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# A REVIEW ON NANOSTRUCTURED LIPID CARRIERS

**SINGH R[1, 2]*, VERMA V[3], KUMAR A[3] AND DHAMA N[3]**

**1:** Research Scholar, Kharvel Subharti College of Pharmacy, Swami Vivekanand Subharti University Meerut -250005, Uttar Pradesh, India

**2:** Department of Pharmacy, LLRM Medical college, Meerut-250004, Uttar Pradesh, India

**3:** Department of Pharmaceutical Chemistry, Kharvel Subharti College of Pharmacy, Swami Vivekanand Subharti University Meerut -250005, Uttar Pradesh, India

***Corresponding Author: Rahul Singh: E Mail: Singh15180@gmail.com**

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## ABSTRACT

Due to their remarkable physicochemical and subsequent biocompatible properties, NLCs (nanostructured lipid carriers) have continuously sparked the creation of beneficial and safe drug delivery systems. In the past few years, the number of research describing formulations based on NLCs has significantly expanded. They are a binary system with both liquid and solid lipids that aims to build a lipidic core that is less organised. The physicochemical characteristics and efficacy of the finished product are particularly influenced by their ingredients. NLCs can be produced using a variety of methods that are categorised based on the amount of energy they use. Increased employment of NLCs is necessary to get around technical challenges in creating lipid-based nanocarriers and to gain knowledge of the basic principles underlying their transport via diverse routes of administration. This review article aims to provide an overview of the records that clearly show how promising NLCs are for developing novel therapeutic applications in the future.

**Keywords: Liposomes, Nanotechnology, nanoparticles, Nanocarriers**

## INTRODUCTION

Nanotechnology has essentially impacted all technical sectors, including pharmaceutics, over the past 20 years. According to industry estimates, solubility and formulation stability problems account for 40% of the failures of lipophilic drug candidates; nevertheless, these problems have been resolved by a variety of unique and cutting-edge lipophilic drug delivery techniques. Physiological lipids (biocompatible and biodegradable) with low acute and chronic toxicity are typically used to create lipid nanoparticles **[1, 2]**.

Recently, researchers have looked into SLNs made from a combination of solid and liquid lipids (so-called nanostructured lipid carriers, or NLCs), as well as large volumes of lecithins, amphiphilic cyclodextrins, and para-acyl-calix-(4)-arenes. The possibilities for medication delivery using nanocarriers are infinite, and they have recently received attention due to their immense potential. According to the National Nanotechnology Initiative, nanotechnology is the study and application of structures with a size between 1 and 100 nm. Similar to medicine, nanotechnology's overarching goal is to diagnose as precisely and promptly as possible, and to cure as effectively and painlessly as possible. In **Figure 1**, some of the crucial features of nanocarriers are emphasised.

