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Nanostructured Lipid Carriers, Novel Approach for Drug Delivery: A Comprehensive Review

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ABSTRACT

In recent decades different drug delivery methods have appeared and an interesting aspect of this has been the development of nanoscale drug delivery systems (DDS). Lipid Nanocarriers in various forms have limitless opportunities in the field of drug delivery, which have been recently investigated for their huge potential. Among them, Nanostructured Lipid Carriers (NLC's) have most evolved for their advantages such as low toxicity, good biocompatibility, higher bioavailability, moreover, better drug release profile, greater drug loading capacity, drug targeting controlled release, physical and chemical stability over other lipid nanoparticles. It has a wide range of applications in the drug delivery system as a novel carrier when compared to other colloidal carriers. It also overcomes the issues with multiple lipid particulate carriers due to tremendous advantages. A novel sort of drug delivery system such as NLC's can form concentrated dispersions as they are stable in various environmental conditions. It is a promising delivery that can be used in the future in the pharmaceutical market. This review outlines the structure, properties, types, advantages and disadvantages, components of NLC's, techniques, and equipment involved in the preparation and evaluation of NLC's, pharmaceutical applications, and its future perspective as a pharmaceutical carrier.

1. INTRODUCTION:

Over the past few decades, several drug delivery technologies have emerged and a fascinating part of this was the development of nanoscience /nanoscale drug delivery systems or devices.[1] Oral drug delivery is the most prominent route for drug administration. However, a variety of drugs are difficult to pass through the intestine into the systemic circulation, which results in poor oral bioavailability.[2] Enhancement in oral bioavailability can be accomplished by diminishing the hepatic first-pass metabolism. Such issues with conventional dosage form can be limited by any suitable novel drug delivery system such as a prodrug concept or by the use of novel lipid-based systems like lipid nanoparticles, microemulsion, and Self emulsifying microemulsion drugs delivery system.

Lipid nanoparticles have attracted special interest in drug delivery in such cases, though it has many limitations widely accepted due to its advantages over other colloidal carriers. The advantages of solid particles, emulsions, and liposomes were combined with the development of solid lipid nanoparticles (SLN's). Solid lipid nanoparticles (SLN's) and Nanostructured lipid carriers (NLC's) have been introduced as potential lipid-based nanoparticles due to their natural components.[3] Nanoparticles produced using strong or solid lipids, known as solid lipid nanoparticles (SLN's).

In the middle of the 1990s, SLN's was an attractive parental carrier system. SLN's adds up the advantages of polymeric nanoparticles such as controlled drug release and evading drug leakage, and the advantages of emulsion and liposomes such as low toxicity, good biocompatibility, and higher bioavailability.[3]

Moreover, when compared with the traditional polymeric nanoparticles, an excellent advantage of solid lipid nanoparticles (SLN's) is that the lipid matrix is composed of physiologically tolerated lipids that, reduce the ability for acute and chronic toxicity. There were some SLN's limitations, namely drug loading capability restriction, drug expulsion during storage, and high aqueous SLN's dispersion water content (70-95%). To overcome these problems, nanostructured lipid carriers (NLC's) were developed in recent years. Conventionally, NLC's is produced by controlled mixing of solid lipids with spatially incompatible liquid lipids [4], which leads to the formation of a special nanostructure that offers the advantages of improved drug loading, modulation of drug release profile, and stable drug incorporation during storage.[5,6,7]

Therefore the solid lipid nanoparticles (SLN's) were stated as the first generation of lipid nanoparticles whereas the nanostructured lipid carrier (NLC's), often called the second generation of lipid nanoparticles. They are perceptible from SLN's by the composition of the solid matrix.[8]

2. Nanostructured lipid carriers

NLC's are the combination of solid lipid and liquid lipid (oil), with an average size range of 10-500 nm. NLC's contain the drug solubilized and/or melted in the liquid and solid lipid blend and dispersed in the aqueous phase containing surfactant.[6]

