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CURRENT DEVELOPMENT IN THE NANOSTRUCTURED LIPID CARRIERS (NLCs)

Anchal Sharma, Amit Sharma*, Davinder Singh and Damandeep Kaur

Rayat-Bahra Institute of Pharmacy, Bohan, Hoshiarpur, Punjab, India, 146001.

***Corresponding Author: Amit Sharma**

Rayat-Bahra Institute of Pharmacy, Bohan, Hoshiarpur, Punjab, India, 146001.

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ABSTRACT

The drug delivery system known as nanostructured lipid carriers (NLCs) is a colloidal system with a core composed of a lipid mixture comprising both liquid and solid lipids. In contrast to polymeric or metallic nanoparticles, this lipid-based nanosystem is presented as a biocompatible, non-toxic, and safe nano-drug delivery method. Because NLC is safer, more stable, and has a higher drug loading capacity than other lipid-based nanocarriers, researchers are interested in using it to create drug carriers that are both secure and efficient. Their capacity to boost drug permeability and solubility while encasing the molecule in a lipidic shell renders them the perfect vehicle for delivering drugs via challenging delivery pathways. The application of different chemicals and surface modification of NLC lead to enhanced residence time and drug targeting. Because of these characteristics, NLCs have the potential to treat a wide range of illnesses, including diabetes, cancer, infections, neurological diseases, hypertension, and pain management. This study focuses on the latest advancements being made to employ these nanocarriers to deliver medicines and genes via various pathways. Here, we also go over the basic information, composition, kinds of NLC, and frequently used processes for producing lipid-based nanocarriers.

KEYWORDS: Nanostructured lipid carriers, Solid lipid nano particles, Bioavailability.

INTRODUCTION

NANO-STRUCTURED LIPID CARRIERS

One kind of lipid-based drug delivery technology called nanostructured lipid carriers (NLCs) which is used to encapsulate and carry out pharmacological substances. Their structure is more stable and flexible than that of traditional lipid nanoparticles because they are made of a solid lipid matrix with liquid lipids added. Enhanced bioavailability, controlled release profiles, targeted administration of therapeutic agents, and increased drug encapsulation efficiency are all provided by NLCs. Numerous sectors, including the culinary, cosmetic, and pharmaceutical ones, use them. The alteration of nanostructured led to the creation of nano-structured lipid carriers (NLCs), which retain the properties of SLN, boost drug stability, and stop drug leakage. NLCs were created in order to get around the drawbacks of the medications that are absorbed by the body by various pathways, including low bioavailability, first pass metabolism, and poor solvency. Delivery of nano-based systems can occur via oral, topical, transdermal, ocular, or parenteral routes. NLCs were created by blending solid and liquid lipids that are spatially incompatible. Even at room temperature, it remains solid. NLCs with drug therapy have better bioavailability and more solubility than NLCs with traditional carriers.[1] Drug delivery devices known as nanostructured lipid carriers (NLCs) use a core matrix made up of both liquid and solid lipids. It was demonstrated that NLCs offer a number of benefits over traditional carriers for medication therapy, such as enhanced solubility, greater permeability and bioavailability, decreased side effects, longer half-lives, and tissue-targeted delivery. In recent years, there has been a growing interest in NLCs. Since parenteral injection and topical distribution are the most popular methods for studying NLCs, particular attention is given to them. Pertinent concerns, such as those pertaining to cosmetic and pharmaceutical uses, for the launch of NLCs.[2] The two main categories of these systems are lipid nanoparticles and polymeric nanoparticles.[3] Polymeric nanosystems are solid colloidal particles made of natural, semi-synthetic, or synthetic polymers that are biodegradable or non-biodegradable macromolecular materials. The cytotoxicity of polymers and the absence of appropriate large-scale production methods are the disadvantages of polymeric nanoparticles. Lipid nanoparticles carry a far lower toxicity risk than polymeric nanoparticles because of the natural and biological origins of the constituent elements. Oil-in-water nanoemulsions are created by substituting solid lipid for liquid oil, and this process yields lipid nanoparticles with a solid matrix, or solid lipid nanoparticles, or SLNs. In early 1990, the first generation of SLNs was created.[4]

