



## NANOSTRUCTURED LIPID CARRIER – A LIPID BASED NOVEL DRUG DELIEVERY TOOL

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Abstract : Nanostructured Lipid Carrier (NLC) are advanced drug delivery systems designed to overcome the limitations of conventional drug delivery methods, including poor solubility, instability, and inefficient bioavailability. NLC are second-generation lipid nanoparticles, composed of a blend of solid and liquid lipids stabilized by surfactants. This unique composition enables the formation of a matrix with increased drug loading capacity, enhanced stability, and controlled drug release properties. The biocompatibility and biodegradability of lipids used in NLC make them a promising carrier for a wide range of therapeutic agents, including hydrophilic and hydrophobic drugs, peptides, and even genetic materials. Their small particle size, typically in the nanometer range, facilitates improved penetration across biological membranes, allowing for targeted and sustained drug delivery. NLC also offer advantages in protecting sensitive drugs from degradation and reducing adverse side effects. Recent advancements have demonstrated the versatility of NLC in various applications, including oral, topical, transdermal, pulmonary and parenteral drug delivery. Additionally, NLC have shown potential in addressing challenges in cancer therapy, central nervous system disorders, and antimicrobial treatments. Emerging research emphasizes their role in enhancing bioavailability and patient compliance, particularly in challenging therapeutic scenarios. This review explores the structure, preparation techniques, advantages, and applications of NLC in modern pharmaceutical science, highlighting their role as a novel and efficient drug delivery tool with significant potential to revolutionize personalized medicine and therapeutic outcome.

IndexTerm – NLC , nanoparticles , solid lipid nanoparticles

### I. Introduction

Lipid nanoparticles can be divided into two classes: solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC). Research on SLN and NLC during the past 20 years has mostly concentrated on non-dermal methods of pharmacological administration, such as parenteral perioral, ocular, and pulmonary administration.<sup>[1]</sup> SLN and NLC have been the subject of much research for dermal application during the past five years because to the numerous benefits

that have been reported following skin application. The lipid matrix, tiny particle size, and associated adhesive qualities all contribute to the extended residence period of SLN and NLC on the skin.<sup>[2]</sup> Further development of this first-generation lipid nanocarrier system allowed for the delivery of drugs via many routes of administration for the treatment of physiological problems.<sup>[3]</sup> After researchers noticed several drawbacks with SLNs, Muller developed a novel lipid carrier in 1999/2000 that he called nanostructured lipid carriers (NLC).<sup>[4]</sup> Oil-in-water nano-emulsions are the source of nanostructured lipid carriers (NLC), a nanoparticulate carrier system. Lipid, emulsifying agents, and water are its main constituents. At room temperature, the lipid phase comprises both liquid (oil) and solid (fat) lipids.<sup>[5]</sup> The formulation based on NLC is justified by the fact that the medication dissolves in oil and simultaneously encapsulates in solid lipid, resulting in a controlled release of the drug and a greater loading

capacity. Reduced polymorphic transition, low crystalline index, higher encapsulation efficiency, drug loading, physical stability, improved chemical stability, bioavailability, and controlled release of encapsulated components are some of the benefits of NLCs.<sup>[6]</sup> The second generation of lipid-based nanoparticles, known as nanostructured lipid carriers (NLC), were created at the start of the new millennium. NLC is produced by substituting a liquid lipid for a portion of the solid lipid used in the SLN formulation. This reduces the ordered structure of the lipid matrix and introduces flaws that are required to

minimize drug expulsion during storage. Like the SLN, nanostructured lipid carriers are systems with a solid lipid matrix at body temperature. When liquid lipid is added to the lipid core of nanostructured lipid carriers, the crystalline arrangement is severely disrupted.<sup>[7]</sup> Compared to emulsions, NLCs can effectively immobilize medications and have a solid matrix that keeps the

particles from clumping together. Furthermore, the solid phase significantly reduces the mobility of the drug molecules that are integrated. In contrast to SLNs, the liquid oil droplets in the solid matrix also boost the drug loading capacity.<sup>[8]</sup> This review is centered on NLC formulations and aims to (i) highlight the main obstacles to overcome in drug delivery when using lipid nanoparticles (LP) and

(ii) provide a comprehensive overview of the recently developed uses of NLC formulations as drug delivery systems by various administration routes.<sup>[9]</sup> Over the last few years, lipid-based drug delivery systems have been created to address the issues of different medications' low bioavailability and delivering them to precise locations for pharmacological activity. In order to

reduce toxicity and increase efficacy, nanoparticles were used to transport the medication to the desired site of action.<sup>[10]</sup> The main components of NLCs, liquid and solid lipids, should ideally be chemically stable, biocompatible, biodegradable, and free of harmful consequences. Because it directly affects drug entrapment and NLC loading efficiency, the solubility of the drug in the lipids is typically taken into consideration when choosing lipids for NLC formulation.<sup>[11]</sup> The main components of NLCs, liquid and solid lipids, should ideally be chemically stable, biocompatible, biodegradable, and free of harmful consequences. Because it directly affects drug entrapment and