3. Structure and properties of nanostructured lipid carriers

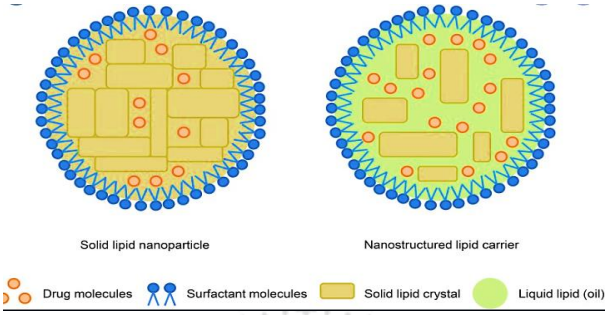


Figure No. 1: Structure of Nanostructured lipid carriers(NLC)

They have an average size range from 10-500 nm and spherical morphology. The matrix of NLC's is produced from a combination of spatially unique lipid molecules, typically a blend of solid and liquid lipid, which makes more imperfection in the network to accommodate more drugs than SLN's. Regardless of the presence of liquid lipids, the NLC's matrix is solid at room/body temperature levels. NLC's embrace blends of a solid lipid and liquid lipid and remain in the solid-state by controlling the content of liquid lipids. NLC's can more firmly immobilize drugs and prevent the particles from coalescing under the solid matrix contrasted with emulsions.[9]

The mixture NLC's comprise a long chain of liquid and lipid (oil) of a ratio 99.9:0.1 and having a short chain of solid and lipid having a proportion of 70:30. The properties are based upon the location of the drug(API) molecule that is going to be integrated. NLC's lipids can be used in higher concentrations (up to 95%).[10]

4. Types of nanostructured lipid carriers

Depending on the nature of chemical active ingredients, lipids, and concentration of surfactants, the solubility of the drug in the melted lipid, type of preparation /production, and temperature for the preparation of NLC's are classified into 3 types as shown below (Fig 2).[1]

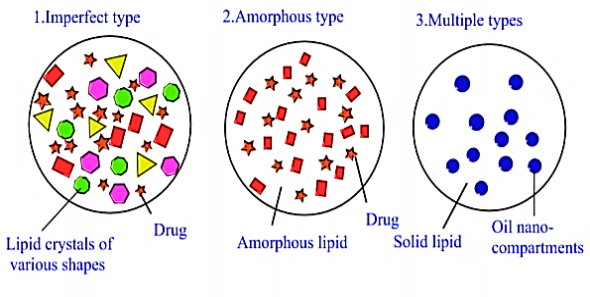


Figure No. 2: Types of NLC's [1]

Type 1: Imperfect- Highly imperfect solid matrix

It is the blend of solid lipid and liquid lipid, the imperfection in this type of NLC is due to the difference in the structure of lipids that are blended. The imperfections are because of the different chain lengths of fatty acids and the mixture of mono, di, and triacylglycerol due to which NLC's fails to form a highly ordered structure thus creating the voids (structural imperfections). This imperfection provides space for the accommodation of drug molecules(API).[11]

Type 2: Multiple oil/fat/water carriers

The active molecule has more solubility in liquid lipid, at high liquid lipid concentration, a miscibility gap between solid and liquid lipids occur during the cooling phase, which leads to phase separation, producing tiny oily nano-compartments surrounded by the solid lipid matrix.[12]

Type 3: Amorphous Matrix - Structureless solid amorphous matrix

In this type of NLC, the solid and liquid lipids are mixed in such a way that they hinder crystallization. The lipid molecule is in solid-state but in amorphous form. During shelf life, these lipids generate amorphous matrices, thus reducing API expulsion during storage time. Lipid particles are suited to incorporate lipophilic drugs.[11,12]

5. Advantages and Disadvantages of NLC's

Advantages of NLCs

- The stability of the chemically labile drugs can be enhanced through protection from the external environment (to protect the drug from biochemical degradation).
- The high entrapment efficiency of the active ingredients(both lipophilic drugs and hydrophilic drugs) hence enhances the bioavailability of low water-soluble active constituents.
- NLCs have better physical stability when compared to SLN's.
- Simple techniques of preparation and scaling up or large production.
- Enhanced dispersibility in an aqueous medium and high drug payload.
- NLC's provide controlled and sustained release of the drug. It also provides control and/or target drug release to improving the stability of pharmaceuticals.
- Small size permits site-specific delivery.
- Severe and prolonged toxicity can be reduced by the use of biodegradable lipids.[11]