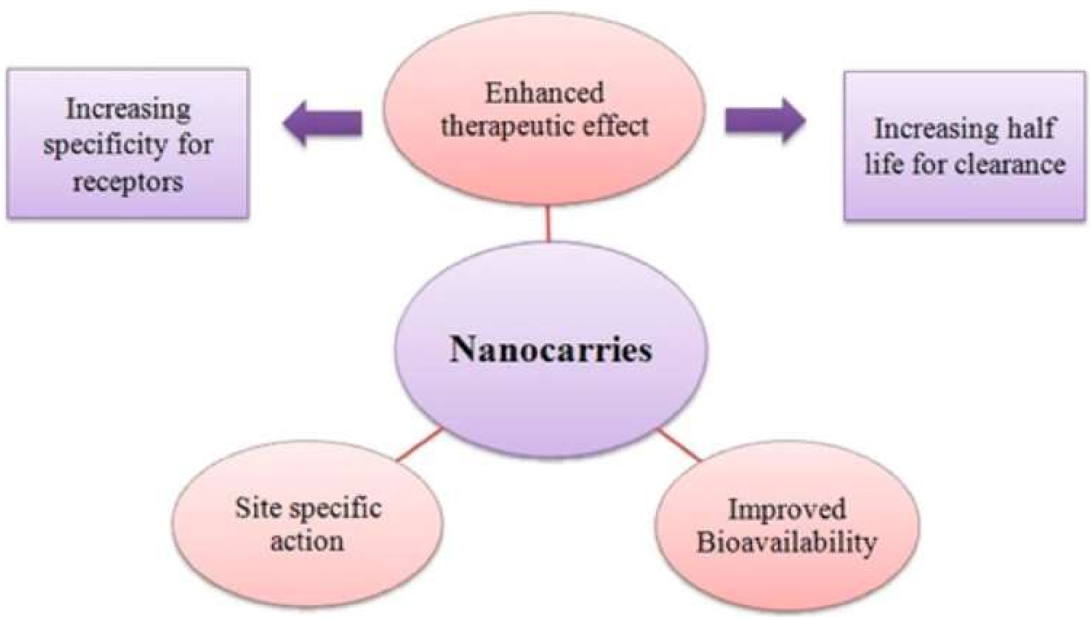


**Figure 1: Key characteristics of nanocarriers**

Invented in 1965, liposomes are classic examples of lipid-based formulations that have undergone much research in recent years. A spherical vesicle having an aqueous interior chamber and a lipid bilayer membrane is referred to as a liposome. The Greek words "lipid," which means fat, and "soma," which means body, are combined to form the name "liposome." In recent decades, they have been studied for dermal, pharmacological, and aesthetic purposes. As a drug delivery system, liposomes offer a number of distinct benefits, including the ability to protect drugs against enzyme breakdown, low toxicity, flexibility, biocompatibility, complete biodegradability, and non-immunogenicity **[3-8].**

Due to their natural components, SLN and NLC have been introduced as possibly appealing and commercial solutions. Since 1990, SLNs and NLCs have been recognised as an alternative carrier system to polymeric nanoparticles, emulsions, and liposomes. **Figure 2** depicts the historical development of the colloidal carrier system. These LNPs are made of solid phase lipid and surfactant and range in size from 40 to 1000 nm on average. Surfactant is utilised as an emulsifier in the dispersed phase, which is solid fat. Lipid components of SLNs can be highly purified triglycerides, intricate glyceride mixes, or even waxes, and they are solid at body temperature as well as ambient temperature. To improve stability, surfactants are utilised in quantities ranging from 0.5 to 5% **[9-11]**.

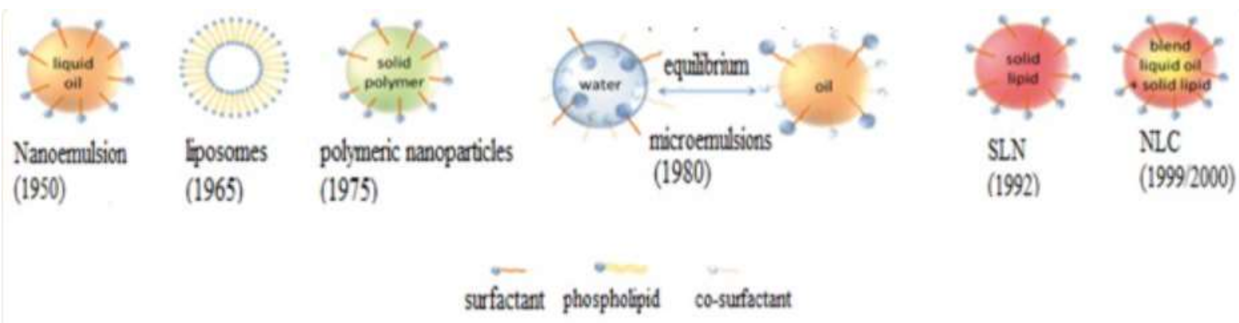


**Figure 2: Historical development of the colloidal carrier system schematic**

The prospective platform for medication therapy offered by nanoparticulate systems can help it perform better and overcome its shortcomings. Lipid nanoparticles hold the greatest promise for medication delivery among the several nano-systems under investigation. In order to avoid using organic solvents in the production of polymeric nanoparticles, Müller and Gasco invented and named solid lipid nanoparticles (SLN) in the 1990s **[12]**.