NLC loading efficiency, the solubility of the drug in the lipids is typically taken into consideration when choosing lipids for NLC formulation.<sup>[12]</sup> Introduced in 1991, solid lipid nanoparticles (SLN) are spherical particles with an average diameter in the nanometer range. They are made up of a solid lipid matrix core that has the ability to solubilize lipophilic medicines. Physiologically acceptable

surfactants and cosurfactants, such as polyorbates, polyoxyethylene ethers, phospholipids, bile salts, and others, stabilize the lipid core at concentrations ranging from 0.5% to 5%.<sup>[13]</sup> The lipid nanoparticles are the perfect delivery vehicles since they are made of lipids that are comparable to physiological ones and have a number of benefits. Lipid nanoparticles of the second generation

are called nanostructured lipid carriers (NLCs). In contrast to solid lipid nanoparticles (SLN), NLC is created by carefully combining solid lipids with liquid lipids that are spatially incompatible. This creates unique nanostructures that have better qualities for drug loading and stable drug incorporation over time.<sup>[14]</sup> The lipid particles known as SLN® are solid both at room temperature and at body temperature. For example, Dynazan 112 or other lipids like Compritol 888 ATO or Imwitor 900 are made entirely of solid lipids.<sup>[15]</sup> Particle aggregation during storage is another issue with the SLN. Aggregation occurs because prekinetic flocculation might result from the low viscosity diffusion of individual drug particles. NLC, on the other hand, are extremely concentrated

viscous dispersions in which the particles form "pearl-like networks." They are stationary and immune to collision and prekinetic flocculation. Additionally, the blood network is broken during dilution with GIT fluids, leading to the production of single nanoparticles.<sup>[16]</sup> Utilizing physiological lipids, avoiding organic solvents, and being suitable for large-scale synthesis are the benefits of

SLNs. SLNs are effective drug delivery vehicles that can enhance bioavailability, shield delicate medications from harsh conditions, and regulate drug-release properties.<sup>[17]</sup> Raman mapping also looked into the distribution of various chemical components in NLCs.<sup>[18]</sup> SLN and NLC are becoming more and more popular as alternatives to other nanocarriers such as liposomes, nanoemulsions, and polymeric nanoparticles, and not just for pulmonary applications.<sup>[19]</sup> At the

moment, dermal creams and cosmetics that are integrated with NLCs are sold.<sup>[20]</sup> NLCs have distinct properties and are made by combining liquid and solid lipids to create less organized structures that provide a firmer inclusion of the drug molecules in the matrix during the course of the shelf life.<sup>[11]</sup> Drug delivery using hydrogel formulations based on nanostructured lipid carriers: A thorough review Low toxicity and strong in vivo tolerance are two benefits of SLN, which are

colloidal carriers made of lipids that are solid at ambient temperature and have a structure substantially comparable to physiological lipids.<sup>[21]</sup> NLCs possess lower melting point due to their oil content, while maintaining their particulate character and being solid at body temperature, greater degree of drug loading, reduced burst release of

drug and better control of drug release.<sup>[22]</sup> In contrast to polymeric nanoparticles, SLNs have more benefits for drug delivery systems, including good tolerability because they use physiological lipids. Their primary difference is that solid lipids are all that are needed to prepare SLNs, whereas liquid lipids are combined with solid lipids to prepare NLCs, giving the system greater flexibility and stability.<sup>[23]</sup> A mixture of solid and liquid lipids, which is also solid at body temperature, is used to create the particles in the second generation of nanostructured lipid carriers (NLC) technology.<sup>[24]</sup> Because of the solid lipid's crystalline structure, SLN are characterized by unexpected gelation tendencies, burst drug release, limited drug loading capacities, and drug expulsion during storage as a result of lipid crystals' polymorphic metamorphosis.<sup>[25]</sup>

## II. BACKGROUND ON DRUG DELIVERY SYSTEM OVERVIEW OF CONVENTIONAL DRUG DELIVERY SYSTEM

### Oral route

Because of its many benefits, including patient compliance, cost-effectiveness, and ease of administration, the oral drug administration route is considered the most widely accepted method for administering medication and offers a valuable alternative for treating a number of fatal illnesses. Additionally, it is strongly favored for long-term use of medications like anti-tumor, anti diabetic, and antihypertensive drugs.<sup>[11]</sup> Although the oral route is the most practical way to administer drugs, it is susceptible to bioavailability issues caused by the physiology of the GI tract as well as the consequences of first-pass metabolism and biotransformation. NLC is becoming a popular drug delivery technology that can administer hydrophilic medications orally with high loading capacity in addition to controlled release.<sup>[16]</sup> In recent years, there has been a growing interest in NLCs for oral medication administration. When NLCs are administered orally, increased bioavailability and extended plasma levels are reported.<sup>[26]</sup> Mixing drugs with food or water is the most straightforward way to deliver them. This is not feasible, though, when the material irritates the gastrointestinal system mucosa or is insoluble, unpleasant, or chemically unstable in drinking water.<sup>[27]</sup> It is feasible to provide SLN orally as an aqueous dispersion or, alternatively, as conventional dosage forms such as tablets, pellets, capsules, or powders in sachets.<sup>[28]</sup> The most common method of administering drugs is orally.<sup>[29]</sup> The primary benefits of oral delivery include systemic delivery, pre-established dosages, and the ease of patient self-administration, all of which are combined into a single tablet or capsule.<sup>[30]</sup> Oral administration of certain drugs on an empty stomach improves absorption.<sup>[27]</sup> Despite using various lipid excipients, oral delivery of drug-loaded NLC demonstrated a comparable increase in bioavailability for medicines that were weakly water soluble.<sup>[31]</sup> Poorly water-soluble medications present a difficulty for oral drug delivery since their low aqueous solubility limits the pace at which many substances can be absorbed. Drug delivery methods based on lipids have demonstrated significant promise in enhancing oral bioavailability. In many animal models, the possibility of solid lipid formulations for the oral delivery of medications that are poorly soluble in water has been examined.<sup>[31]</sup> It is important to remember that drugs might be metabolized by the digestive tract's microflora's enzymes when using oral administration routes. Microorganisms are only found in the large intestine under physiological conditions, and typically, this type of enzymatic metabolism only applies to substances that have not yet been absorbed in the upper tract. This indicates that the drawback of oral delivery is that chemicals may be changed by the enzymatic activity of microbes prior to their absorption in the gut.<sup>[27]</sup> Oral delivery is the most popular and commonly accepted method of drug delivery among the several routes since it is simple for patients to administer. The GI tract's overall absorptive surface area is increased to 30-400 m<sup>2</sup> by the extremely absorbent human intestinal epithelium, which is made up of villi. However, because of its distinct structure and physiology, intestinal epithelium may have an impact on medication absorption. Additionally, presystemic hepatic metabolism affects oral delivery as well. As a result, many medications may be difficult to reach therapeutic levels through the GI tract.<sup>[32]</sup> Oral administration is regarded as one of the most patient-acceptable administration techniques. Approximately 60% of medications are administered orally. Oral administration often consists of tablets, capsules, pills, etc., which can be hard for patients who have trouble swallowing or who need medication but refuse to take it orally because of behavioral problems brought on by medical or psychological illness.<sup>[33]</sup> Aqueous dispersion or more conventional dose forms as pills, pellets, capsules, or powders in sachets can be used for oral delivery of SLN.<sup>[28]</sup> With good patient compliance worldwide, oral delivery is the most widely used noninvasive drug application method. It is possible to administer SLN and NLC orally as dispersions or by combining them with a dosage form like tablets, pellets, or capsules.<sup>[34]</sup> For oral delivery, NLC can take use of all the benefits associated with lipid nanoparticles. It is possible to increase drug loading and improve drug inclusion in comparison to the other systems. Traditional dosage forms that the patient is familiar with, such as tablets, capsules, or pellets, can be processed more easily using NLC.<sup>[35]</sup>

