Nanoparticulate Carrier Drug Delivery System: A Versatile Tool for Drug Administration

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Abstracts: For over 25 years, the biomedical field has employed a range of adaptable drug delivery systems, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). Because they naturally pass the blood-brain barrier (BBB), SLNs and NLCs have been used to treat a variety of illnesses, including cardiovascular and cerebrovascular. For the latter, they are regarded as a standard treatment. The most common brain diseases—brain cancer, ischemic stroke, Alzheimer's, Parkinson's, and multiple sclerosis—are discussed in this review. Next, the fundamental methods for creating SLNs and NLCs are covered. A thorough analysis of the published research over the previous seven years is also conducted, focusing on the use of SLNs and NLCs for both active as well as passive targeting in the treatment of neurological conditions and glioblastoma multiforme and other brain tumors. Lastly, a succinct overview of the benefits, drawbacks, and potential applications of these nanocarriers is provided in an effort to provide readers with an understanding of the obstacles that must be surmounted in order to produce a delivery system that is both highly therapeutically effective and free of the constraints of currently available nano systems.

Keywords: Delivery Systems, Solid Lipid Nanoparticles, Nanostructured Lipid Carriers, Fundamental Methods, Nanocarriers, Nano Systems

1. INTRODUCTION

A type of nanoparticulate carrier system called nanostructured lipid carrier systems (NLCs) is derived from oil-in-water nano emulsions. Emulsifying agents, lipid, and water are its main constituents. At room temperature, the lipid phase is composed of both liquid (oil) and solid (fat) lipids. Because the drug disintegrates in oil and simultaneously encapsulates in solid lipid, the idea behind NLC-based formulation is to create the particles in which the fluid is incorporated into the solid lipid core, resulting in superior capacity for loading and controlled drug release. Reduced polymorphic transition, minimal crystalline index, improved drug loading, encapsulation efficiency, physical strength, enhanced chemical stability, bioavailability and controlled dispersion of enclosed components are some of the benefits of NLCs.(1)

The unique qualities that lipid nanoparticles exhibit is necessary and crucial to their therapeutic activity. The unique characteristics of nanoparticles (NP), such as their surface to weight ratio and ability to bind and transport substances, make them more intelligent for use as medical products. NPs are also more colloidal particles.(2)

As an alternative carrier scheme to emulsions, liposomes, and polymeric nanoparticles, SLN has been proposed. SLN are made exclusively of solid lipids. Consequently, following the smallest amount of groundwork, a portion of the particles crystallizes in an energy level modification (α or β).(3)

A well-known biologically active substance produced by plants exposed to radiation or infection is called resveratrol. The so-called "French Paradox"—which links regular and moderate wine consumption to potential health benefits—was first linked by Renaud and De Lorgeril to wine polyphenols like resveratrol.(4)

STRUCTURE OF NLC'S

Although NLCs and SLNs have somewhat similar structures, NLCs have three very distinct characteristics. These characteristics depend on where the medication will be incorporated. Three distinct approaches were used in the creation and formulation of nanostructured NLCs.(2)

- NLC type I (Imperfect Crystal).
- NLC type II (Multiple Type).
- NLC type III (Amorphous Type).

1. NLC Type I

NLC class I, or insufficient crystalline forms, has an ill-structured crystalline core.Glycerides and other different fatty acids can be used to alter and improve the structure. The attribute of a good drug that can be readily increased is caused by and beneficial to the entire number of structural flaws. By combining spatially dissimilar lipids, one can prepare type I NLCs, which may result in crystal lattice imperfections. The drug molecules lodge in amorphous clusters and extra disorderly crystals in molecular form.(2)

Imperfect NLCs are made by combining lipids with different structural properties, like glycerides and fatty acids, which leads to crystal order imperfections.(5)

