

Nanostructured Lipid Carriers As Oral Delivery for Poorly Water-Soluble Drugs

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Abstract: The colloidal system based on lipids has attracted attention during the last two decades as a delivery method of poorly soluble drugs in water. For poorly soluble pharmaceuticals, the development of suitable novel formulations can achieve sufficient bioavailability. In recent years, formulations composed of lipids as excipients, called lipid-based drug delivery systems, have gained significant importance because lipids offer the potential to enhance the bioavailability of poorly water-soluble drug candidates. It has been shown that lipids provide an appealing excipient in medicinal formulations. The biocompatibility & safety of lipids have been well established as they are distributed throughout the body & play a vital role in the functionality & architecture of all living cells. Nanostructured lipid carriers composed of a biocompatible blend of liquid and solid lipids are a viable option. When administered orally, NLC improves the solubility and dissolution of poorly water-soluble medications in the gastrointestinal tract. To enhance therapeutic benefits, the development of nanocarriers with diverse shapes and properties has shown significant promise as a drug-delivery mechanism. Various methods for fabricating NLCs have been reported in the literature. The present paper focuses on the lipids used and the different methods for fabricating NLCs for the delivery of a poorly water-soluble drug.

Keywords: Nanostructured lipid carriers, nanotechnology.

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1. Introduction

Today's technology has seen a major increase in research and its use in the field of medicine. Nanomedicine is one use of nanotechnology that enables the creation of therapeutic nanoparticle carriers [1-3]. Over the past few years, lipid-based drug delivery systems have been developed to address the issues of poor bioavailability of certain medications and their limited distribution to specific areas to achieve the pharmacological effect [4,5]. To deliver the drug to the desired site of action, with low toxicity and high efficacy, nanoparticles were used [6-9]. The oral route is preferred for administering medications to provide both therapeutic and preventive effects against various diseases, especially for chronic therapies [10]. The advantages of taking medications orally include comfort, self-administration, self-sufficiency, low cost, and safety. The Food and Drug Administration approved 46% of new drugs in 2014 intended for oral administration [11,12]. Oral absorption requires the presence of drug

molecules dissolved in gastrointestinal fluids, but the efficient oral delivery of the drug exhibits inconsistent gastrointestinal absorption [13,14]. In consequence, the increased lipophilicity and the corresponding decrease in solubility in physiological media are the major obstacles that reduce the bioavailability of drugs [15,16]. Even if a candidate has a strong effect on the pharmacological target in vitro, drugs with poor water solubility exhibit slow absorption, resulting in inadequate and variable bioavailability and rendering the treatment ineffective. [17] It is widely accepted that 40% of new drug candidates & 90% of molecules in the drug discovery pipeline are poorly water-soluble. Often, such drug candidates show great potential for improved therapeutic outcomes; however, they pose challenges for the formulation scientist. Increased lipophilicity & a corresponding decrease in solubility in physiological media are major obstacles that reduce the overall bioavailability of many drug candidates [18,19]. In recent years, formulations composed of lipids as excipients, called lipid-based drug delivery systems, have gained significant importance because lipids offer the potential to enhance the bioavailability of lipophilic drug candidates [20,21]. The lipids have been proven to be attractive excipients for the formulation of pharmaceuticals. The biocompatibility & safety of lipids has been well established as they are distributed throughout the body & play a vital role in the functionality & architecture of all living cells [22]. Manufacturing lipid particles with a solid lipid core is simple and scalable, and they have lower toxicity due to their natural lipid components and the avoidance of chemical solvents. They also have higher cellular absorption than other more traditional colloidal carrier systems [23].

At the beginning of the 2000s, researchers attempted to develop a nanoscale lipid carrier system. They have been proposed as among the most promising systems for the oral delivery of poorly water-soluble drugs [24,25]. Recently, more studies on NLC systems have been reported. In this study, the state of the art of NLCs is discussed, with a focus on oral delivery of poorly soluble medications. The methods of preparation, the mechanism of absorption of NLCs through the GIT, the applications of NLCs for oral delivery of various categories of drug candidates, and the molecular-level absorption factors for improving bioavailability are highlighted in this article [26].