### Sublingual route

The layer of epithelial cell membrane in the sublingual mucosa is just 100–200µm thick, compared to the buccal mucosa. Because the sublingual mucosa has a larger blood supply than the buccal membrane, absorption following sublingual administration can occur more quickly.<sup>[33]</sup> For the systemic and local administration of some medications, the sublingual route is the recommended method. Because of its plentiful vascular supply, quick onset of action, enhanced bioavailability, avoidance of hepatic first-pass metabolism, dietary effect, better patient compliance, and ease of self-medication, this route is beneficial for oral medications. Compared to taking medication, it offers a number of clear benefits. Sublingual medication delivery has been used in numerous novel drug delivery systems that have been successfully released onto the market in recent years. The permeability of the sublingual membrane, the physicochemical characteristics of the medication, and the dosage form design all affect sublingual drug administration and subsequent absorption.<sup>[36]</sup> Analgesics like morphine, bronchodilators like fenoterol, antihypertensive pharmaceuticals like nifedipine, and antianginal drugs like nitrites and nitrates are a few examples of medications that are given this way. It is also possible to inject specific peptides, like oxytocin, and steroids, like estradiol. G. Prochlorperazine dimaleate {PRO}, apomorphine, fentanyl citrate, and hydrazinehydrochloride<sup>[37]</sup>. Bypassing first-pass metabolism, sublingual medication administration enables direct absorption into the systemic circulation, leading to a rapid beginning of action and increased bioavailability.<sup>[38]</sup> Steroids, some barbiturates, enzymes, and cardiovascular medications are among the medications that are administered sublingually. The administration of numerous vitamins and minerals, which are discovered to be easily and completely absorbed by this approach, has been a burgeoning field. Drugs administered by this method include bronchodilators like fenoterol, analgesics like morphine, antihypertensives like nifedipine, and antianginals like nitrites and nitrates.<sup>[39]</sup> Among the many benefits of a sublingual drug delivery system are its ease of use for patients including children, elderly, and psychiatric patients—who are unable to swallow tablets. It is possible to achieve a comparatively quick onset of effect in contrast to the oral route. The mouth cavity's broad contact area helps ensure that drugs are absorbed quickly and thoroughly. The intermediate gastrointestinal tract's pH and digestive enzymes prevent the liver from being damaged and also shield the medication from deterioration. The technology offers quick disintegration or dissolution in the oral cavity. Among its many drawbacks are that it is not well adapted for sustained delivery systems; medication cannot be administered through this route when a patient is asleep or uncooperative.<sup>[40]</sup>

### Nasal drug delivery

The pharmaceutical industry has been very interested in using the nasal cavity as a drug delivery channel over the past ten years, particularly for systemically acting medications that are challenging to provide through methods other than injection.<sup>[41]</sup> The nasal septum, a central bone and cartilage partition, divides the nasal cavity into two symmetrical halves. The nasopharynx connects each side to the mouth, while the nostrils open at the face.<sup>[42]</sup>

## ADVANTAGES OF NASAL DRUG DELIVERY SYSTEMS

1) Self-medication is made easier by easy accessibility and needle-free drug application without the need for trained personnel, which improves patient compliance when compared to parenteral routes; 2) Good penetration of low molecular weight drugs, particularly lipophilic ones, through the nasal mucosa; for example, fentanyl's absolute nasal bioavailability is approximately 80%<sup>[43]</sup>; 3) Rapid absorption and fast onset of action due to relatively large absorption surface and high vascularization; therefore, the T<sub>max</sub> of fentanyl after nasal administration was less than or equal to 7 minutes, comparable to intravenous [i.v].<sup>[43]</sup> Nasal administration of an appropriate drug would therefore be effective in emergency therapy as an alternative to parenteral administration routes; 4) Avoiding the harsh environmental conditions in the gastrointestinal tract (chemical and enzymatic degradation of drugs).<sup>[44]</sup> Nasal administration is an alternative route for increasing the bioavailability of active agents that are unstable in the GI tract and/or have absorption problems due to their large molecule size. Nasal mucosa is highly permeable and intensely vascularized, which together lead to fast drug absorption and a rapid onset of action. Drugs administered through the intranasal route avoid enzymatic degradation in the GI tract and bypass the hepatic first pass effect. The nasal route has been used extensively for a number of years for the local treatment of nasal diseases through the administration of corticosteroids, decongestants, and antihistamines.<sup>[45]</sup> Nasal administration is an alternative route for increasing bioavailability of active agents, which are unstable in the GI tract and/or have absorption problems due to their large molecule size. Nasal mucosa is highly permeable and intensely vascularized, which together lead to fast drug absorption and a rapid onset of action. Drugs administered through intranasal route avoid enzymatic degradation in the GI tract and bypass the hepatic first pass effect.<sup>[34]</sup> The potential to access the brain through the nose without having to pass through the blood-brain barrier (BBB) has drawn more