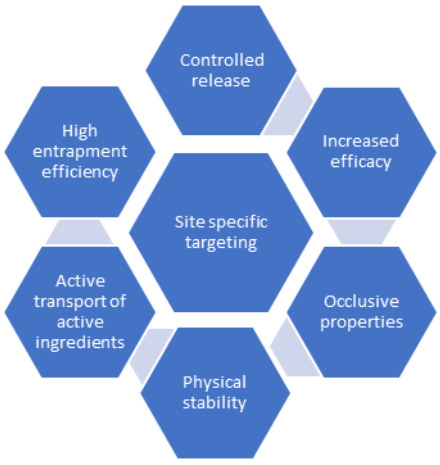


Figure No. 3: Advantages of Nanostructured lipid carriers

- Improve the ratio of benefit/risk.
- Due to their solid lipid matrices, these carriers are highly efficient systems, which are also generally identified as safe and easier to validate or have a regulatory accepted status.

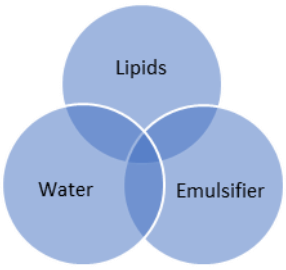
- NLC has excellent biocompatibility as most of the lipids used are biocompatible and biodegradable.
- It is a water-based method so that Organic solvents can be avoided.
- NLC's releases great and higher drug content as related to other carriers which are available in the market.
- Economic than other polymeric or surfactant-based delivery systems.[11,12]

Disadvantages of NLC's

Despite the great potential of NLC's in targeted delivery, they encounter certain limitations like:

- The concentration and nature of the matrix might result in cytotoxic effects.
- Few surfactants may cause Irritative and sensitizing action.
- In the case of protein and peptide drugs and gene delivery systems, the application and efficiency still need to be better utilized.
- Nanoparticles have a lack adequate preclinical and clinical studies in case of bone repair.[11,12]

6. Formulation of NLC's



The NLC consists of Lipids (solid lipid, liquid lipid), Emulsifier, and Aqueous medium (water).

Figure No. 4: Components of NLC's [11]

NLC comprises an unstructured solid lipid matrix made of a mixture of blended solid and liquid lipids and an aqueous phase containing a surfactant or blends of different surfactants.

Generally, solid lipids are mixed with liquid lipids in the ratio of 70:30 up to a ratio of 99.9:0.1 whereas, the surfactant content ranges from 0.5 to 5% (w/v).[13,14]

1. Lipids

❖ Solid lipids: A mixture of several chemical compounds that have a high melting point (higher than 40^{o}C). These solid lipids are well-tolerated GRAS (Generally Recognized As Safe) status, also in vivo biodegradable. Depending on high solubility, the lipids were selected for the preparation of NLC. This is achieved by dissolving the increasing amount of the ingredient in liquified solid lipids and determining the highest amount of the action that could be dissolved in each lipid.[13-15]

Example: Glyceryl tristearate/tristearin, Stearic acid, Glyceryl monostearate, Propylene glycol monostearate, Cetyl palmitate, Cholesterol, Precirol ATO 5, Emulcire, Beeswax, Carnauba wax, Precifac. etc,

❖ Liquid lipids(oils): These liquid lipids are well tolerated of GRAS (Generally Recognized As Safe) status. For the selection of liquid lipids, the trial batches should be prepared with a fixed ratio of liquid lipids to solid lipids.[13-15]

Examples: Soyabean oil, α-tocopherol/vitamin E, Cetiol V, Miglyol, Corn oil Castor oil, Oleic acid, Davana oil, Palm oil, squalene, Olive oil 9, caprylic/capric triglyceride, and propylene glycol dicaprylate/caprate.