Nanotechnology has essentially impacted every technical discipline in the last 20 years, including pharmaceutics. According to industry estimates, formulation stability and solubility problems account for about 40% of the failures of lipophilic drug candidates. These problems have been resolved by a number of cutting-edge and innovative lipophilic drug delivery methods. Physiological lipids with low acute and chronic toxicity are typically used to make lipid nanoparticles. These lipids are also biocompatible and biodegradable.[5] NLCs are a second generation of lipid-based nanocarriers that feature an unstructured matrix because their constituents have various moieties. They are made of a mixture of liquid and solid lipids. NLCs were created to get around the restrictions of SLNs. Because of their defective crystal structure, NLCs offer a larger capacity for drug loading and can prevent drug expulsion by preventing lipid crystallisation throughout the manufacturing and storage phases. The formulation of NLCs contains liquid lipids, which minimise the ejection of loaded medication both during and after formulation. Comparing NLCs to SLNs, they can exhibit more controlled release profiles and enhance drug solubility in lipid matrices. Despite having a lower melting point than SLNs, NLCs are nonetheless solid at body temperature. Their crystalline behaviours are imperfect and unstructured, which allows for greater space for drug breakdown and payload in the liquid portion of the NLCs. In this sense, NLCs have a higher loading capacity than SLNs. Another benefit of NLCs is that they can help with dosage form preparation for parenteral administration and the separation of nanoparticles from the rest of the medium. Previous studies have also confirmed that NLCs are less susceptible to gelation than SLNs during the preparation and storage phase.[6]

MATERIALS AND METHODS

Structure and properties of Nano-structured lipid carriers

Their spherical form and average size range from 10 to 500 nm. In order to accommodate more pharmaceuticals than SLNs, the matrix of NLCs is created by combining a variety of spatially distinct lipid molecules, usually a mixture of solid and liquid lipid. This results in increased network imperfection. At room temperature or body temperature, the NLC's matrix is solid regardless of the presence of liquid lipids. NLCs accept mixtures of liquid and solid lipids and maintain their solid state by adjusting the liquid lipid content. Compared to emulsions, NLCs are able to immobilise medicines more firmly and keep the particles from aggregating beneath the solid matrix.[7]

The mixture NLCs consist of a short chain of solid and lipid with a proportion of 70:30 and a long chain of liquid and lipid (oil) with a ratio of 99.9:0.1. The location of the medication (API) molecule that will be incorporated determines the characteristics. Lipids from NLC can be utilised at higher (up to 95%) concentrations.[8]

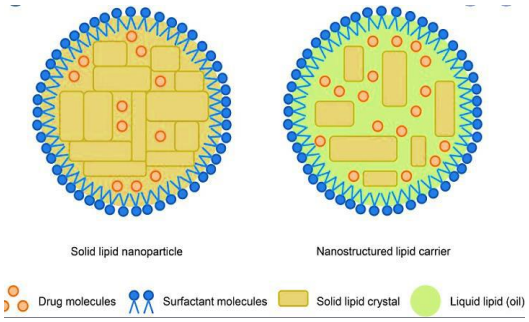

Figure 1.1: Structure of NLCs.

Advantages of NLCs

- Enhanced Drug Loading Capacity: NLCs have a greater drug loading efficiency because they can encapsulate more drug molecules than conventional lipid nanoparticles.
- Improved Stability: NLCs' unique structure, which combines liquid and solid lipids, offers improved stability against drug leakage and degradation during transportation and storage.
- Controlled Release: NLCs make it possible for medications to be released gradually and under control, resulting in longer-lasting therapeutic effects and fewer dose intervals.
- Enhanced Bioavailability: By making poorly water-soluble medications easier to absorb and distribute throughout the body, NLCs increase the therapeutic efficacy of these medications.
- Targeted Delivery: NLCs can be designed to specifically target one or more tissues or cells, lowering systemic toxicity and minimising off-target effects while increasing therapeutic efficacy.
- Versatility: NLCs are appropriate for a broad range of therapeutic applications because they are easily functionalized and changed to integrate different kinds of medicines, imaging agents, or targeting ligands.
- Scalability: NLCs are appropriate for large-scale manufacture and commercialization because they can be made using scalable manufacturing procedures.

Disadvantages of NLCs

- Cytotoxic effects as a result of matrix and natural concentrations.

- Some surfactants have an irritating and sensitising effect. research on these nanocarriers for potential use in bone mending.

Historical Review from SLN to NLC

The nature of the solid particle matrix distinguishes solid lipid nanoparticles (SLN) from nanostructured lipid carriers (NLC). As an alternative carrier system to emulsions, liposomes, and other polymeric nanoparticles, SLNs were created.[9]

With the exception of the liquid lipid (oil) portion of the emulsion being replaced with a solid lipid with particles ranging in size from 50 nm to 1000 nm, SLN are identical to an oil-in-water emulsion. A solid lipid or a combination of solid lipids, the lipid matrix of which is solid at room temperature and body temperature, is substituted for the liquid lipid (oil) in an o/w emulsion to create SLN. NLC was created to reduce or eliminate some issues that arise from SLN drug loading, such as gelation issues and drug leakage during storage. Higher lipid concentration NLC may be made, which makes the end product's production easier.[10]