2. NLC type II

Several oil-in-lipid-in-water form of NLCs is one among the II forms, or numerous types. Compared to solid lipids, and type II NLCs have more ability to dissolve crude oil. Because type II NLC's oil molecules can easily spread into the matrix of lipid at low oil concentrations, large amounts of oil are incorporated with solid lipids. The addition of more oil than is necessary for it to dissolve can cause different phases to separate, which ultimately results in the formation of tiny, oily nano compartments that are enclosed by a solid lipid matrix.(2)

Benefits of the Type II model include reduced drug leakage, controlled drug release, and high drug entrapment efficiency.(6)

3. NLC type II

The NLS III type is also referred to as the amorphous type. This method of NLC preparation involves mixing the lipids so as to avoid crystallization during the mixing process. The lipid matrix in the type III method is still solid but amorphous.(2)

When liquid lipids are combined with solid lipids that retain their α polymorph after solidifying and storage, an amorphous core is typically formed. Since there is no crystallization and the medication is still embedded in the amorphous matrix, this is preferable to Type I NLCs.(7)

ADVANTAGES OF NLC'S

- Regularity bodies find it easier to validate and approve NLCs.(2)
- NLC exhibits outstanding biocompatibility.(2)
- Increased physical steadiness.(8)
- Simpleness of setup and expansion.(8)
- Enhanced water-soluble dispersibility.(8)
- Boost the benefit-to-risk ratio.(6)
- Enhanced skin hydration and suppleness.(6)

- Compact dimensions guarantee intimate contact with the stratum corneum.(6)
- Increased drug stability.(6)

DISADVANTAGES OF NLC'S

- It is still necessary to make the most of the delivery of genes methods, protein and peptide therapies, and their capabilities.(6)
- Lipid Stability.(6)
- Drug release during storage as a result of a flawless crystal forming.(9)
- Unpredictable tendency to gel.(9)
- Dynamics of a polymorphic transitions that are unexpected.(9)
- High SLN dispersions' water content.(9)

MATERIALS AND METHODS

1. INGREDIENTS THAT GO INTO MAKING NLC

Lipid (s), both liquid and solid, surfactant(s), organic solvent, and additional agents such as surface modifiers and counter-ions make up NLCs in general. Various of the excipients employed to formulate NLC are listed in Table.(6)

1. Lipids

Lipid is the main ingredient in nanostructure lipid carriers, which controls drug loading capacity, action prolongation, and formulation stability. A blend of several substances with melting temperatures above 40 °C. These fats are quickly absorbed and solid.(10)

- ✓ Suitable for usage by humans.
- ✓ Moreover, biodegradable in vivo.

2. Solid lipids

Edible commercial goods such as entirely modified sunflower oils or saturating sunflowers oil (HSF or sat. sunflower), completely modified rapeseed crude oil or saturating rapes seeds oil (HRO or sat. rapeseed), and a combination of palm seed oil and palm stearin (PO + ST or palm mixture) were produced by Kerry Specialty Fats Co. Ltd. (Shanghai, China).(11)

3. Liquid oils

Natural sources of oils that are easily absorbed make up the liquid oils that are commonly used for NLCs. Because they share a structure with Compritol®, medium chain triglycerides like Miglyol® 812 are frequently used as liquid lipid constituents. Included are additional oily ingredients like paraffin oil, 2-octyl dodecanol, isopropyl myristate, propylene glycol dicaprylocaprate (Labrafac®), and squalene. Alternatively, because they have oily components and improve topical delivery penetration, fatty acids like oleic acid, linoleic acid, and decanoic acid are included in NLCs.(12)

4. Surfactants

Surfactant-wise, NLCs can be stabilized using 1.5% to 5% (w/v) of an individual surfactant or a mixture of many surfactants. However, surfactant form and amount are important considerations when constructing NLCs. Various surfactant kinds attach onto particle surfaces in an efficient manner, reducing surface tension and stabilizing NLCs.(13)

2. METHODS OF PREPARATIONS OF NLC'S

1. High Pressure Homogenization

For drugs that are thermostable, this process involves hot, high-pressure homogenization (HPH); for drugs that are thermosensitive, it involves cold, high-pressure homogenization (HPH).