attention recently, particularly in an effort to better treat disorders of the central nervous system (CNS), such as multiple sclerosis, epilepsy, Alzheimer's disease, Parkinson's disease, and gliomas, among others.<sup>[45]</sup> A nasal medication delivery system called "Nasya Karma" is used to treat 31 distinct systemic and local illnesses.<sup>[46]</sup> These days, the most typical uses for intranasal medication application are to relieve nasal congestion, cure local inflammation, and treat allergic and common rhinitis. Glucocorticoids, decongestants, and antihistamines are examples of frequently used active chemicals that are present in nasal sprays and drops worldwide. Because of the physical characteristics of the nose, such as the nasal mucosa's strong blood circulation, nasal drug administration has the enormous benefit of rapid drug absorption, which produces a rapid local effect.<sup>[47]</sup>

### Ocular drug delivery

Pharmaceutical technology researchers continue to face difficulties with ocular drug delivery because of the physiological and anatomical features of the eye. Due to the unique anatomical and physiological features of the eye, a complex organ with various defensive barriers that can be overcome to reach intraocular tissues, ocular medication administration is still difficult.<sup>[49]</sup>

### Introduction to need of novel drug delivery systems

The creation of innovative drug delivery systems (NDDS) for herbal medications has received a lot of interest in recent decades. Two requirements should preferably be met by the innovative carriers. First and foremost, over the course of therapy, it should administer the medication at a pace determined by the body's requirements. Second, it ought to transport the herbal medication's active ingredient to the place of action.<sup>[50]</sup> There are numerous carriers with advantages over those based on the types of new drug delivery systems (NDDS). The first pass effect, fluctuating plasma drug levels, high dose and low availability, and rapid release of pharmaceuticals are all characteristics of classic dosage forms. By: product shelf life, patient compliance, performance, and protection. Three NDDS will lessen the issues.<sup>[51]</sup> Among the many advantages of novel drug delivery systems (NDDS) are enhanced therapy by extending the duration and effectiveness of drug activity, improved targeting for a particular site to minimize undesirable side effects, and increased patient compliance through fewer doses and more convenient administration methods.<sup>[50]</sup>

### Emergence of NLCs

#### BASIC CONCEPT AND DEFINITION OF NLC

NLC was created in order to address the shortcomings of SLN. They are regarded as lipid nanoparticles of the second generation<sup>[1]</sup>. The foundation of NLC formulation is the idea of adding a medicine to a mixture of different proportions of liquid and solid lipid. To get over the restrictions brought on by the crystallinity of the SLN's core, NLCs were created to have a solidified core and less or no crystalline matrix.<sup>[4]</sup> Furthermore, it is feasible to include both lipophilic and hydrophilic medicines into NLCs. Additionally, they can deliver medications to the site of action and offer continuous release.<sup>[11]</sup> NLCs made of lipids, both liquid and solid. A flawless crystalline structure is deviated to produce a crystal lattice with many voids when liquid lipids (oil) are incorporated into solid lipids, causing structural defects.<sup>[52]</sup> In general, solid and liquid lipids, water, and emulsifiers make up NLCs<sup>[11]</sup>. Lipids, water, and emulsifiers are the three main components of NLCs. NLCs include both liquid and solid lipids to build the inner core.<sup>[26]</sup> Oil-in-water nano-emulsions are the source of nanostructured lipid carriers (NLCs), a nanoparticulate carrier system. Lipid, emulsifying agents, and water are its main constituents. Both liquid (oil) and solid (fat) lipids are present in the lipid phase at room temperature. Since the drug dissolves in oil and simultaneously encapsulates in solid lipid, the formulation based on NLCs aims to produce particles with an oil integrated into the solid lipid core, which results in a greater loading capacity and controlled drug release.<sup>[6]</sup> The primary technique for preparing NLC is high pressure homogenization<sup>[23]</sup>. NLCs are colloidal structures made up of an unstructured lipid matrix and a core that contains a mixture of liquid and solid lipids.<sup>[53]</sup> There are already over 40 NLC products on the cosmetics market, and NLC for nutritional and pharmacological applications is being developed<sup>[54]</sup>. Although the NLC is a more intelligent system, the SLN itself is a reliable technology<sup>[55]</sup>. The usual particle size of NLC is between 150 and 250 nm.<sup>[56]</sup> Retinol was the first substance created in NLC.<sup>[53]</sup> NLCs include at least one liquid lipid in addition to solid lipid, unlike SLNs. By partially replacing solid lipids with liquid lipid pro-motes, the apolar nucleus became more structurally disorganized, which promoted the encapsulation of nonpolar medications and inhibited their ejection. Numerous research groups have examined NLC