NLC is made up of a composite of several lipids; the liquid and solid lipids are combined in varying proportions.[11] Because of their liquid components, NLC exhibit a greater loading capacity and a regulated, quicker release profile when compared to SLN, earning them the distinction of being the more intelligent, new generation of lipid nanoparticles.[12]

Because of the solid lipid matrix that crystallises and promotes drug ejection, SLN has an almost flawless crystallised structure with identically shaped molecules that are comparable to brick and mortar and have a restricted loading capacity for active chemicals.[13] Nonetheless, the NLC's lipid matrix has flaws akin to those found in a structure made of wildly disparately shaped stones; as a result, the loading capacity for active chemicals increases.[14]

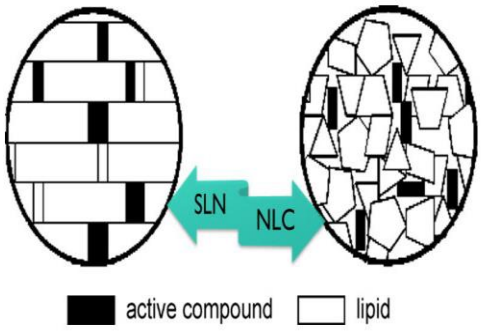

Figure 1.2: Structure of SLN to NLC.

Types of NLC

NLC is a combination of some incompatible liquid lipids and solid lipids. Even at room temperature, it stays solid. Its benefits include regulated drug release from the carrier, biocompatible lipids, large-scale production viability with current technology, prevention of first pass metabolism, and drug protection against biochemical degradation. Lipids can be employed in NLC at larger ratios (up to 95%).

Based on the nanostructure, content, and ratios of solid and liquid lipids, NLC has been divided into three groups
1. Type I (The imperfect type)
2. Type II (The Multiple O/F/W type)
3. Type III (The amorphous type)

Type I (The imperfect type): Liquid and solid lipids, or oils, are combined in this process. Liquid lipids have a higher drug solubility than solid lipids. The liquid lipid particles (nanoemulsions) are cooled to room temperature during the manufacturing process in order for them to crystallise and become solid particles. A miscibility gap between the two lipids—the solid lipid and the oil—occurs during the chilling phase at high oil concentrations, causing phase separation and the precipitation of tiny, oily nano compartments.[15]

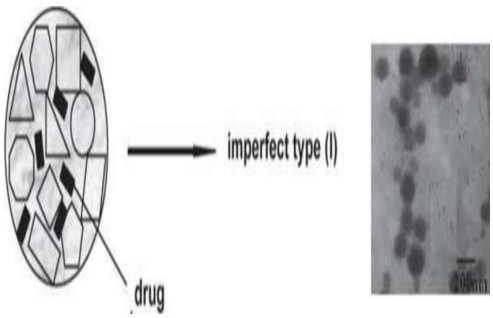

Figure 2.3: Structure of Imperfect type.

Type II (The Multiple O/F/W type): Type II drugs can be accommodated in the solid but at higher solubility in the liquid lipids or oily components in this multiple oil/fat/water combination. The lipid matrix's oily sections are where the medication dissolves. By use of lipid-lipid precipitation, these NLC were produced.

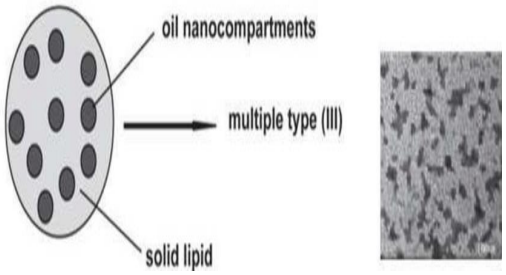

Figure 2.4: Structure of O/F/W type.

Type III (The amorphous type): This kind of NLC is made by carefully combining particular kinds of liquid and solid lipids (such isopropylmyristate). Lipids are combined in this way to avoid crystallisation. In its amorphous condition, the lipid matrix is solid. Drug ejection caused by crystallisation is prevented when there is no crystallisation. Water-soluble medications were coupled with a lipid to create a water-insoluble lipidic conjugate in an additional lipid matrix variety. To create a lipid drug conjugate (LDC) nanoparticle, the lipid conjugate powder was melted and treated similarly to the other varieties. Covalent bonding or salt production are the methods used in conjugation.[16]

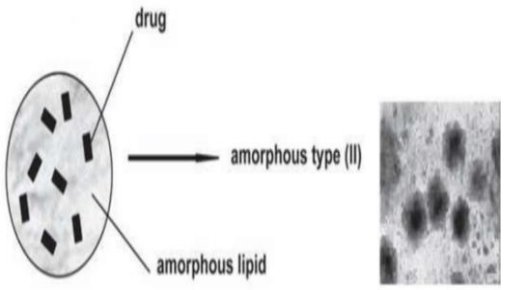

Figure 2.5: Structure of Amorphous type.