Hot homogenization is done at pressures above the point of melting of the lipids. The fluid phase, including aqueous solvents and doubly distilled water, and lipid stage, comprising lipophilic emulsifiers and both fluid and solid lipids, are prepared separately. The two processes are separately heated to high temperatures before being mixed. The combination can be homogenized with a high-shear homogenizing device and then sonicated once more to get a narrow and uniform size distribution.(14)

In order to address the issues with the hot homogenization technique, cold homogenization was developed. These issues include: a) drug degradation caused by temperature changes; b) the distribution of drugs into the aqueous phase that occurs during homogenization; and c) the complexity of the nano emulsion'scrystallization step, which can result in multiple modifications and/or supercooled melts.

Comparable to hot homogenizing, cold HPH entails heating a solid lipid and incorporating the drug molecules into the molten lipid by scattering or dissolving them. The drug-containing lipid melting is rapidly solidified by chilling with cold water or nitrogen solution. Rapid cooling promotes uniform medication distribution across the lipid matrix. To make a powder with a fine texture, the material is then ground into tiny particles using a mill. The tiny particles are subsequently dispersed in a cold-water surfactant liquid. The mixture is homogenized at high temperatures to produce SLN.(15)

2. Melt Emulsification and Ultrasonication

In this procedure, the drug-lipid combination is first melted and combined at the same temperature with a surfactant solution that has been heated beforehand. After that, the mixture is agitated with a mechanical or magnetic stirrer and then subjected to a probe sonicator. After that, the mixture is quickly chilled to promote the development of nanoparticles. This method's benefit is that solvents are not required at all. Because the intensity of agitating the samples with a probe sonicator is higher than with a bath sonicator, it is recommended. However, depending on the length of the sonication, the age of the probe, and the mixing procedure, using a probe sonicator may result in metal contamination of the sample. In addition, the duration of the sonication process needs to be adjusted to achieve the desired particle size without overheating the material.(16)

3. Microemulsion Method

Since its initial development in the early 1990s, this technique has been the subject of numerous investigations by scholars. By blending a microemulsion in a cold fluid, the method creates a nano emulsion, which in turn causes lipid precipitation to form SLNs and NLCs. In short, an aqueous phase comprising water and a surfactant (preheated to the same temperature) is added under gentle agitating to form a translucent and thermodynamically stable microemulsion. A drug is dispersed in molten state lipids at a temperature beyond the lipids' melting point. Next, the microemulsion is gently mixed mechanically while being added to a cold fluid solution (2–10 ◦C). The cold aqueous phase's volume is usually 25–50 times larger than the hot emulsion's. Lipids instantly crystallize to create SLNs or NLCs after dilution creates a nano emulsion. (17)

4. Solvent Emulsification/Evaporation

The drug and lipid combination dissolves in a water-immiscible organic solution and subsequently homogenized in a water-based solution using ultrasonic treatment or high shear homogenized. After that, the organic mixture is maintained at low pressure (40–60 mbar) until the organic solvent has completely evaporated. As the organic solvent is removed using low pressure rather than high temperature and the drug-loaded NLCs precipitate, this process is appropriate for preparing of NLCs including heat-sensitive drugs. The procedure is constrained, though, by the final product's lingering organic solvent traces, which may have harmful systemic effects following ingestion. Furthermore, this preparation process might need an additional filtration step, which would not be cost-effective for large-scale producers and typically lowers the yield percentage.(18)

5. Solvent Injection Method

The solvent displacement technique is another name for this process. It functions based on the idea that lipids that come into contact with a liquid fluid would quickly diffuse the solvent across them. Using this technique, both liquid and solid lipids are quickly injected into the solution of surfactant while being constantly mixed into a water-miscible solution or combination of water-miscible solutions. As a result, as the solvent swiftly moves through the aqueous solution, the lipid nanoparticles precipitate. This method does not require complex equipment such as a high-pressure homogenizer, and it is more adaptable with a higher production rate, less shear stress, and high efficiency. However, since more lipophilic solvents result in larger particles, particle size can be an issue when using lipophilic solvents. The method's potential for leaving behind organic solvent residues may also be problematic.(19)