as a viable drug delivery technology due to its great tolerability and capacity to integrate large quantities of lipophilic medicines<sup>[57]</sup>. For some active chemicals, NLC has a higher drug load potential than SLN, and it prevents or reduces probable ejection during storage.<sup>[58]</sup> When given through a new drug delivery system, standardized plant extracts or mostly polar phytoconstituents such as flavonoids, terpenoids, tannins, and xanthenes exhibit a considerably superior absorption profile that allows them to pass across the biological membrane, leading to increased bioavailability. Therefore, compared to a traditional plant extract or phytomolecule, a greater quantity of the active ingredient is present at the site of action (liver, brain, heart, kidney, etc.) at a comparable or lower dose. As a result, the therapeutic effect is improved, more noticeable, and lasts longer. With NDDS, a number of superior phytoconstituents have been effectively provided. Therefore, there is a lot of promise for creating innovative medicine delivery methods using plant extracts and active ingredients.<sup>[59]</sup> Compared to other lipid systems, such as emulsions, which need large amounts of surfactants and cosurfactants, NLCs have low toxicity, which is a significant advantage. Furthermore, NLC production and sterilization are less complicated and costly than other systems; for example, liposomal formulation sterilization is challenging because phospholipids are sensitive to heat and radiation, their production is expensive, and achieving batch-to-batch reproducibility and large-scale manufacturing is challenging and costly.<sup>[60]</sup> The lipid blend in NLC has a low crystallinity index and a slower polymorphic transition. An O/W nanoemulsion is the source of the nanoparticulate carrier system known as NLC. Lipid, surface active agent, and water are the main components of NLC, same like in nano- and micro-emulsions.<sup>[61]</sup>

### Why lipid nanoparticles?

Lipid nanoparticles can help in reaching some of the most important goals in drug therapy. Lipid-based nanoparticle formulations influence the oral absorption of active ingredients via various mechanisms, such as modifying the release of active ingredients, improving their bioavailability, changing the composition and hence the character of the intestinal environment, stimulating the lymphatic transport of active ingredients, interacting with enterocyte-based transport processes and reducing unwanted drug side effect.<sup>[64]</sup> Lipid nanoparticles (LN) constitute promising nanoscale systems that have recently raised high interest for drug and gene targeting and controlled delivery. They present as main advantages, small and controllable size, biocompatibility, biodegradability, physicochemical stability, cost-effectiveness and solvent-free production method suitable for high-scale manufacturing. Furthermore, derived from their structure, they confer chemical protection of incorporated drugs while their surface can be easily functionalized.<sup>[65]</sup> In recent decades, lipid nanoparticles have received special attention due to their advantages of compatibility with the skin, ability to enhance penetration of drugs in the stratum corneum, protection of the encapsulated substance against degradation induced by the external medium, and control of drug release.<sup>[66]</sup> Owing to lipid biocompatibility and versatility, lipid nanoparticles (LNPs) showed many advantages over polymeric nanoparticles, and have been widely used for drug and active delivery.<sup>[67]</sup> One fundamental advantage of LNPs with regard to other lipid colloidal drug delivery systems (liposomes, niosomes, etc.) and to nanoemulsions, is their great kinetic stability and rigid morphology. Nanoparticles can be divided into two main families: nanospheres, which have a homogeneous structure in the whole particle, and nanocapsules, which exhibit a typical core-shell structure.<sup>[68]</sup> Main advantages of lipid carriers over other traditional drug carriers are good biocompatibility, lower cytotoxicity, good production scalability, the modulation of drug release, the avoidance of organic matrix, the payload for active compounds is increased and expulsion of the compound during storage is avoided. NLCs can be produced by HPH and the process can be modified to yield lipid particle dispersions with solid contents from 30 to 80%.<sup>[53]</sup> Lipid nanoparticles (LNPs) are a safe vehicle for drug delivery, made of physiological or physiologically related lipids.<sup>[69]</sup> Nanoparticles and nanomaterials are increasingly being explored for their potential applications in medicine. One of the most promising areas of application is drug delivery, where nanoparticles can be used as carriers to deliver drugs to specific cells or tissues in the body.<sup>[70]</sup> LNPs can improve the bioavailability of lipophilic drugs owing to their hydrophobic internal and hydrophilic surface structures, excellent biodegradability, and low toxicity, which can overcome the limitations of conventional DDS.<sup>[71]</sup> It begins in the late 1950s with the discovery by Saunderson and Thomas<sup>1</sup> and Bangham and Horne<sup>2</sup> that simple hydration of dry lipid film coated on a glass surface produces spherical vesicles or liposomes. This basic observation not only enabled the exploration of lipid-drug and lipid-protein interactions, but it spurred the development of liposomes and lipid nanoparticles as drug carriers to enhance therapeutic benefits.<sup>[72]</sup> Optimized lipid nanoparticle dispersions proved to be physically stable for at least 3 years.<sup>[73]</sup>

## WHY LIPID NANOPARTICLES?

- Better control over release kinetics of encapsulated compound.
- Engineering via size and lipid composition.
- Melting can serve as trigger.
- Enhanced bioavailability of entrapped bioactive.
- Chemical protection of labile incorporated compounds.
- Much easier to manufacture than biopolymeric nanoparticle.
- No special solvents required.
- Wider range of base materials (lipids).
- Conventional emulsion manufacturing methods applicable.
- Raw materials essential the same as in emulsions.
- Very high long-term stability.
- Application versatility:
  - a. Can be subjected to commercial sterilization procedures.
  - b. Can be freeze-dried to produce powdered formulation.<sup>[1]</sup>
- Lipid nanoparticles are becoming an emerging tool for lipid-based substances delivery across epithelial barriers.<sup>[74]</sup>

**ADVANTAGES LIPID CARRIER** 1. targeted release and management of pharmaceuticals. 2. Excellent treatment and high consistency (in comparison to other carriers). 3. The majority of lipids are biocompatible, and SLNs are biologically degradable. 4. The ease of handling hydrophilic and lipophilic materials. 5. Increase the security of prescription drugs. 6. Easier oversight and enforcement of compliance.<sup>[62]</sup> 7. Systems centered on liquids (avoid organic solvents). 8. Less costly than polymers, making it more accessible.

### Types of Nanostructured Lipid Carriers

Depending on the production method and composition, three types of NLC have been proposed (Muller et al., 2002b).

#### 1. Imperfect type

These types of NLC generally have imperfections in the lipid matrix to accommodate drug in molecular form and amorphous clusters. Imperfect lipid crystals are formed by judiciously using chemically different lipid molecules to form the matrix, e.g., using solid lipids or liquid lipids.