Composition of NLC

The following are some of the components that are utilised in the preparation of NLC.

Solid Lipids

Solid lipids are made of compounds with high melting points, or those that are higher than 40 °C. It need to be secure and biodegradable. Triglycerides are made of several solid lipids, such as trimyristin, tristearin, and tricaprin. Types of hard fats: cetyl alcohol, stearic acid, and glyceryl monostearate.[17]

Liquid Lipids

Digestible oils derived from natural sources are the liquid lipids utilised. It must to be accepted for usage by humans and have a well-tolerated GRAS rating. Oils such as medium chain triglycerides, oleic acid, mustard oil, codliver oil, and castor oil are employed, both natural and manufactured.[17]

Aqueous Surfactant

Emulsifying agents, commonly known as surfactants, reduce the interfacial tension that separates two immiscible liquids or components. The majority of surfactants are hydrophilic. Emulsifiers that are either lipophilic or ampiphillic are utilised to create NLCs. For instance, Pluronic F-68 and Tween-80.[18]

Excipients used in NLCs

Lipids

Lipids that are both solid and liquid make up the inner cores. Solid lipids commonly utilised for NLCs included glyceryl behenate, glyceryl palmitostearate, fatty acids, triglycerides, steroids, and waxes. These lipids are in the solid state at normal temperature. At elevated temperatures, the lipids dissolve. Natural sources of digestible oils were utilised in NLC. One component of liquid lipids is called Miglyol 812, a medium chain triglyceride (MCT) with a structure resembling that of Compritol®.[19] Additional ingredients include paraffin oil, isopropyl myristate, propylene glycol dicaprylocaprate, 2-octyl dodecanol, and squalene. Topical administration also made use of penetration enhancers such as oleic acid, linoleic acid, and decanoic acid. A - For the nanoemulsions, tocopherol and other protocols were utilised. Tocols are highly effective oils because of their stability and strong solubility in

lipophilic medicines. Plant-based natural oils are used to make the widely used NLCs today.[20]

Liquids Lipids

Natural sources of digestible oils are the most commonly utilised liquid lipids for NLCs. The well-known liquid lipids are MCT and oleic acid. Liquid lipids, such as food oils like sunflower and soy bean oil, can be utilised to create NLCs. One prevalent ingredient in natural edible oils is oleic acid.[21] Vegetable oils can be hydrolyzed to produce oleic acid. Low viscosity oleic acid was employed as an emulsifier in neutraceutical formulations. MCT, which is food graded, is obtained via fractionation and esterification processes.[22] MCT has been approved by the USFDA as safe and having good stability against oxidation and emulsifying agents. The free fatty acids that are produced by the breakdown of MCT have an impact on food odour. These oils are used as antioxidants to shield food from oxidation; some of them contain γ-tocopherol, which is often found in maize oil.[23] In addition, they are more affordable when compared to MCT and oleic acid. They cannot be used to encapsulate several hydrophobic food actives because of their higher consistency and degree of unsaturation. Soybean oil demonstrated poor encapsulation efficacy when compared to MCT and oleic acid, for instance, paraffin oil.[24]

Solid Lipids

Stearic acid, glyceryl monostearate (GMS), glyceryl palmitostearate, and glyceryl behenate are the most commonly used in the production of NLC. They are particularly effective transporters of food-active and surface-active compounds.[25]

Stearic acid is an endogenous long-chain saturated fatty acid that is an essential component of both vegetable and animal lipids and a notable component of hydrogenated fats. The biocompatibility of stearic acid with human tissues and bodily fluids has been taken into consideration.[26] Stearic acid has superior biocompatibility and moderately lower toxicity when compared to its synthesised competitors. GMS, which contains at least 40% of monoacylglycerol saturated fatty acids and is non-poisonous and non-irritating, is widely used in the nutraceutical industry.[27] GMS functions as a non-ionic plasticizer and emulsifying agent. Glyceryl palmitostearate, which has shown potential sustained release patterns, contains mono-, di-, and triacylglycerols of palmitate together with stearic unsaturated fats. Glyceryl behenate contains segments of behenic acid that are accessible as mono-, di-, and triacylglycerols. The glyceryl behenate solid lipids demonstrate a high entrapment efficiency, and the many flaws in the crystalline cross-section indicate potential stability.[28]