CHARACTERIZATION OF NLC'S

Similar to other colloidal carriers, To assess the purity, strength, and releasing dynamics of the system that delivers NLC needs to be characterized. It's a difficult task for SLN and NLC to do separately. In addition to its minuscule size, the system's dynamic properties stem from the intricate makeup of the lipids. The measurements of particle size and distribution, structural characteristics, surface charge, and particle morphology, as well as alterations in crystallinity, polymorphism, and thermal behavior of the lipids, are some of these methods of characterization. The following is a discussion of the significant characterization methods.(20)

1. Particle Size Analysis

Using a Malvern Zetasizer (ZS90, Malvern Instruments, UK), dynamic light scattering (DLS), also referred to as photon correlation spectra (PCS), was used to analyses the size of the nanoparticle and the polydispersity index (PDI). Each sample were diluted by 200 with ultrapure water to attain a weak opalescence before the measurements. The average of three figures at 25 ◦C and an angle of scattering of 90◦ was used to calculate the mean size of the particles (z-ave) and PDI metrics for the samples under investigation.(21)

2. Zeta Potential

An oral dosage form passed by the gastrointestinal tract (GIT) after being swallowed. The dosage form experienced significant anatomical and physiological changes during the passage. It is essential to investigate the stability of particles in relation to pH since pH has a major impact on particle morphology. By tracking changes in dimension and zeta value beneath different environments, the impact of pH on particle dimension and zeta value was investigated. To put it briefly, different phosphate buffers were combined with 0.5 mL of lipid nano capsules to create nano capsule suspensions with varying pH values (1.0, 3.0, 5.0, 6.8, 7.4, and 8.0, respectively). Then, using a DelsaTM Nano C Particle Analyzer (Beckman Coulter, Inc. US), the particle dimension and zeta power of the aforementioned suspension systems were investigated. The measurement was done three times for every sample.(22)

3. Encapsulation Efficiency

The free FP, which was not part of the FP-NLC, was separated using the ultrafiltration centrifugation process. To put it briefly, 1 mL of FP-NLC colloids was paired with an ultrafilter (Amicon ultra, Millipore Co., USA, MWCO 10 kDa) in the top portion of a tube for the centrifuge. The container was spun at 4000 rpm for a duration of fifteen minutes. The entire quantity of medications in FP-NLC was determined in this manner: Aliquots of 1 mL FP-NLC emulsion were dilute with alcohol in accordance with the ratio to dissolve the lipid component, and the resultant solution was filtered via 0.45 millimetre filter membranes. Using HPLC, the resultant solution was examined. The following were the HPLC conditions: The column used was a Diamasil® C18 (200 mm × 4.6 mm, 5 m, Dikma, China). The particle size and zeta power of the previously mentioned suspension structures were then examined applying a DelsaTM Nano C Particles Analytical device (Beckman Coulter, Inc. US). For each sample, the measurement was performed three times.

$$EE\ (\%) = WTotal - WFree / WTotal \times 100$$

$$Drug\ loading\ (\%) = WTotal - WFree / WLipid \times 100$$

Where, the weights of the total drug in the NLC, the weight of the drug that was not entrapped in the ultrafiltrate, and the weight of the lipid that was added to the system were, respectively, WTotal, WFree, and WLipid.(23)

4. TEM Analysis

Using a transmission electron microscope, the morphology of labelled NLC was examined (TEM, JEM-1200EX, JEOL). Samples were prepared for TEM investigation by first drying a mixture of poured the nanocarriers on a copper grid coated in an amorphous carbon sheet, and then staining the grid with 1% phosphotungstic acid.(24)

5. Differential Scanning Calorimetry (DSC) Analysis

DSC was used to record the thermograms (CDR-4P, Shanghai, China). Ten milligrams of the sample were placed in an open aluminum pan for the DSC measurement, and the sample was heated between 0 and 400 degrees Celsius at a scanning rate of 10°C/min. The DSC equipment's temperature and energy scale were calibrated using magnesia as the conventional reference material.(25)