2. Emulsifiers

It is a surfactant, which is absorbed in interfaces and lowers the interfacial tension. When a surfactant is present in small amounts, it enhances its colloidal stability by decreasing either or both of the rates of aggregation.[13-15]

Surfactant is used to stabilize the structure of lipid nanoparticles in dispersion media during the formulation. Hydrophilic surfactants are commonly used. Using two emulsifiers, with respective hydrophilic and lipophilic natures, yields better stabilization of the dispersive system. High surfactant concentration at a given temperature was believed to produce the

burst release. Moreover, the high surfactant concentration is more challenging for the application in the drug delivery system.[4-5]

The affinity of the surfactant towards the lipid differs. Depending upon the HLB value of the surfactant and the molecular weight of the surfactant molecules suitable surfactants should be selected.

a) Hydrophilic emulsifier-

Pluronic® F68(poloxamer 188), Pluronic® F127 (poloxamer 407), Tween 20,

Tween 40, Tween 80, Polyvinyl alcohol, Solutol® HS15, Trehalose, Sodium deoxycholate, Sodium glycocholate, Sodium oleate, Polyglycerol methyl glucose distearate.

b) Lipophilic emulsifier-

Myverol®18-04K, Span 20, Span 40, Span 60

c) Amphiphilic emulsifier-

Hydrogenated soy phosphatidylcholine (Lipoid S PC-3, Hydrogenated egg phosphatidylcholine (Lipoid E PC-3) Phospholipon 80 H, Phospholipon 90 H)

Egg lecithin, Soya lecithin. Gelucire® 50/13.

3. Water

The water utilized in the analysis was purified water by reverse osmosis.

Commonly used ingredients in the preparation of NLC.[15]

Table No. 1: Ingredient's used in NLC preparation [16]

Sl. No.	Ingredients	Examples	Reference
1.	Lipids		
(a)	Solid lipid	Stearic acid	Tamjidi F, Shahedi M, Varshosaz J, Nasirpour A. (2013)
		Glyceryl tristearate/tristearin)	Tamjidi F, Shahedi M, Varshosaz J, Nasirpour A. (2013)
		Glyceryl monostearate	Zhang et al. (2010), Zheng et al. (2013), Zhang (2011),
		Cetyl palmitate	Schmidt, & Müller (2005), Xia, Saupe, Müller, & Souto (2007)
(b)	Liquid lipid	Oleic acid	Kuo & Chung (2011), Yuan, Wang, Du, You, Hu, & Zeng (2007)
		Soybean oil	Chinsriwongkul et al. (2011); Zhang, Chen, Zhang, Shen, & Pan (2011)
		α-tocopherol /vitamin E	Tamjidi F, Shahedi M, Varshosaz J, Nasirpour A. (2013)
		Corn oil	Tamjidi F, Shahedi M, Varshosaz J, Nasirpour A. (2013)
		Squalene	Chen, Tsai, Huang, & Fang (2010), Fang, Fang, Liu, & Su (2008)
2.	Emulsifier	Tween 80	Han, Li, Yin, Liu, & Xu (2008)
		Sodium dodecyl sulphate (SDS)	Tamjidi F, Shahedi M, Varshosaz J, Nasirpour A. (2013)
		Poloxamer 188	Liu & Wu (2010), Liu, Liu, Wang, Zhang (2011), Tsai et al. (2012)
		Tween 20	Tamjidi F, Shahedi M, Varshosaz J, Nasirpour A. (2013)
		Sodium deoxycholate (SDC)	Tamjidi F, Shahedi M, Varshosaz J, Nasirpour A. (2013)

7. Approaches for NLC's preparation and equipment used

There are several chemical approaches have been developed for the production of nanoparticles. Many traditional, physical methods with reasonable modifications in their methodology have been developed for the controlled synthesis of nanoparticles.