Emulsifiers

Emulsifiers have been used extensively to stabilise lipid dispersions. Polysorbates (Tween) and Pluronic F68 (poloxamer 188) were found to be the most often used hydrophilic emulsifiers.[29] Lipophilic emulsifiers like lecithin and Span 80 are commonly used in the production of NLCs.[30] The combination of more effectively employed emulsifiers can stop the particle aggregation. Polyethylene glycol (PEG) in the nanoparticle shell delays the absorption of medicines via the reticuloendothelial framework and extends their half-life. Preservatives may cause lipid dispersions to lose their physical stability.[31]

UV blockers

UV blockers are used to shield skin from UV rays from the sun and reduce the chance of developing skin cancer.[32] Some sunscreen creams, including avobenzone, absorb UV-A rays due to the presence of organic chemical compounds.[33,34]

Aqueous medium

Reverse osmosis was employed to purify the water for use in the NLCs.[35,36]

Preparation techniques of NLCs

There are several methods for preparing NLC, one of which is high pressure homogenization. The techniques for evaporating and diffusing solvent emulsification include high shear homogenization, ultra-sonication, micro-emulsion, double-emulsion, solvent injection, and so on. While there are several conventional methods for producing NLC, high pressure homogenization is the most widely employed technique due to its capacity for large-scale production.

1. High pressure homogenization

In terms of commercial NLC production, this is a stable and effective technique. Environmentally friendly preparations can be made by eliminating the need for organic solvents due to the high pressures used in the homogenization process. Besides, high-pressure homogenization is a very easy-to-scale-up method. It is also used to make cosmetics and pharmaceuticals for topical application. Heat is the driving force behind hot homogenization, whereas cold is the driving force behind cold homogenization. The active ingredient is dissolved in molten lipid in both processes prior to high pressure homogenization. A high pressure fluid (100–2000 bar) passes through the homogenizer's tiny gap.[37]

2. Hot homogenization technique

This approach involves homogenization at a high temperature. At a temperature higher than 5–10 degrees Celsius above their melting point, the solid lipids are melted. Dispersion is produced by mixing the medication to be encapsulated with liquid fat. Then, this mixture is distributed in an aqueous surfactant solution that has been heated to the same temperature using a high shear mixing apparatus. After that, a pre-emulsion is produced. The resulting pre-emulsion is injected into a high-pressure homogenizer at a controlled temperature. At 500–1500 bar, homogenization typically requires three to five rounds. Nanoparticles are produced when the lipid

recrystallizes in the cooling nanoemulsions. Should high temperatures be maintained during the process, heat-sensitive components could be deteriorated. Since surfactants have a cloud point below 85°C, a decrease in their ability to emulsify due to high temperatures is another potential problem. This could lead to the instability of nano carriers.[38]

3. Cold homogenization technique

Using liquid nitrogen or dry ice, a lipid melt containing an active agent is quickly frozen to solidify. The lipid melt is then ground and milled, dispersed in a cold surfactant phase, and homogenised at room temperature. This technique is known as cold homogenization. A high pressure of five to ten cycles at 1500 bar is typically used in cold homogenization. This method minimises the exposure of drugs to temperature and works especially well with thermolabile medications. This method also has the benefits of constant drug dispersion inside the lipid and enhanced drug entrapment efficiency. It does, however, produce unevenly shaped nanoparticles.[39]

4. Solvent-emulsification evaporation method

In the solvent-emulsification evaporation procedure, the drug and lipids (solid lipid + liquid lipid) are dissolved in a water immiscible organic solvent (cyclohexane, chloroform). An o/w emulsion is produced by dispersing the resultant combination in an aqueous emulsifier solution. A lower pressure is employed during evaporation to extract the solvent from the emulsion. Nanoparticles scatter in the aqueous phase as a result of this evaporation (via lipid precipitation in the aqueous medium). This method has one disadvantage: it needs the use of an organic solvent, but it does not cause any heat stress. The solid lipid and surfactant used will determine the particle size, which can vary from 30 to 100nm.[40]

5. Solvent-emulsification diffusion method

In this method, both the water and the solvent are saturated to preserve the initial thermodynamic equilibrium. After that, a solvent saturated with water is used to dissolve the drug and the lipids. To make an o/w emulsion, lipids and medication are emulsified in a solvent-saturated aqueous emulsifier solution using a homogenizer. The organic solvent diffuses from the emulsion droplets to the continuous phase during dilution with excess water (ratio: 1:5–1:10), causing lipid nanoparticles to precipitate. The solvent can then be eliminated by lyophilization or ultrafiltration. Solvent diffusion has advanced. Most of the solvents that are used have better safety profiles than volatile solvents.

