharm Biopharm*. 2007; 66:8–18.
36. Üstündağ Okur N, et al. NLCs for ocular delivery. *Int J Pharm*. 2014; 473:73–82.
37. Culmone C, et al. Ocular NLCs improve bioavailability. *J Ocul Pharmacol Ther*. 2022.
38. Haider M, Abdin SM, Kamal L, Orive G. NLCs for chemotherapeutics. *Pharmaceutics*. 2020; 12:288.
39. Anwar H, et al. Curcumin-NLC: Improved pharmacokinetics & anticancer activity. *J Pharm Pharmacol*. 2017.
40. Quercetin loaded lipid nanocarrier comparative studies. *LWT*. 2014; 59:115–121.

41. Rachmawati P, et al. SLN vs NLC topical gels: Permeation & retention. *SSRN*. 2025.

42. Cui J, et al. Agomelatine-loaded NLCs for antidepressant delivery. *ResearchGate*. 2025.

43. "Beyond liposomes: Recent advances on lipid based nanostructures." *PubMed*. 2017.

44. Pardeike J, Hommoss A, Müller RH. Lipid nanoparticles in cosmetic & dermatological preparations. *Int J Pharm*. 2009;366:170–184.

45. Han F, Li S, Yin R, et al. Surfactant effects on NLC formation. *Colloids Surf A Physicochem Eng Asp*. 2008; 315:210–216.

46. Almeida H, et al. Thermoresponsive NLC eyedrops for ibuprofen. *Pharm Dev Technol*. 2017; 22:336–349.

47. Santos RL, et al. NLCs with essential oils for improved stability. *China J Chin Mater Med*. 2020; 45:523–530.

48. Magalhães J, et al. Rifapentine-loaded lipid nanoparticles optimization. *Pharmaceutics*. 2020; 12:75.