SLN became one of the most popular systems because it was more stable than previously created liposomes, hardened at body temperature, which controlled drug release, and had no hazardous side effects from the use of organic solvents **[13]**. Low drug payload is the main issue for applicability due to internal rearrangement of crystal structure and subsequent drug ejection, as its lipid content is exclusively represented by solid lipid. The development of nanostructured lipid carriers (NLCs), a second generation of lipid nanoparticles, was done to increase drug loading. The lipidic core of NLCs, which are binary systems containing both solid and liquid lipids, is less organised **[14]**.

The researchers have tried a variety of methods to increase bioavailability, including salt formation, prodrug synthesis, drug encapsulation in nanosized carriers such polymeric micelles, nanoparticles, liposomes, and emulsions, as well as drug nanosizing of the drug molecules. Researchers have also investigated several chelating agents and ionic polymers for improving medication molecule absorption. Additionally, investigations have demonstrated that P-gp blockers can be used to increase oral bioavailability **[15-20]**.

Lipid-based drug delivery technologies have given encapsulated medications a better chance of being absorbed throughout the past few decades. Various lipid-based systems are shown in **Figure 3** and are being investigated for use in drug delivery applications. When searching for "lipid nanoparticles" in PubMed, **(Figure 4)** a vast amount of published literature (9461) from 2006 to the present is find, and 7.3% of those were found under the heading "lipid nanoparticles in oral delivery," demonstrating the great interest that researchers have in using them as a promising oral delivery method. Although conventional lipid-based systems, such as micelles, liposomes, and nanoemulsions, have produced a number of exciting results, reports suggest that these systems are vulnerable to degradation during storage and in the gastrointestinal tract (GIT) because of the acidic environment of the stomach, intestinal enzymes, and bile salts **[21-23]**.

In order to get around these restrictions, Muller *et al*. worked hard to produce solid lipid nanoparticles (SLNs) in the early 1990s, which solved the stability and toxicity problems with the traditional lipid-based delivery systems. But SLNs also have a number of drawbacks, including a low drug loading capacity and drug ejection during storage. Due to their transition from high-energy modification to more ordered modification on storage, they developed a drug leakage problem. Beginning in early 2000, modified lipid nanoparticles also known as nanostructured lipid carriers (NLCs) were developed to alter the physical state and drug-loading capacity of SLNs **[23-25]**.