6. Micro emulsion method

The liquid lipid is added after the solid lipid has melted, and the drug is then dissolved in the resulting combination. One by one, the emulsifier, co-emulsifier, and water mixtures are heated to the same temperature. The right ratios are used to mix the aqueous and lipid phases. Then, an oil in water hot micro emulsion that is thermodynamically stable is produced by gently churning it. The micro emulsion droplet size and the temperature difference between the ice water and the micro emulsion control the size of the nanoparticles. It is possible to prevent particle aggregation by quickly cooling and solidifying. Subsequently, smaller particles are generated. This procedure produced NLC dispersions with a high percentage of particles in the micron range. As a result, the amount of medication, the percentage of lipids, and the stirring period were adjusted to reach the required size and entrapment efficiency. Commercialising the technology is straightforward as it doesn't require any additional equipment or energy to generate NLC.

7. Double emulsion technique

This process is mostly used to make lipid nanoparticles that contain hydrophilic medications. This strategy solves the issue of the water soluble moiety separation in the aqueous phase from the oily phase, as demonstrated by the micro emulsion method. First, the drug is dissolved in an aqueous solvent (inner aqueous phase) to create a primary emulsion (w/o). Next, the drug is dispersed in a lipid phase (molten solid lipid + liquid lipid + lipophilic surfactant + lipophilic active part). The temperature of the aqueous and lipid phases is maintained at the same level. During solvent evaporation, the stabiliser stops medication loss to the external phase. To make a double emulsion (w/o/w), the primary emulsion is combined with a significant amount of surfactant aqueous solution and sonicated. After that, lipid nanoparticles are refined by solvent evaporation or ultrafiltration.[40]

8. Solvent injection technique

This is a workable new way to make lipid nanoparticles. In this process, lipids are dissolved in a mixture of water-soluble and water-miscible solvents, such as ethanol, methanol, acetone, or isopropyl alcohol. Then, with steady stirring, the mixture is quickly injected into an aqueous surfactant solution. After that, the dispersion is filtered to get rid of any extra lipid. The strategy relies on quick solvent diffusion into the aqueous phase through the solvent–lipid contact. The size of the particles in nano carriers is determined by the pace at which the organic solvent diffuses through the solvent-lipid interface. The use of approved organic solvents and the lack of technical equipment (such as a high-pressure homogenizer) are just a few of the benefits of this process. Other benefits include variety, efficiency, and convenience of usage.[41]

9. High shear homogenization and ultra-sonication

Ultra-sonication or high shear homogenization are two processes used to produce NLCs. In these dispersion processes, devices are employed to prepare nano carriers. When solid and liquid lipids are melted and distributed during high shear homogenization or ultra-sonication in an aqueous surfactant solution, nano dispersion is created. Ultrasonic cavitation produces the strong shear forces necessary for nano-emulsification by forcefully

and asymmetrically collapsing vacuum bubbles and breaking particles down to the nanoscale.[42]

Probe-type ultrasonication is preferred for its ability to achieve homogenization, emulsification, deagglomeration, dispersion, and milling. A repeatable method that yields smaller Nano carriers requires fine-tuning a number of factors, including the kind and quantity of lipid and surfactant, their ratio, sonication or agitation time, and speed. One disadvantage of high shear homogenization and ultra-sonication is low dispersion quality. Furthermore, a significant problem with ultra-sonication is metal contamination from the apparatus.[43]

Characterization of NLCs

1. Particle size

Particle size is measured using photon correlation spectroscopy (PCS). Another term for it is dynamic light scattering. It is a precise and delicate method in contrast. PCS has a 3 m particle detection limit. In actual use, the tool uses the angle of light scattering and the intensity of scattered light to determine the average particle size (z-average). Generally speaking, particles with diameters less than 400 m are preferred since they show sufficient penetration. The kind and concentration of surfactants have a significant impact on particle size. Particle size decreases with increasing surfactant content. Moreover, the quantity and percentage of different solid and liquid lipids have an impact on particle size.[44]

2. Drug entrapment efficiency

By centrifuging a predetermined volume of NLC dispersion and analysing the supernatant, the concentration of medicine in the dispersion media is ascertained. After centrifugation, the free medicine will remain in the supernatant and form NLC sediment. Subtract the original drug concentration in dispersion from the concentration of free drug to determine the concentration of entrapped drug. Drug escape from the matrix in the media is decreased and entrapment efficiency is increased when a drug is more soluble in a lipid blend.

$$\%EE = \frac{Ic - Fc}{Ic\ X\ 100}$$

EE= Entrapment efficiency
Ic= Initial concentration of drug in dispersion
Fc= Concentration of drug in supernatant.