2. Different NLC Types

Three different morphological model types have been presented, depending on where the integrated drug moieties are located in NLC (Figure 1).

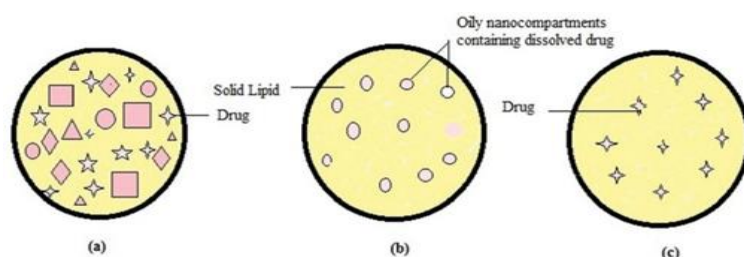


Figure 1. Types of the nanostructured lipid carrier.

An imperfect sort of crystal, the extremely disorganized matrix of the NLC has numerous holes and spaces that can hold additional drug molecules in amorphous clusters. These flaws in the crystal arrangement are created by combining sufficient amounts of liquid lipids with solid lipids (oils). The matrix of NLC cannot form a highly ordered structure because of the variety of mono-, di-, and triacylglycerols and the different chain lengths of fatty

acids. Drug payload capacity is increased by spatially mixing various lipids, although this model has the lowest entrapment effectiveness [27].

2.1. Multiple types.

Oil, lipid, and water-type NLC are multiple kinds. Liquid lipids have a higher solubility for lipophilic medicines than solid lipids do. Low quantities of oil moieties effectively spread in the lipid matrix. The solid matrix surrounds the tiny oil nanocompartments produced by phase separation driven by oil injected in excess of its solubility. Type II models provide benefits such as reduced drug leakage, regulated drug release, and high drug entrapment efficiency. [28].

2.2. Amorphous mode.

Lipids are carefully mixed to produce amorphous NLC, thereby minimizing drug leakage during crystallization. Certain lipids, such as dibutyl adipate, isopropyl myristate, hydroxyl octacosanyl, and hydroxyl stearate, form solid but non-crystalline particles. The lipid matrix is in an amorphous and homogenous state. NLCs are typically composed of organic solvents, lipids (both liquid and solid), surfactants, and other substances, such as surface modifiers and counter-ions. [29].

3. Absorption mechanism through the GIT

Various techniques have been proposed for the disposal of NLCs within the body, including selective uptake via lacteals or Peyer's patches. Drug-loaded NLCs undergo lipid digestion stepwise as they pass through the digestive tract.[30] Triglycerides in the lipid nanoparticles are mostly broken down into monoglycerides and free fatty acids (long-chain and short-chain) by the activity of pancreatic enzymes in the duodenum. Released bioactives can enter lacteals via a chylomicron-mediated pathway or be actively or passively transported by enterocytes.[31] In the latter pathway, amphipathic bile salt molecules in the intestinal chyme encircle long-chain fatty acids, monoglycerides, and bioactive substances, forming "micelles" that can withstand the brush border of the intestinal absorptive cells.[32]

As monoglycerides, fatty acids, and bioactives are released from enterocytes, micelles are left behind, further rearranging triglycerides within intestinal cells. These lipid constituents combine with phospholipids and cholesterol to form chylomicrons, which ultimately undergo exocytosis and contain bioactives. Since chylomicrons are too large to enter blood capillaries (about 80 nm in diameter), they must enter through lacteals instead, thereby preventing first-pass metabolism of the bioactive they carry. In other words, a size below 300 nm is preferable for their passage across the colon and should be adequately managed. NLC particle size also plays a crucial role in intestinal transport [33,34].