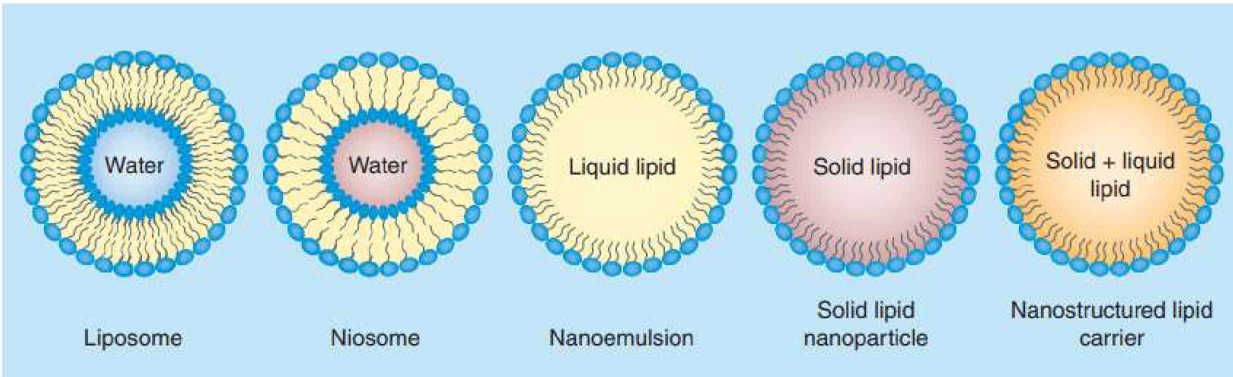


**Figure 3: Different lipid-based methods were investigated for use in medication delivery**

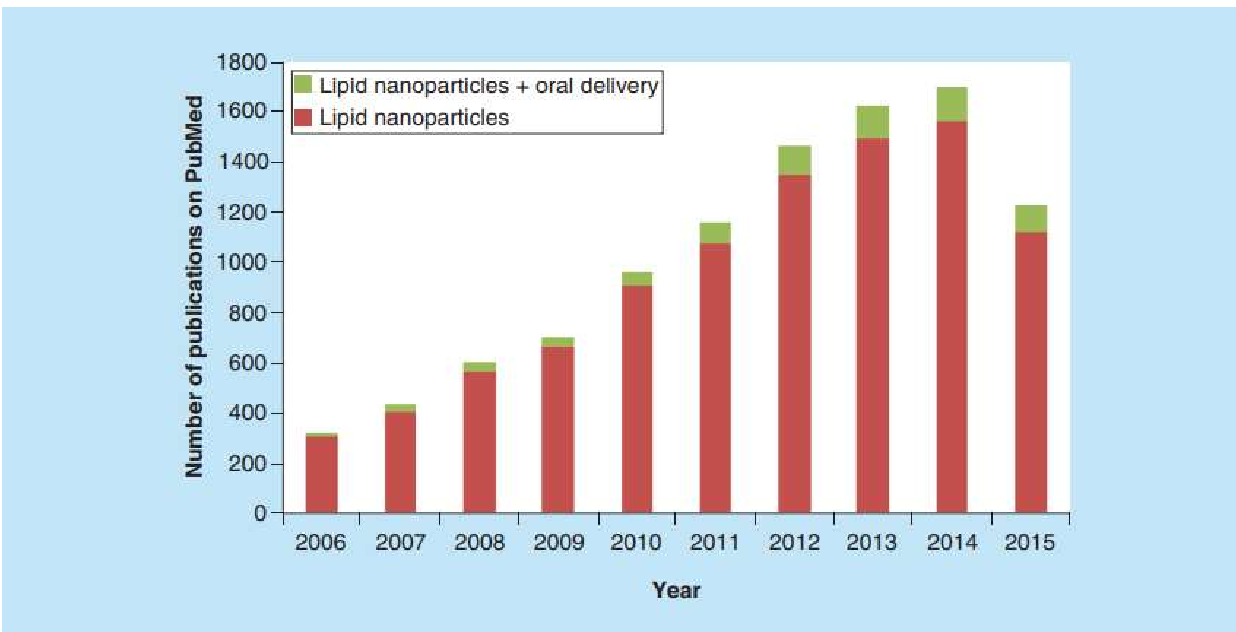


**Figure 4: Total number of publications related to "lipid nanoparticles" and "lipid nanoparticles + oral" on PubMed**

## NLCs versus SLNs

Due to the utilisation of a combination of solid lipid and liquid lipid in their formulations, NLCs enable increased drug loading, a faster release rate, and storage stability, thus overcoming the drawbacks associated with SLNs. Numerous comparison studies have been published that show NLCs to be a superior carrier to SLNs. For instance, it was found in a study comparing SLNs and NLCs of simvastatin that the latter's (93.33%) greater drug entrapment efficiency when compared to the former's (75.81%) was attributable to the latter's generation of additional room for loading by liquid lipid **[26]**.