The properties of NLC's are the major factor that is influenced by the techniques utilized in their production. There are several techniques by which the NLC's can be produced or formulated. These are methods that are based on different approaches as energy requirement, degree of hazard generation, ease of applicability, feasibility, and higher yield potential, etc. such as

- ❖ High energy approach
- ❖ Low energy approach
- ❖ Approach with organic solvents

In general, the formulation of NLC's involves nano emulsification of a lipophilic phase composed of a mixture of Liquid lipid and Solid lipid. The below techniques are included under the above-mentioned approaches.[17]

1. High-pressure homogenization (HPH)

The most common and popular traditional strategies for the preparation of drug-loaded NLC's are high-pressure homogenization. Liquid lipids may be in the form of molecules or oil clusters injected into the NLC solid matrix and form homogeneous particles based on the number of liquid lipids applied to the NLC. The lipid content is usually in the range of 5-10%. One may prevent the use of an organic solvent in high-pressure homogenization to make it an eco-friendly solution process. Light pressure (from 100 to 200 bars) and high pressure (100 to 2000 bars) are used in this process. High shear stress on the lipid process reduces the size of the particle to a set of submicron or nano homogenization may be performed either at elevated temperature (hot homogenization) or below room temperature (cold homogenization).

Figure No. 5: Homogenizer [11]

Types of homogenizer available in the market:

a) Jet-stream homogenizers

b) Piston-gap homogenizers

1) Hot homogenization technique

In this technique, a high shear system in the aqueous surfactant solution with the same temperature disperses the substance along with melted lipids under continuous stirring. Using a high-pressure piston gap homogenizer (e.g. APV Gaulin LAB 40) at a pressure range from 100 to 1500 bar, the coarse pre-emulsion obtained is homogenized. The obtained nano-emulsion is cooled at room temperature, where the lipid recrystallizes and allows the formation of nanoparticles. This approach can be easily extended to lipophilic and insoluble drugs, but it is not completely sufficient for hydrophilic drugs. During homogenization, the aqueous step of the hydrophilic drug partitions results in poor trapping ability. The temperature of homogenization has to be carefully chosen because the loss of hydrophilic drugs to the water phase can be too high.[17,18]

2) Cold homogenization technique

Cold homogenization is carried out with a drug containing stable lipids. To overcome the problems of the hot homogenization technique, such as temperature-controlled accelerated drug payload degradation, partitioning, and thus drug loss during homogenization into the aqueous process. The first step remains the same with both cold and hot homogenization processes. In the subsequent step, the drug-containing melt is rapidly cooled using ice or liquid nitrogen to distribute the drug into the lipid matrix, to improve the lipid's brittleness, and to ease the milling process. The thermal sensitivity of the sample is minimized by cold homogenization. For hydrophilic drugs, this approach is far more appropriate. If the solubility

of the hydrophilic substance in the lipid is too low, it is possible to use surfactants to solubilize the substance. The microparticles collected (approx. 50 to 100 mm) are spread after milling (e.g. in a mortar mill) in a cold aqueous surfactant solution. At room temperature or below (0^0C), this lipid suspension is homogenized.[18]

2. High shear homogenization and/or ultrasonication

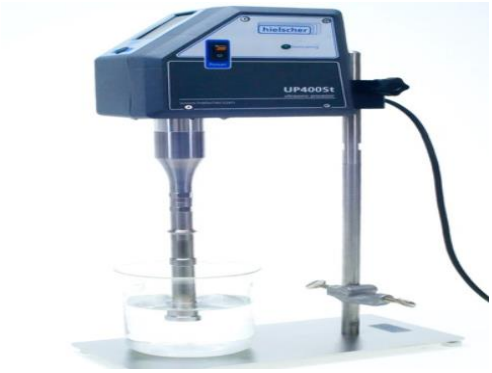


Figure No. 6: Probe Type Ultrasonic Homogenizer

High shear homogenization and ultrasonics are dispersion methods that do not use organic solvents, surfactants, or contaminants in significant amounts. Under high shear homogenization or ultrasonication, melting lipid is applied and dispersed in an aqueous surfactant solution. Then it cools down the emulsion to room temperature. While for high shear homogenization, a homogenizer such as a rotor-stator homogenizer is needed, ultrasonics can be done using a probe. The consistency of the dispersion of lipid nanoparticles provided by these techniques is also influenced by the existence of microparticles, resulting in physical storage instability. The lipid concentration is low (< 1 percent) and the concentration of surfactants is moderately high. The other critical concern with ultrasonics is metal contamination.[18,19]