During GIT transit, NLCs can either be collected by M cells of Peyer's patches, which deliver them to the lymphatic system, or they can be carried to the portal circulation through a paracellular pathway, thereby evading metabolism by enterocyte enzymes. 24 A thorough examination by Hu *et al.* on conventional lipid nanoparticles (without any surface modification) to determine the *in vivo* fate and precise absorption mechanism did not find any sign of intact nanoparticle absorption through the intestinal wall following oral administration.[35]. It has been shown that altering lipid nanoparticles, for example, adding

biotin to their surface or changing their charge, encourages cellular uptake of the particles into intestinal cells, bypassing the mucosal barrier that would normally prevent it.

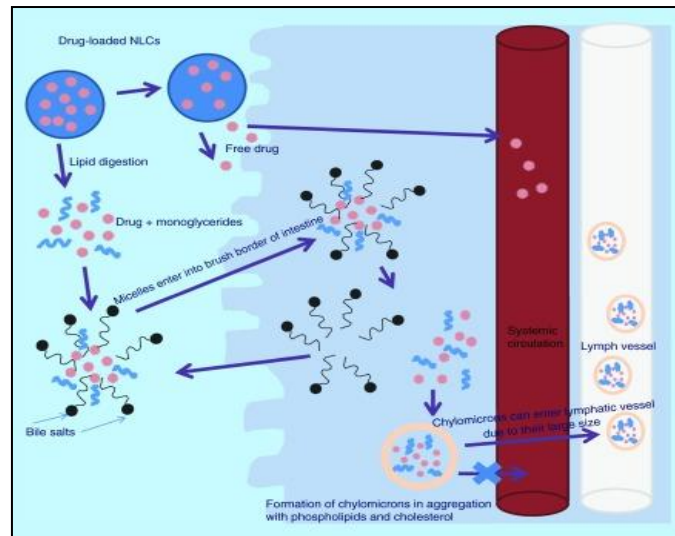


Figure 2. Mechanism of nanostructured lipid carrier's disposition

In addition, research on lipid nanoparticles coated with cell-penetrating peptides (CPPs) is based on the idea that CPPs will facilitate the passage of intact nanoparticles across the gastrointestinal tract and into the systemic circulation, where the reticuloendothelial system plays a role. In-depth future investigations are required to determine the effects of composition, physicochemical characteristics, and surface modification on the fate of lipid nanoparticles, as in vivo studies on modified NLCs are insufficient [36].

Numerous mechanisms, including direct uptake through the digestive tract (via the lymphatic route), induction of pancreatic and biliary secretion, promotion of micelle formation, and reduction of metabolic degradation by gut wall enzymes, have been linked to improved intestinal absorption of NLC (CYP3A4). Additionally, because of the NLC formulations' incredibly small particle size, their surface area is increased. [37] Due to its small size, the gut, particularly its lymphoid portion, can effectively absorb substances, bypassing first-pass metabolism. Their great dispersibility is another element that makes NLC easier to absorb in the intestinal environment. In addition, the NLC can adhere to the gut wall, prolonging its residence time and, in turn, its absorption. Another significant explanation for the increased drug bioavailability is that excipients/surfactants, such as poloxamer and gelucire, can be incorporated into NLCs to reduce P-gp-mediated drug efflux. This approach has been used by numerous researchers to produce oral lipid nanoparticles of drugs that are P-gp substrates [38].

4. Methods of Preparation of NLCs

4.1. High-pressure homogenization (HPH).

A highly effective method for producing NLCs, lipid drug delivery systems, solid lipid nanoparticles, and parenteral emulsions has been HPH. The high-pressure homogenization process can be carried out in one of two ways: Cold and hot homogenization is the first two. Strong pressure (100–2000 pressures) and high shear stress are used to forcefully press the lipid, which causes disruption of particles down to the sub-micrometer or nanometer range. The lipid contents typically vary from 5 to 10%. High-pressure homogenization exhibits no scaling-up issues in comparison to other preparation methods. It is possible to homogenize