Additionally, the in vitro release patterns of SLNs and NLCs were comparable, but NLCs showed higher cumulative drug release rates in 55 hours than SLNs did. The slower drug release was caused by the drug's poorer mobility in SLNs (a crystalline system) compared to NLCs (a disordered arrangement). Differential scanning calorimetric investigation revealed NLCs to have a higher long-term stability than solid lipids and physical mixtures of solid and liquid lipid. It also revealed NLCs to have a lower recrystallization index than solid lipids, which favours the formation of disordered arrangements. Another study comparing progesterone and domperidone-loaded SLNs and NLCs concluded that the NLCs were the superior delivery system for both drug loading and release rate **[27-29]**.

**Preparation techniques and categories of NLCs**

NLCs can be produced using a variety of techniques. Methods can be divided into three categories based on the amount of energy they require. NLCs can be produced using a variety of techniques. Methods can be divided into three categories based on the amount of energy they require.

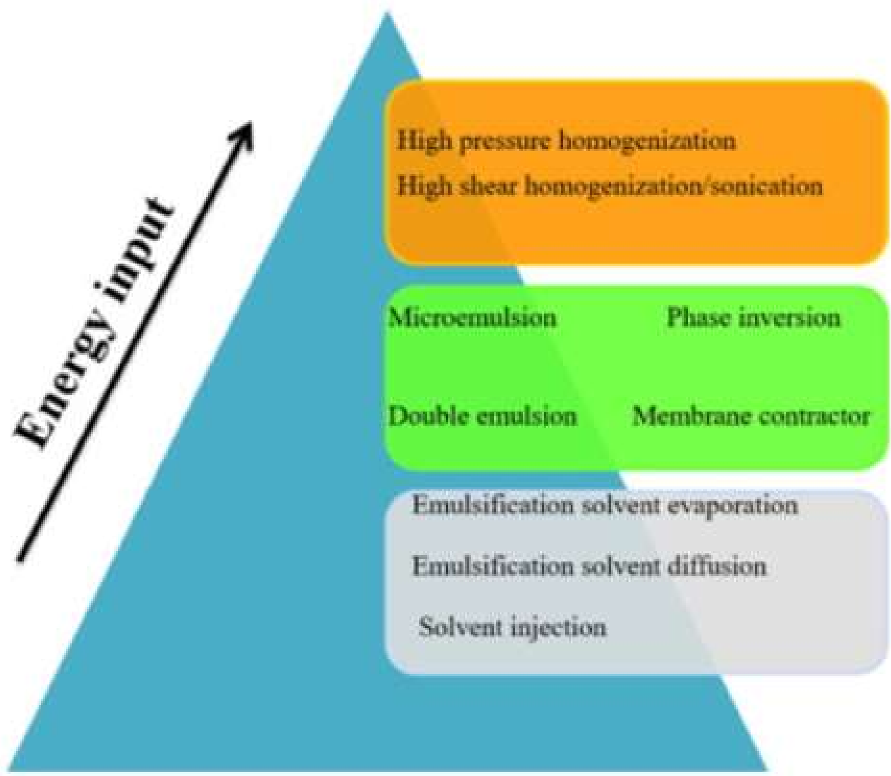


**Figure 4: Shows different ways to fabricate NLCs based on energy input**

A variety of methods, including high pressure homogenization (HPH), high shear homogenization/sonication, supercritical fluids, and microwave-based methods, are employed to produce NLCs. One of the most used techniques is high pressure homogenization, which doesn't require the addition of any solvents during preparation. As it creates highly stable particles and doesn't need for the use of organic solvent, it has been regarded as a reliable and effective method for the large-scale manufacturing of NLCs. In the hot homogenization procedure, the medication is infused into a molten lipid mixture that has been rapidly stirred into a heated surfactant aqueous solution. Finally, a high pressure homogenizer is used to further homogenise the pre-emulsion. Once the obtained nanoemulsions recrystallize at room temperature, NLCs are created **[24, 30, 31]**.