3. Polydispersity index (pdi)

For PDI (PCS) determination, the dynamic light scattering method can be employed. The size distribution of Nano carriers is described by the product's PDI. Formulations are homogeneous and monodisperse if their PDI value is less than 0.5, and non-homogeneous and polydisperse if their PDI value is larger than 0.5. The PDI will decrease as the particle size decreases because smaller particles have less size distribution variations. A PDI value of 1 is ideal as colloidal carrier systems aren't always monodisperse.[45]

4. Zeta potential

Zeta potential can be found via photon correlation spectroscopy. The stability of colloidal dispersion is gauged by the zeta potential. By building up surface charge (30 mV) on the particles, aggregation of the particles is prevented. Lipid Nano carriers typically gain a negative charge, however when BBB crossing or mucoadhesion are needed, the carrier surface needs to be positively charged. The adsorption of coating ingredients and surfactants also contributes to surface charge.

5. Shape and Morphology

While Transmission Electron Microscopy (TEM) produces images by passing electrons through the specimen, Scanning Electron Microscopy (SEM) uses a focussed electron beam to scan the surface in order to create images of the components. On the other hand, SEM and TEM reveal the internal structure and surface shape of particles. While TEM shows the structure of the particle from the inside and offers details on particle diameter and matrix structure, SEM shows the particle's surface morphology, shape, porous nature, and size.[46]

6. Drug lipid (excipient) interaction

In Fourier Transform Infrared Spectroscopy (FTIR), peaks indicate the wave number at which particular molecular functional groups emit infrared radiations. It is possible to measure the gearbox between 4000 and 400 cm-1. The FTIR technique is frequently employed to ascertain how medications interact with lipids or excipients. The shifting or weakening of the drug functional group peaks or the appearance of previously unidentified peaks in the physical combination are indicative of the drug-excipient interaction. Peaks of lipid functional groups are visible in NLCs when a medication is inserted into the matrix.[47]

Applications of NLCs

Oral drug delivery

Oral drug delivery is the most patient-friendly, economical, and well-received method of medication administration. Low oral bioavailability, however, must be overcome due to a number of factors, including a significant hepatic firstpass effect, reduced drug solubility and/or efflux pumps of P-glycoprotein (P-gp), and enzymatic and chemical degradation.[48] The ability of LNPs, such as NLCs and SLNs, to provide continuous drug release gives them the advantage of stable plasma levels.[49] Their rapid dissolution and saturation solubility accelerate the onset of pharmacological activity due to their higher specific surface area and solubility. When these LNPs are synthesised, certain lipids and surfactants can suppress P-gp efflux pumps. Because drugs are integrated into the lipid matrix, they are less likely to be broken down chemically or by enzymes.[50]

IV drug delivery

The IV technique is usually applied to drugs that are injected into muscles or other tissues or cannot be absorbed by the digestive system.[51] Bypassing the first-pass metabolism and absorption phase, the drug enters the circulatory system immediately through the IV route, providing a dependable and expedited method of administration.[52] Since this kind of delivery allows for more uniform delivery and 100% bioavailability, drugs with short half-lives or durations of action are better suited for this kind of administration.[53] Moreover, individuals who are comatose, unconscious, or prone to vomiting after taking medication orally would benefit more from receiving it by IV.[54]

Ocular drug delivery

The eyes are a highly intricate and sophisticated organ. The unique physiological and anatomical features of the eyes, along with numerous constraints that must be overcome in order to obtain particular ocular tissue, make ocular delivery challenging. Using LNPs as a novel and inventive drug delivery technique, these obstacles were removed and the bioavailability of ocular tissue was increased.[55] Topical administration to the eyes is the most common method of delivering medication to the anterior regions of the eyes. The primary barriers in this system are the blood-ocular barrier, corneal epithelium, conjunctival blood flow, and tear drainage. Because LNPs are a novel technology, they can pass the blood–ocular barrier, accomplish controlled and sustained drug release, shield medications from lacrimal enzymes, and prolong the time that a drug is deposited and remains in the eyes. Ocular issues are difficult to treat, especially when they affect the back of the eyes. In targeting intraocular tissues, topical treatment is not always thought to be the most effective approach.[56]

Pulmonary drug delivery

The researchers employed a novel approach to drug delivery called pulmonary drug delivery, which has several benefits including being non-invasive for both local and systemic administration, having a high drug accumulation rate in the target site, having an accelerated onset of action through direct inhalation, having a large surface area within the pulmonary system, having a high drug permeability through thin alveolar epithelium, requiring less dosage, and resulting in fewer side effects.[57,58] Since LNPs have outperformed traditional formulations in terms of sustained drug release, biodegradability, low toxicity, increased stability, and biocompatibility, they have been given consideration for pulmonary delivery. Here, we've compiled a few outstanding studies that fell into this category and helped us comprehend how drug-loaded nanoparticles are delivered into the lungs.[59,60]