6. Fourier Transform Infrared Spectroscopy

A JASCO FT/IR—4,200 the spectrometer (Jasco Inc., Easton, MD, United States) via 256 inspects number for experience correction, a high-energy ceramics source, and a DLARGS detector were used to study the interactions among the encapsulated drug and the matrix of the NPs. Every sample was made in a solid phase with 5% (w/w) KBr.(26)

7. Additional Colloidal Structures

For examining the dynamic phenomena and properties of SLBNs, magnetic resonance techniques such as electron spinning resonance (ESR) and nuclear magnetic resonance (NMR) are helpful. 1H NMR spectroscopy can be used to detect supercooled melts because of the low line dimensions of the lipid protons. The various proton relaxation periods in the fluid and semisolid/solid states serve as the foundation for this technique. The fluid nanocompartments in SLBNs can also be characterised by NMR. To evaluate SLBNs, ESR needs a paramagnetic spin probe. ESR can carry out a direct, repeatable, and non-invasive characterization of the spin probe's distribution between the lipid and aqueous phases. NMR and ESR haven't, however, been used much to describe SLBNs.(27)

8. Wide angle X-ray diffraction (WAXD)

The particles' crystalline structures were examined with a WAXD (D8 Advance, Bruker Axs, Germany).From the starting angle of 2θ = 10° to the ending angle of 2θ = 60°, diffractograms were created. Using a Cu K α radiation source with a wavelength of λ = 1.5418 nm, 0.3 S/step was the scanning rate.(28)

9. Statistical Analysis

Every experiment was run three times. The information was presented as the average ± standard deviation (SD). One-way analysis of variance (ANOVA) and the Tukey-Kramer multiple comparison test were used for statistical analysis. At $P<0.05$, values were deemed statistically significant.(29)

10. In Vitro Drug Release

A dialysis bag technique was used to study the drug release behavior of SLN in vitro. The bag for dialysis (molecular weight cutoff: 12–14 kDa) was immersed in Milli Q water with double distillation for 12 hours before the test. 50 milliliters of phosphate-buffered saline (PBS, pH 7.4) was used to soak dialysis bags containing free drug and formulations (2 milliliters each). The bottle containing the culture medium was placed on the thermostatic vibrating screen, set at 37 °C and 100 rpm. Two milliliters of the in vitro release a vessel were taken out within the allotted time frame and immediately replaced with new medium. As mentioned in Section, high-performance liquid chromatography, or HPLC, was used to determine the amount of drug released.(30)

SLN/NLC APPLICATIONS IN GENE AND PEPTIDE DELIVERY SYSTEMS

The highly anionic nature of nucleic acids and macromolecules in biology prevents them from diffusing through the membrane of mammalian cells. Therefore, their intracellular delivery can be improved by combining them with cationic lipid nanoparticles. It has been established that SLNs/NLCs are safe and efficient lipophilic colloidal medium for the delivery of pharmaceuticals and a range of biological macromolecules, including DNA, peptides, and others. Because of their substantial nanostructures, NLCs can hold more genes and drugs, resulting in higher loading abilities. To improve the co-delivery of a plasmid encoding a green fluorescent protein, NLCs were decorated with Tf. In both in vitro and in vivo models, paclitaxel-loaded Tf-DNA-NLC demonstrated high-efficiency gene transfection, minimal cytotoxicity, and enhanced anticancer efficacy. Two distinct kinds of nanocarriers (doxorubicin and pEGFP) were placed on NLCs and SLNs in this study.(31)

LIPID NANOPARTICLES DIFFERENT ROUTES OF ADMINISTRATION

1. Topical Route of Administration

Skin diseases are common all throughout the world. Due to insufficient penetration into the skin or skin absorption of some popular products, one of the primary challenges in treating these disorders is the poor efficacy of the medications. By changing the stratum corneum of the epidermis's penetrating pathway beyond transcellular to paracellular or follicular, one can bypass the primary skin barrier. Since lipid nanoparticles, such as SLNs and NLCs, have been developed, skin penetration has increased. These particle formulations are made by combining SLNs or NLCs with conventional formulations. They might be produced instantly, producing SLNs or NLCs that are laden with drugs. Lipid nanoparticles have several advantages for topical drug delivery: they are biocompatible and biodegradable, have a regulated and prolonged release profile, high epidermal adherence at close proximity, hydrate the skin, and create films that improve skin and dermis penetration.(32)