In the cold homogenization process, the drug and molten lipid combination are rapidly cooled while being affected by liquid nitrogen or dry ice, solidifying the mixture. It is then pulverised and mixed with a cold aqueous surfactant solution. High pressure homogenizer is used to process the resultant dispersion in the end. The shortcomings of hot procedures, such as avoiding heating of medications and surfactants, can be somewhat resolved by this technique. Controlling the crystallisation process is another way to get the desired crystal structure. However, compared to the heat homogenization procedure, the generated particles could have larger particle sizes and more heterogeneity **[32]**.

A water-immiscible solvent is used in the emulsification solvent evaporation procedure to dissolve both the active ingredient and the lipids. Aqueous surfactant solution is then used to emulsify the resulting solution. The solvent then evaporates while being continuously stirred, producing NLCs. This approach is appropriate for heat-sensitive actives because there is no heat involved. The main drawbacks of this technology are the toxicity of the solvent residue and the diluted NLC particles caused by the insufficient solubility of the lipids in the solvents utilised **[33]**.

**Safety and toxicity issues**

One of the biggest concerns is the safety/toxicity of NLCs. However, safety profile received little attention from researchers in the literature. Therefore efforts have been made to compile a succinct report on the safety/toxicity of the NLCs described in the literature. Because they include biodegradable and physiological lipids that are well tolerated in both in vitro cytotocity and in vivo experiments, NLCs are regarded as relatively safe nanocarriers when used orally. In contrast, NLCs have a better safety profile than emulsions because they have lower levels of surfactants and cosurfactants. After oral delivery, Rahman *et al*. investigated the toxicity of zerumbone-loaded NLCs on a BALB/c mouse model.(34).They reported that NLCs did not show any symptoms of toxicity on the lungs, liver, or kidney based on histopathological abnormalities, and a higher lethal dose (LD50) of NLCs was reported. Studies on the cytotoxicity of Caco-2 cells in vitro revealed that the NLCs system did not exhibit any discernible cytotoxicity and that cell viability was above 90%. Another study showed that the amount of NLC particles per millilitre affected the cytotoxicity of NLCs (on lymphocytes); at 2.1 1011 particles/ml, lymphocyte viability dropped by around 55% **[35, 36]**.

According to Fang *et al*., the skin irritation caused by enhancers is often not connected to their ability to penetrate the skin. Additionally, they noted that Azone, D-limonene, and L-alpha-lecithin were the next most irritating substances, followed by fatty acids. In this study, a full picture of the effectiveness and safety of widely used enhancers was established. Due to their biocompatible lipids, non-ionic and biocompatible surfactants, and organic solvent-free formulations, NLCs are thought to be substantially safer for ocular distribution. However, the place of administration largely determines the level of clearance and toxicity (topical, intravitreal, intravenous, transscleral, suprochoroidal or subretinal) **[37, 38]**

**CONCLUSION**

The creation of medication delivery systems is an ongoing, difficult project that incorporates diverse research efforts in various fields. The binary lipid-based nanocarriers known as NLCs allow for the trapping of lipophilic actives, preventing their deterioration and enhancing their stability. They contain a blend of both solid and liquid lipid. They are safe to use because they are made of biocompatible lipids and surfactants that have received FDA approval. NLC components should be carefully chosen as they have a direct impact on the stability and efficacy of the final product. The convenience of large-scale production, notably through high pressure homogenization, was made possible by their ease of successful fabrication. However, they have seen a lot of use in the pharmaceutical and biomedical fields over the past ten years as they combine key elements of smart formulation, including high drug payload, the ability to target particular sites through surface modification, and increased understanding of the basic mechanisms of transport via a variety of administration routes. As a result, they can be applied in numerous ways to treat and control a variety of ailments. NLCs are top contenders for improving medication bioavailability, treating inflammatory bowel disorders, and reducing drug-induced toxicity because of decreased particle disintegration and prolonged GIT residence periods following oral administration. NLCs should have a reasonable probability for accurate clinical translation and pharmaceutical marketing in all applications given the rising number of patents in recent years.

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