3. Solvent emulsification-evaporation or diffusion

In an aqueous environment, the Coacervation and development of lipid nanoparticles result in the addition of water to the resulting organic solution under mechanical agitation. The organic solution is then retained under low pressure 40-60 m bar until the organic solvent is fully evaporated. The concentration of particles obtained using this method (up to 15 percent) is smaller than that obtained with high-pressure homogenization.[18] This technique is ideal for the preparation of NLC's containing heat-sensitive products because the removal of

organic solvent and precipitation of drug-loaded NLC's uses low pressure instead of elevated temperature.[19]

4. Microemulsion

The development of lipid nanoparticles by this method is dependent on the precipitation by microemulsion breakage of fine lipid droplets. The development of lipid nanoparticles happens by dispersing the warm o/w microemulsion under mechanical stirring in a cold aqueous solution. An aqueous phase is applied to the lipid melt under stirring, comprising the co-surfactant(s) and surfactant heated to the same temperature. This hot microemulsion is then spread under mechanical stirring in cold water (2–3°C), thereby retaining a limited particle size due to precipitation. Typical hot microemulsion to cold water volume ratios is in the range of 1:25 to 1:50. Drawbacks of this approach are comparatively high water content, problems in extracting the excess water and using surfactant and co-surfactants at high concentrations.[18,19]

5. Melt Emulsification

The solid and liquid lipids are heated and combined in this process, to form an organic phase, then an active ingredient is added. A water phase containing the surfactant is applied to the organic phase and mixed to create a coarse emulsion. To form the NLC's, high-pressure homogenization is subsequently added. This is useful because, at the initial stage, there is no organic solvent trace, no burst release, and dispersions of high lipid concentration. The drawbacks to this strategy are that it is not completely acceptable for commercial processing and there are residual organic solvents.[20]

6. Supercritical fluid (SCF) technology

The lipids are melted and SCF (preferably carbon dioxide) solubilization is carried out. Depending on the solubility of compounds in the SCF, this constitutes either gas-soaked suspension or solution. It is then atomized and sprayed into a chamber through a nozzle. Decompression and evaporation of gas occur at this stage, creating solid NLC's.[21]

7. Solvent evaporation

Lipids dissolved in an organic solvent are emulsified in a water bath under mechanical stirring. A lipid nanoparticle dispersion is produced by the precipitation of the lipid content in

the aqueous medium after the solvent is evaporated. Particles with average diameters of 30–100 nm can be obtained depending on the solid lipid and surfactants used. The most significant value of this procedure is the elimination of heat during this method. [11, 17, 21-25]

8. Solvent injection (or solvent displacement) technique

The fundamental concept of the solvent injection process is similar to the solvent diffusion process. A technique in which a solvent (DMSO, ethanol) distributes very easily in the water. Firstly, the lipid is dissolved in the solvent and then quickly injected through an injection needle into an aqueous solution of surfactants. In the bath, the solvent migrates quickly, and lipid ions in the aqueous solution precipitate. Particle size depends on the velocity of the distribution processes. In smaller particles, higher velocity effects. The system provides benefits without technically advanced machinery (e.g. high-pressure homogenizer), such as low temperatures, low shear stress, simple handling, and rapid manufacturing operation. The principal drawback is the use of organic solvents.[11, 17, 21-25]

9. Spray-drying and lyophilization

To achieve the long-term stability of a product containing hydrolyzable drugs or a suitable product for oral administration, spray-drying and lyophilization are necessary. However, due to the high temperature and shear forces, spray-drying will destabilize the system as an alternative method to lyophilization.[18] In the preparation of NLCs, the spray drying method is most widely used for high melting point lipid phases and/or as an alternative solution to lyophilization techniques.[19]

10. Phase inversion

In this method of phase inversion, all the NLC elements i.e., the drugs, lipids that are solid and liquid, surfactants, co-surfactants, and water are blended with constant stirring. Then this mixture is subjected to three subsequent heating and cooling cycles. Besides, by rapid dilution with cold water (at 0^0C), phase inversion occurs. Often this approach is appropriate for thermosensitive and bioactive drugs.[11, 21-25]