2. Oral Route of Administration

It is possible to administer SLN and NLC orally as an aqueous dispersion or after they have been transformed into tablets, pellets, capsules, or powder in sachets. The aqueous SLN distribution can be used in place of a granular fluid during the tablet-making process. Alternatively, SLN can be added to the tableting powder mixture after being

reduced to a powder (for example, by spray-drying). The SLN distribution can be employed as an adhesive in the process of extrusion to produce pellets. Hard gelatin capsules can be filled with SLN powders, or SLN can be made straight in liquid PEG 600 and put inside soft gelatin capsules. Powders that have been lyophilized or spray dried can also be used to make sachets. In both situations, having a higher number of solids helps prevent the need to remove excessive amounts of water.(9)

3. Pulmonary Route of Administration

A viable noninvasive method for administering medications for both systemic and local effects is the pulmonary route. Additional benefits include a low enzymatic activity, slow drug metabolism due to low surface area (ca. 100 m2), and the ability to avoid first-pass metabolism. These factors make this route ideal for treating a variety of diseases, especially pulmonary diseases, with the potential for precise administration and a reduction in side effects. This approach has demonstrated potential in the delivery of treatments for a variety of other illnesses, including cancer, infections, autoimmune diseases, acute pain, metabolic conditions like diabetes, and immune deficiencies. For pulmonary drug delivery, colloidal carriers—particularly lipid nanocarriers—offer a number of benefits, including: a) uniform drug distribution in the alveoli; b) improved mobility; c) safeguard from deterioration; d) sustained release, which extends therapeutic efficacy and lowers dosing frequency; e) the ability to deliver macromolecules efficiently; f) a decrease in side effects; and g) improved patient compliance. Drug delivery to the lungs is primarily accomplished through inhalational delivery systems, which include dry powder formulations and dispersed liquid droplet forms of dosage like nebulizers and metered dose inhalers.(20)

4. Ocular Route of Administration

SLNs and NLCs for ophthalmic administration have less restrictive regulatory criteria and greater local sensitivity since physiologically appropriate lipids are employed. The capacity to ensnare lipophilic medications, safeguard labile substances, and control release behavior are additional advantages. In recent decades, SLNs have been employed for the delivery of drugs to the eyes. More research using NLCs as ocular delivery systems has recently come to light. Currently used as an intravitreal injection, triamcinolone acetonide, also known as is a corticosteroid used to treat inflammatory, swollen, and angiogenic corneal conditions. For increased bioavailability through ocular injection, Araújo et al. entrap this medication in NLCs. High-pressure homogenization yields negatively charged, unimodal, and nanometric (~200 nm) NLCs. The findings show that over a six-month period, the backscattering was less than 1.5%, indicating that there would be little tendency for particulate aggregation while being kept at room temperature.(12)

CONCLUSION

Numerous colloidal transporters have been investigated for use in the transdermal delivery of APIs. This review presents a relatively fresh kind of system made of NLC-loaded semi-solid. A multitude of biomedical applications may be possible for this system if the NLC molecules are physiochemically stabilized in the hydrogel network, combining the best features of both material classes. Because the penetration into the skin degree of the API can be precisely controlled, this versatile delivery system is relevant for topical, dermal, and transdermal administration. Its biocompatibility and stability, as well as its capacity to deliver a wide range of APIs, and its individual particularity of both instances (gel versus NLC), further enhance its usefulness. Regarding NLC as multifunctional carriers, new research on the reversible and irreversible gathering of particles may lead to innovative combined drug delivery systems.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors contributed equally and have given their approval of the final version of the manuscript.

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