Because of the difference in their structure, they cannot fit together very well leading to more imperfections in the crystal lattice leaving enough space to accommodate the drug, thus leading to improved entrapment efficiency and higher drug loading capacity.<sup>[16]</sup> These NLCs are produced

by the mixing of solid lipids and chemically very different liquid lipids. To increase the drug loading capacity, glycerides composed of different fatty acids are used. Because of the distance in the fatty acid chain leads to the formation of imperfections in the crystal. The imperfections are the result of the incompatibility between lipids and intentionally utilized for the achievement of higher loading capacity, hence thus makes important to choose incompatible lipids.<sup>[52]</sup> In the imperfect type, lipid crystallization is altered by small amounts of oils, while in the amorphous type, the lipid matrix is solid but not crystalline.<sup>[60]</sup>

#### 2. Amorphous type

The lipid matrix of this type of NLC is solid, devoid of crystallinity, and is in the amorphous state. They are produced on mixing solid lipid and liquid lipid in such a combination that the particles solidify upon cooling but do not recrystallize, thus remaining in the amorphous state. The reason that they do not have crystalline matrix, no drug expulsion takes place after crystallization to stable  $\beta$  form.<sup>[16]</sup> The crystallization process leads to the expulsion of drug and therefore NLCs which are solid are preferred over crystalline one with the use of special lipids (hydroxyl octadecanoylhydroxy-stearate, isopropyl myristate) by which particle acquires solid state rather than crystalline.<sup>[52]</sup>

#### 3. Multiple O/F/W type

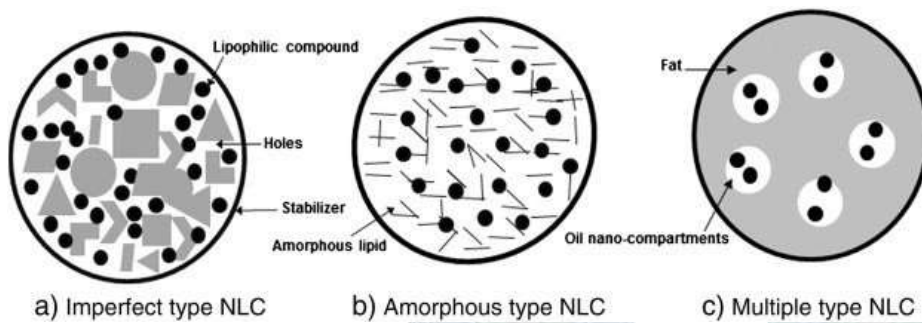
For many drugs, liquid lipids normally show considerably higher solubility than solid lipids. This fact led to the development of multiple O/F/W type of lipid nanoparticles characterized by the presence of tiny nanocompartments of oil in the solid matrix. This controlled nanostructure results on mixing a solid lipid with a higher amount of liquid oil. The liquid needs to be chosen so that the melted solid lipid and liquid lipid are miscible at the production temperature of the lipid particles.

Nanocompartments are formed when the liquid is used in such a high concentration that is well above its solubility in the solid lipid at room temperature. These NLC enable high incorporation capacity due to liquid lipid, which solubilizes the drug to a much higher extent and control of drug release due to encapsulating solid lipid particles matrix. Lipid-lipid precipitation technique is one

of the techniques that can be employed to create tiny oily droplets within a nanoparticle.<sup>[16]</sup>

Multiple NLCs are prepared by mixing solid lipids with large amount of oil (liquid lipids), small nano compartments within nanoparticles are created by a phase separation process during particles production. The solid matrix of the lipid nanoparticles contains tiny liquid nano compartments of oil. In these oil compartments the drug has high solubility. The oil

compartments formed are surrounded by solid lipids and hence controlled drug release was observed.<sup>[52]</sup> The third type of NLC is a multiple system, being comparable to w/o/w emulsions. In this case it is an oil-in-solid lipid-in-water dispersion. The solid lipid matrix contains tiny liquid oil nanocompartments. This NLC type uses the fact that for a number of drugs, the solubility in oils is higher than their solubility in solid lipids.<sup>[1]</sup> In the multiple type, the solid lipid matrix contains tiny oil compartments. The composition and structure of NLCs allow a high drug load; the formation of a less ordered lipid matrix lowers the burst effect, improves the release properties and, also, increases the stability upon storage.<sup>[60]</sup>



### NLC AND SLN = NLC V3 SLN

NLCs are improved SLNs in which the lipid phase is contained of both solid (fat) and liquid (oil) lipids that form a matrix.<sup>[76]</sup> NLC had higher entrapment in comparison to SLN due to the presence of high oil content in NLC when same amount of drug was loaded into it. In case of SLNs, solid lipid was weighed in an amber glass colored bottle and heated at 75 C to melt the lipid. In case of NLCs, solid and liquid lipids were first put together in an amber colored glass bottle and then heated at 75 C with continuous stirring to homogeneously mix the lipids.<sup>[78]</sup> Nanostructured lipid carriers (NLCs) have been developed to overcome the limitations of SLN. NLC have been explored for dermal delivery in cosmetics and dermatological preparations Nanostructured lipid carrier (NLC), a new generation of solid lipid nanoparticles (SLN), was developed in early 1990s; now it is a good alternative carrier of traditional colloidal controlled release drug delivery system.<sup>[79]</sup> NLCs would be able to overcome limitations associated with the SLN such as lower drug/nutraceutical loading efficiency, loading capacity, and more encapsulant leakage during storage time due to their imperfect crystal lattice and their lipid composition.<sup>[80]</sup> The SLN and NLC were developed by hot homogenization followed by ultrasonication.<sup>[81]</sup> Both the SLN and NLC are attractive carriers for topical cosmetic and pharmaceutical products. They possess the potential to develop as the new generation of carrier systems after the liposomes.<sup>[82]</sup> Drug delivery to the posterior segment of ocular tissue was investigated by formulating and characterizing indomethacin loaded SLNs and NLCs. Based on the parameters like drug loading, % entrapment efficiency and ocular tissue penetration of drug NLC formulation was considered as a suitable lipid carrier as compared to SLN.