8. Evaluation and characterization of NLC's[22]

1. Polydispersity Index and Particle Size

2. Zeta-Potential (ZP)

3. Entrapment Efficiency and Drug Loading

4. Morphological Study (Scanning Electron Microscopy[SEM])

5. Differential Scanning Calorimetry (DSC)

6. X-ray Diffraction (XRD)

7. In-vitro Drug Release

9. Drug delivery and Applications of NLC's[6,22,25]

NLC's have a relatively wide variety of applications and have been shown to control the penetration of many active ingredients onto the skin, food and drug delivery, cosmetics, and other applications.

Therapeutics applications

Application for oral drug delivery

Oral drug administration is a popular and favored method, due to strong patient compliance, non-invasiveness, and clinical success, but low water-solubility of drugs restricts measures for their absorption which further affects the bioavailability. For this reason, lipid-based delivery systems have shown several advancements in recent decades. NLC is such a method that is used to tackle the problem of solubility which enhances bioavailability by incorporating the low water-soluble or lipophilic drug.

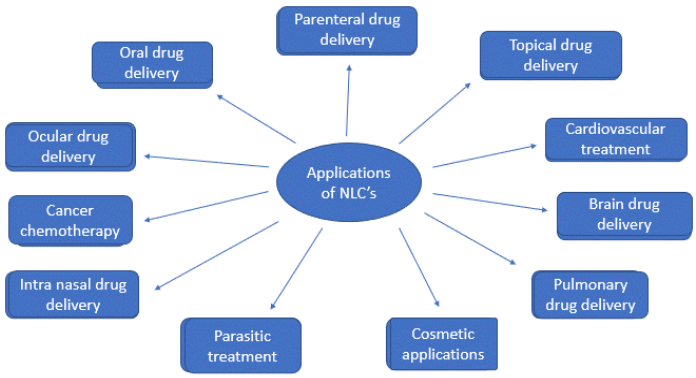


Figure No. 7: Applications of Nanostructured lipid carriers [6,22,23,25]

Application for topical drug delivery

The topical route was greatly utilized for the drug delivery to the dermal section by NLC's to increase the local bioavailability of the drug onto the skin and enhance the dermal delivery of the drug. NLC's have special properties that can enhance the apparent solubility of the entrapped drug to promote drug permeation and can from a high concentration gradient onto the skin. The NLCs tightly adhere due to their nano-sized particles to the skin surface and release the drug in a controlled way therefore used for topical application in different drug types for penetration enhancement along with sustained-release. [6,22,23,25]

Application for parenteral drug delivery

For the past two decades, nano-drug delivery mechanisms such as nano-micelles, nano-emulsions, and nanoparticles have demonstrated tremendous promise for enhanced parenteral delivery of hydrophobic agents. Due to improved properties such as ease of processing, high drug packing, increased versatility in modulating drug release profile, and along with these, their aqueous nature and biocompatibility of excipients have allowed NLC to be considered as an alternative to liposomes and emulsions for parenteral delivery of the lipophilic drug.[23,25]

Application for pulmonary drug delivery

Lipid nanoparticles have been used as a delivery mechanism for lung targeting. These particulate systems have shown positive outcomes, such as improving the bioavailability of drugs compared to traditional formulations. Lipid nanoparticles have been considered for pulmonary delivery with better drug delivery, including NLC's Drug loaded with NLC for pulmonary delivery may result in high local concentration and may decrease in systemic adverse effects. For systemic delivery, NLC's can achieve greater bioavailability.[25]

Applications for ocular drug delivery

There are several drawbacks of ocular drug delivery and because of the complex physiological and anatomical characteristics of the eye, it remains daunting. To overcome these barriers and improve the ocular tissue bioavailability novel drug delivery system such as lipid nanoparticles are utilized. NLC's used for the ocular drug delivery system are capable of passing the ocular barrier of the blood, achieving sustained and controlled drug release,

protecting the drug from lacrimal enzymes, and prolonging drug deposition and eye residence time. [6,22,25]

Other applications

Chemotherapy

The latest studies have shown that NLC's have not only increased the effectiveness and safety of multiple cytotoxic drugs but have decreased side effects. For example, the albumin-paclitaxel nanoparticles were created with anti-cancer drugs.