Nose to Brain drug delivery

One of the most vital organs is the brain, and maintaining its equilibrium is crucial. Barriers regulate the passage of endogenous and exogenous substances between the cerebrospinal fluid (CSF) and peripheral blood, which is essential for normal brain function.[61] Drug delivery to the brain is the most challenging undertaking because of its anatomy and physiological barriers, such as the blood-brain barrier (BBB), which is the main barrier to active molecules entering the central nervous system (CNS).[62] The majority of active CNS medications (98%) are unable to cross this barrier because their physicochemical characteristics differ from those needed for molecular admission into the central nervous system.[63] Lipophilic medications having a molecular weight of less than 600 Da and a log P-value of 1.5–2.7 are those that cross the blood–brain barrier.[64]

Brain drug delivery

Brain targeting, as opposed to oral drug delivery, improves the drug's concentration in the CSF, lowers the frequency of doses, has fewer side effects, circumvents first-pass metabolism, and acts more quickly.[65] Reduced drug penetration through the blood-brain barrier and efflux of administered medications from the brain into the bloodstream are the two main problems. LNPs' compact size and excellent drug encapsulation are their primary advantages. They are therefore the best option for focusing on particular brain tissues.[66] Widening tight junctions to promote entry from the blood-brain barrier and transcytosis of drug-loaded LNPs via the endothelium layer, as well as lengthening the duration of drug retention in the blood of brain capillaries, are some advantages of colloidal drug delivery systems, such as SLNs and NLCs. They can also initiate a drug gradient from blood to brain tissues. They are also capable of holding both lipophilic and hydrophilic medications.[67]

Transdermal drug delivery

Since ancient times, drugs and therapies have been applied via the transdermal drug delivery system (TDDS) to produce therapeutic effects on the surface, epidermis, dermis, and hypodermis of the skin.[68] Furthermore, it's critical to address a number of problems with conventional skin preparations, such as skin barrier impermeability, restricted efficacy, and overuse of applications.[69] The presence of physiologically active and biodegradable lipids, which exhibit reduced toxicity and offer properties such as adhesiveness, skin hydration, lubrication, smoothness, emollience, enhanced skin penetration, and modified medication release, is one of the many benefits of NLCs. Researchers are currently concentrating on altering topical and dermal applications of NLCs in order to advance the cosmetic and pharmaceutical industries.[70] Few processes are known in the literature regarding NLCs, despite their small size ensuring improved skin penetration of active chemicals through interaction with the stratum corneum.[71]

Tumor targeting by NLCs

Tumour targeting has emerged as one of the key components of therapeutic delivery in recent years. Improvements in drug trapping and tumour targeting depend on the creation of a new carrier system, which is

now under debate and might carry a variety of anti-cancer drugs. After adequate investigation, NLCs as nanocarriers may be the drug delivery option of choice for some anticancer medications due to their improved cytotoxicity, chemical stability, and drug release.[72] Encapsulating camptothecin and topotecan in the NLC system was found to have better cytotoxicity and cell uptake against leukaemia and melanoma cells, according to a research study. They might be combined with folate-poly-PEG-cyanoacrylate-co-cholesteryl cyano-acrylate, an amphiphilic copolymer, to give a long-lasting circulatory impact and superior tumour targeting.[73]

Stability and safety of NLCs

Although there are stability issues with SLNs, alternative lipid-based nanoformulations, like NLCs, have been created to mitigate these issues. New unstructured matrix SLNs is another name for NLCs. The claim that NLCs won't be used in the future is untrue; there is a solution for every issue. Without using any organic solvent during the preparation process, the HPH method used to make NLCs can be effortlessly moved from small-batch to large-batch manufacturing in the pharmaceutical sector. All in all, NLCs are a perfect drug delivery system contender for the pharmaceutical industry due to the use of GRAS components, large-scale production methods for their synthesis, and increased medication safety shown by the use of lipid-based nanocarriers.[74]

CONCLUSION

In conclusion, research has shown that a nano-based delivery system has great potential for enhancing the bioavailability of lipophilic medications that are poorly soluble and even for directing the drug's location of action. As a new generation, the smart NLC is considerably more adaptable when it comes to drug loading, modulating drug release, and developing final dosage forms like pills, creams, capsules, and injectables. It is also more efficient in this regard. It is important to keep expanding the usage of NLCs to create alternate paths and cure different illnesses. From everything that has been discovered in the most current literature, it is clear that NLC is a superb enhanced drug carrier system for the treatment of illnesses.

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