Properties of SLN and NLC required from a colloidal drug delivery system include: SLN and NLC are acceptable by regulatory authorities around the world. Constituents used for SLN and NLC have GRAS status (Generally Recognized As Safe) due to their low toxicity. They are composed of high melting point short- and middle-length chain triglycerides, phospholipids, and waxes used in pharmaceuticals and cosmetics (CFR—Code of Federal Regulations Title 21—FDA). They can be produced using surfactants at much lower concentrations compared to microemulsions. A SLN dispersion containing a lipophilic phase composed of a maximum 30% solid lipid is generally stabilized by the addition of surfactants up to 5%. 453 15.2 Types of SLN and NLC They are safe systems even for long time circulation in the body due to their low toxicity. SLN and NLC may have a wide potential application spectrum such as intravenous, per oral, dermal, and topical. They are suitable systems for large-scale production by HPH technique, which has been used in the food industry for many years. HPH method provides convenient, fast, and cost-effective production for SLN and NLC with excellent reproducibility. Use of organic solvents is not required in their production by HPH and a few methods such as membrane contactor technique, ultrasonication, and high-shear homogenization. They are chemically and physically stable systems for up to two

years. They are stable against moist heat sterilization such as autoclaving. In the case of production below  $0.22\ \mu\text{m}$  particle size, they can be sterilized by membrane filtration. Additionally, they can be safely lyophilized.<sup>[34]</sup>

## PRODUCTION PROCESSES FOR NLC =

### 1. High-Shear Homogenization and Ultrasound

High-shear homogenization and ultrasound were initially used for the production of lipid nanodispersions. Both methods are widespread and easy to handle. However, in many cases, bimodal size distributions are obtained with one population in the micrometer range. In addition, metal contamination has to be considered if ultrasound is used.<sup>[84]</sup> Ahlin et al. used a rotor-stator homogenizer to produce SLN/NLC by melt-emulsification. They investigated the influence of different process parameters including emulsification time, stirring rate, and cooling conditions on the particle size and the zeta potential. In most cases, average particle sizes in the range of 100 to 200 nm were obtained using stirring rates of 20,000 to 25,000 rpm for 8 to 10 min and controlled cooling with a stirring rate of 5,000 rpm.<sup>[1]</sup>

### 2. Film-ultrasonication method

This method is adopted from the preparation methods of vesicular drug delivery systems. Lipids and drug are dissolved in an organic solvent preferably in ethanol. Aqueous phase is prepared by dissolving a surfactant in water and this is kept at elevated temperature. This phase is maintained at elevated temperature with stirring to obtain proper blend of drug-lipids. Organic phase is removed by applying vacuum using rotary evaporator. This will tend to form a thin film of drug-lipid blend which is collected and dispersed in heated aqueous phase under sonication. This dispersion is cooled at room temperature to obtain dispersed solidified NLCs.<sup>[4]</sup>

### 3. Solvent diffusion method

Solvent diffusion method can be employed as an alternate production method for producing NLC under mild conditions.<sup>[85]</sup> The NLC obtained by HPH technique generally show burst release of drug. High temperature and high surfactant concentration are believed to be the main reason. The high homogenization pressure may cause coalescence of particles. This method, comparable to the production of nanoparticles with synthetic polymer, is easy. It is easy and does not require any special equipment. First, the lipid phase (mixture of solid lipid and liquid phase) and the drug are dissolved into the organic phase at  $50^\circ\text{C}$ . The resultant organic solution is then dispersed quickly into the acidic aqueous solution containing dispersing agent (e.g., polyvinyl alcohol) under mechanical agitation. After adjusting the pH value of the acidic aqueous phase to 1.2 by the addition of 0.1 M hydrochloric acid to form aggregation of nanoparticles, the entire dispersed system is then centrifuged at high speed and resuspended in distilled water. The resultant dispersion finally dried by lyophilization. Recently, NLC for clobetasol propionate developed by Hu et al. (2006) were prepared by this method in an acidic aqueous system using monoolein (solid lipid) and caprylic/capric triglycerides (liquid material). However, a major disadvantage of this method is the need to use organic solvent.<sup>[16]</sup>

### 4. Solvent emulsification evaporation method

This name is used interchangeably with above method i.e. diffusion. In this method instead of using water miscible organic solvent, water immiscible organic solvents such as chloroform, cyclohexane, etc. are used to dissolve drug and lipids.<sup>[18]</sup> Use of organic solvents is the prime limitation of solvent diffusion and evaporation method as some traces of it may remain in the formulation.<sup>[4]</sup>

### 5. Cold homogenization method

As the name suggests that the temperature used in the whole process is lower than that used in a hot homogenization

process which ultimately rule out disadvantage that may be produced due to heat. The mixture of the lipids with the drug is rapidly cooled by the utilization of liquid nitrogen. The lipid matrices obtained are milled and then the particles are dispersed in the emulsifier solution and subsequently homogenized to produce fine particles. Various advantages of this process over the hot homogenization process are: 1. Thermal degradation is minimized. 2. Improved drug entrapment efficiency 3. Uniform distribution of drug within the lipid.<sup>[86]</sup> In comparison to the hot homogenization method, larger particle sizes and a broader size distribution are observed in cold homogenized method. Although cold homogenization minimizes the thermal exposure of the sample, but it cannot be completely avoidable as melting of the lipid/ drug mixture is required in the initial step.<sup>[52]</sup>

### Application of NLCs in drug industry & drug delivery

Recent pharmaceutical application of NLCs encompasses various conditions like hypertension, diabetes, Parkinsonism, epilepsy, hyperlipidemia, cancer, alopecia, hormone deficiency, topical inflammation, ocular, hepatic, and fungal diseases. It also has broad applications in nutraceutical and functional foods.<sup>[6]</sup> NLCs can be used in a wide variety of drug delivery systems such as oral drug delivery system, transdermal drug delivery system, injection drug delivery system, and gene transfection. Zhuang and Chen studied NLC as a carrier for oral administration. They prepared insoluble drugs or ones that were easily damaged by digestive enzymes such as antibiotics and enzymes for oral administration. The particles can be absorbed through the lymphatic system.