Gene transfer applications

The distribution of bioactive and their release activity to various sites directly dependent on particle size. The effectiveness of gene therapy (with the conversion of DNA and RNA) relies on new methods of bioactive transmission. More than 400 clinical trials in gene therapy were published during 1980. Because of the reduced ability of naked DNA transmission to cells due to the potential for enzymatic degradation, delivery vectors are used in gene transfer. NLC's can be used effectively as a modern nonviral gene transfer vector that provides a promising approach to gene therapy. [6,22]

Cosmetic applications

One of the excellent vehicles for cosmetic and dermatological use is LNPs, such as NLC's. They have some special qualities that make them extraordinary carriers for cosmetic applications, such as protection of sensitive components from chemical degradation and enhancing the skin's water content. The use of NLC's as carriers has been studied for sunscreens, anti-acne, and anti-aging agents. Because of the high behavioral control of NLC's on the skin, they have UV-blocking and skin hydration behavior, penetrating active substances. Since these formulations mimic the composition of the skin, there is no damage and toxic effect when topically applied. [23]

Food applications

NLCs in the pharmaceutical field are commonly used due to their good stability and high loading capacity. It was reported that NLC's was used as a dietary supplement carrier in the food industry for the preparation of capsules and beverages.

For example, NLC's incorporated with coenzyme Q10 for food applications have been developed to increase physicochemical stability and bioavailability, Beta carotene, lutein, and lycopene are some examples of active compounds that are incorporated in NLC's for food applications. [6,22,25]

10. Commercially available products as lipid nanoparticle in market

Today, the greater part of economically available products from nanostructured lipid carriers are cosmetic products, Some of the products with their uses are listed in below Table 2.

Table No. 2: Commercially available NLCs products [26]

Product	Uses
Intensive Serum Nanorepair Q10	Antiwrinkle serum fights the sign of aging
Cutanova Cream Nanovital Q10	Antiaging treatment with UV-protection, protective,
Iope Supervital Extra Moist Eye Cream	Removes dullness, eye wrinkles, and poor elasticity
Surmer Masque Creme Nano-Hydratant	Restricting dry and dehydrated skin, reduction of fine lines and wrinkles
Cutanova-Cream Nanorepair Q10	Smoothing of fine lines promotes restructuring of skin & aging
Olivenol Anti Falten Pflegekontrat	Skin tightening and Antiwrinkle
Regenerations Cream Intesive Ampoules	Smoothes wrinkles and Promotes cell regeneration

11. Perspective for future

NLC's are lipid-based structures that include solid lipids and liquid lipids, resulting in strongly hydrophobic drug coverage. NLC allows the protection of the drug and sustained drug release activity. Their formulation contains surfactants, biocompatible lipids, and is endorsed by the FDA for oral administration. Methods for NLC's formulation are simple and can be prepared without an organic solvent. Scaling up the process into a broad batch size is simple. In the pharmaceutical and cosmetic sector, NLC's formulations have undergone continuous improvement. In the implementation of the NLC's, these amendments played a significant role. The examples mentioned in this review through the oral route demonstrate the potential of these NLC's as pharmaceutical carriers. Taking into account the growing amount of patented NLC- based formulations and the increasing evidence of available

research papers, it can be predicted that the number of clinical trials related to NLC will be expanded in the future.

12. CONCLUSION:

In summary, It has been discovered that there is a tremendous potential for a nano-based delivery system to improve the bioavailability of poorly soluble lipophilic drugs, and even to target the site of action. As the new generation, the smart NLC has much more versatility in the drug loading, drug release modulation, and increased efficiency in the development of the final dosage type such as pills, creams, capsules, injectables. The use of NLC's to establish alternative routes and to treat other diseases should continue to be expanded. It can be inferred from all the knowledge obtained from recent literature that NLC is an outstanding advanced drug carrier system for the treatment of diseases.

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