substances at high temperatures (hot homogenization) or low temperatures (cold homogenization). Hot homogenization is done at temperatures higher than the materials' melting points. The lipid phase comprises solid and liquid lipids and lipophilic emulsifiers, and aqueous phase comprises hydrophilic emulsifiers and double-distilled water, are prepared separately. [39] The two phases are heated separately to a high temperature before being mixed. The mixture can be homogenized by a high-shear homogenizer and can be further sonicated to obtain small and uniform size distribution. Cold HPH involves mixing the drug with the lipid phase at a temperature slightly higher than the lipid melting point. This is followed by immediate cooling of the mixture using liquid nitrogen or dry ice to allow the rapid recrystallization of the solid lipid particles. Separate preparations are made for the aqueous phase, which consists of double-distilled water and hydrophilic emulsifiers, and the lipid phase, which is made up of solid and liquid lipids and lipophilic emulsifiers. Before being mixed, the two phases are each heated to a high temperature. A high-shear homogenizer can homogenize the mixture, and it can then be further sonicated to produce a tiny and homogeneous size distribution. In cold HPH, the medication is combined with the lipid phase at a temperature just above the lipid melting point, and then the mixture is immediately cooled with liquid nitrogen or dry ice to promote the quick recrystallization of the solid lipid particles.[40]

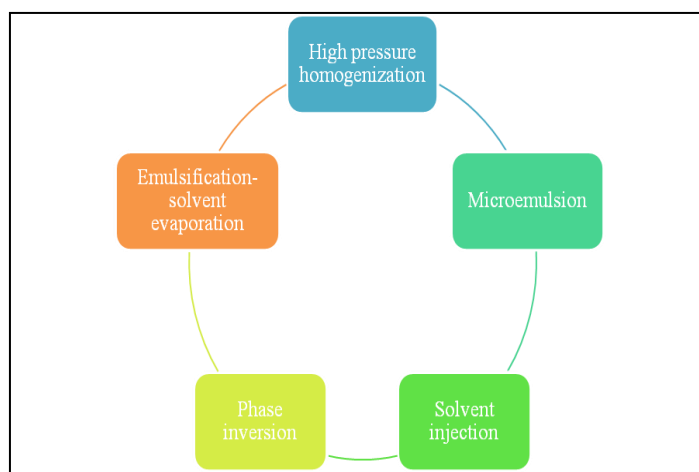


Figure 3. Various methods for the preparation of NLCs.

To create smaller nanostructures, the particles are ground and emulsified in a cold aqueous phase using a high-pressure homogenizer. Large-scale manufacturing, avoiding organic solvents, and enhanced product stability are a few benefits of this process, though it may be difficult to meet the high-pressure and high-temperature requirements. Additionally, insufficient homogeneity could lead to the formation of microparticles rather than a uniform size distribution [41].

4.2. Microemulsions.

In this procedure, melted lipids are combined with an aqueous phase containing a hydrophilic cosurfactant and a surfactant to create an emulsion that can be w/o or o/w, depending on the ratios used. After that, the emulsion is forcefully agitated to reduce the particle size to the micron range. A transparent, thermodynamically stable microemulsion is then formed by its dispersion in a chilled hydrophilic phase for particle size reduction and NLC generation. This process is straightforward, affordable, and repeatable, ideal for thermolabile pharmaceuticals, and doesn't require specialized machinery or energy to produce NLCs.

However, this approach's fundamental drawback is the introduction of large amounts of surfactants [42].

4.3. Solvent injection method.

The solvent injection method involves rapidly dissolving lipids in a water-miscible solvent using an injection needle, then immediately injecting the dissolved lipids into an aqueous solution containing surfactants. This approach has the benefits of easy preparation and does not require specialized machinery, high heat, or shear stress. Its principal drawbacks are the usage of organic solvents and the method's low particle concentration.