The controlled-released particles can slow down drug degradation and elimination, thereby enhancing the bioavailability of drugs.<sup>[88]</sup> Puglia and Junyaprasert investigated a carrier for transdermal delivery systems. NLC was similar to SLN: its small particle size can form a thin film on the skin, so that drugs entrapped in NLC avoid chemical decomposition. Meanwhile, NLC controls drug release, protects the skin, and prevents skin atrophy from repeatedly taking the medication.<sup>[89]</sup> Joshi researched the injection drug delivery system and showed that NLC made into a colloidal solution or freeze-dried powder can be used for intravenous injection to achieve sustained release and prolong the residence time of the drug in the circulatory system or target site.<sup>[90]</sup> Zhang revealed that NLC could be used as a transfer gene carrier, generally divided into two categories: viral vectors and non-viral vectors. The viral vector can efficiently transport genes, but the carrier immunogenicity, tumorigenicity, limited amount of transport DNA, and higher costs restrict its application. However, the NLC is a non-viral vector, so it cannot only overcome the above shortcomings of viral vectors, but also can be sterilized and freeze-dried as a result of the high stability.<sup>[91]</sup> A recently discovered area of applications is the combined use of iontophoresis and

NLC in improving skin penetration parameters. There have been several reports in the literature describing the role of iontophoresis in enhancing the transport of hydrophilic, low molecular weight molecules across the skin. The first report regarding the use of NLC as vehicles for transdermal iontophoretic drug delivery has been given by Liu et al. (2005).<sup>[16]</sup> Cancer Chemotherapy The role of NLC in cancer chemotherapy is always seen and the workforce is stressful. It is planned for nanostructured lipid carriers to be more efficient and reliable and to protect cytotoxic anticancer compounds. ZER's anti-proliferative function in NLC has not been impaired.<sup>[92]</sup> Food technology -Food and cosmetics industry is now-a-days replacing several synthetic excipients with natural ones. Antimicrobial agent menthol having low stability and insolubility problems was formulated as NLC which showed enhanced antimicrobial activity against gram positive bacteria.<sup>[93]</sup> An antioxidant, lycopene was added for food fortification in the form of NLCs in order to improve its solubility and stability.<sup>[94]</sup> Cosmetics and cosmeceuticals -As lipids are responsible for skin hydration and moisturization, lipid nanocarrier system is a promising approach for cosmetics purposes. The effect of incorporation and the concentration of propylene glycol and lecithin were investigated on the skin hydration, surface occlusion and transepithelial water loss which showed positive effects.<sup>[95]</sup> Investigators were developed argan oil based NLCs and incorporated it into hydrogel for dermal therapy which improved skin hydration. Argan oil NLCs can be used for incorporation of other APIs for synergistic effects in transdermal application.<sup>[96]</sup> For the manufacture of cosmetics with active ingredients such as prolonged perfume release, lipid nanoparticles SLN and NLC may be used. Incorporating topical products and controlling release using NLC is much more robust. In fact, the development of pest repellents was summarized.<sup>[97]</sup> Cardiovascular treatment -Lipid nanoparticles have superiorities as a carrier network, mainly prolonged diffusion times and increased under the curve region (AUC), with a controlled bursting effect. NLCs will have highly appealing physical-chemical

characteristics as a delivery system for lipophilic products.<sup>[92]</sup>

### Current & Future Developments

Over the past decade, the number of studies describing formulations based on nanostructured lipid carriers has risen exponentially. The increase in the development of NLC is majorly attributable to the surmounted barriers within the scientific formulation phase of lipid based nanoparticles and improved awareness of the fundamental transport mechanisms of NLC through various routes of administration. Due to its rapid absorption, bio-acceptability, and biodegradability, NLC is identified as a key drug delivery strategy without any alteration to the therapeutic agent. The influence of such delivery systems is steadily expanding and therefore has optimistic prospects for the future. It is indeed essential to further explore their application and effectiveness in food and pharmaceuticals.<sup>[6]</sup>

### Conclusion

A major development in drug delivery systems, nanostructured lipid carriers (NLC) provide a flexible and efficient answer to a number of problems with traditional drug administration techniques. NLC offer a special matrix structure that improves drug loading capacity, stability, and bioavailability by fusing liquid and solid lipids. Improved permeability, targeted distribution, and sustained release are made possible by their nanoscale size, which guarantees effective therapeutic results while reducing adverse consequences. NLC's capacity to transport a wide variety of pharmaceuticals, including as peptides, genetic materials, and hydrophilic and hydrophobic medications, is further highlighted by their biocompatibility and biodegradability. Their usefulness across multiple therapeutic disciplines is demonstrated by their use in a variety of administration routes, including oral, topical, transdermal, parenteral, and pulmonary. NLC are a game-changing tool in contemporary medicine because they have demonstrated remarkable promise in treating difficult medical issues like cancer treatment, problems of the central nervous system, and antibiotic resistance. Regulatory approval, long-term stability, and large-scale production continue to be obstacles despite their many benefits. To get over these restrictions and improve the structure and operation of NLC, more research and technical developments are essential.

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