4.4. Phase inversion.

This procedure involves gently combining the medication with the lipid, water, and surfactant, then heating the mixture to a temperature above the surfactant's phase-inversion temperature. The emulsion inverts when the surfactant is dehydrated during heating (above the inversion temperature), altering its hydrophilic-lipophilic balance and, as a result, its affinity for each phase. Rapid freezing (using an ice bath, for example) causes the surfactant to revert to its hydrophilic state, which permits the creation of NLCs in the form of tiny particles. This method's minimal energy need and avoidance of organic solvents are advantages. However, NLCs created may be unstable, and occasionally, many temperature cycles are needed.

4.5. Emulsification solvent evaporation.

Vander Off, *et al.* created this technique in 1979 as a polymer emulsification procedure to enable the creation of polymeric particles [43]. This process involves dissolving lipids and medicines in an organic water-impermeable solvent (such as cyclohexane, dichloromethane, toluene, or chloroform), followed by emulsification in an aqueous phase containing the surfactant, all before the solvent is evaporated. The created pre-emulsion goes through sonication. The aqueous NLC dispersions are then produced by cooling the dispersions to room temperature. This method is associated with a quick, simple production procedure. On the other hand, it uses organic solvents, and the resulting suspension requires additional evaporation or ultrafiltration because it is so diluted [44].

5. Applications of NLCs for delivery

Oral administration of NLCs has been one of the most frequently used methods. Most of this research has focused on NLC's potential to enhance the oral bioavailability of medications classified as Biopharmaceutics Classification System II or IV, due to their higher drug-loading capacity. Examples of highly lipophilic medications with increased oral bioavailability when packaged as NLC are shown in Table 1.

Table 1. Different applications of NLCs.

Name of drug	Applications	References
Raloxifene Hydrochloride	This study made use of the potential of nanostructured lipid carriers to increase raloxifene hydrochloride's oral bioavailability. Glycerylmonostearate was used as a solid lipid in the solvent diffusion approach to create RLX-loaded NLCs.	[45]
Atorvastatin	High-speed homogenization and ultrasonication were used to manufacture atorvastatin NLCs, which enhanced the drug's pharmacological and oral bioavailability.	[46]

Name of drug	Applications	References
Methotrexate	The developed formulation by Garg <i>et al.</i> showed a remarkably high amount of methotrexate that penetrated the receptor compartment and greatly increased the amount in various skin layers.	[47]
Pioglitazone	According to Giffy <i>et al.</i> , pioglitazone is one of the most researched antidiabetic medications that may be used to treat Alzheimer's disease. A sustained release of the medicine from the NLC has been demonstrated by the in-vitro drug release investigation. It was found that the formulation considerably increased pioglitazone's nasal permeability ex vivo.	[48]
Aceclofenac	In comparison to the marketed formulation, the modified Aceclofenac NLCs-based gel formulation demonstrated superior texture, rheological profile, and cell uptake efficiency on hyperkeratinocytic cells with increased ex vivo skin permeability efficiency.	[49]
Salvianolic acid B	A prior study was modified by the transferrin receptor monoclonal antibody OX26 to transport Baicalin and Salvianolic acid B to the brain tissue to ameliorate cerebral ischemia-reperfusion injury and heal neuron damage.	[50]

6. Conclusion

NLC are lipid-based nanoparticles with an unstructured solid lipid core that can encapsulate highly lipophilic medicines, preventing drug deterioration and enhancing therapeutic stability. NLCs are beneficial for increasing the bioavailability of poorly soluble medications, and they have recently shown promise for delivering medications for IBD, diabetes, and inflammation. Enhancing drug apparent solubility and dissolution in the GIT, and/or modifying drug permeability and fate across the intestinal barrier, are among the mechanisms involved. The formulation of NLC offers fresh opportunities to develop creative solutions to the problem of oral administration of medicinal molecules.

Author Contributions

Formal analysis, S.M., D.M., N.K., and A.C.; investigation, S.M., D.M., N.K., and A.C.; writing—original draft preparation, S.M., D.M., N.K., and A.C.; formal analysis, P.S.; writing—review and editing, P.S. All authors have read and agreed to the published version of the manuscript.

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Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

The authors report no conflicts of interest.

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