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Review Article

Nanostructured Lipid Carriers: A Potential Era of Drug Delivery Systems

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ABSTRACT

Nanotechnology is rapidly evolving in the development of new drug delivery systems. Nanostructured lipid carriers are the second era of Solid Lipid Nanoparticles (SLN). These are the alternative carrier system over the solid lipid nanoparticles. Nanostructured lipid carriers are composed of a mixture of solid and liquid lipids, resulting in a solely crystallized lipid system with various advantages over solid lipid nanoparticles, such as higher drug entrapment efficiency, drug release modification versatility, and improved stability. Lipid biocompatibility is responsible for their evolution as a viable drug delivery technology. It was observed that it had superior qualities to other lipid compositions. Various drug-distribution technologies have arisen in the last few decades, with the improvement of nanoscale drug-delivery devices being a fascinating component of this. This review explains the nanostructured lipid carriers in terms of structure, fabrication methods, characterization, future developments, wide applications, patents, and benefits over first-generation lipid nanoparticles. The review is primarily concerned with the forthcoming view of nanostructured lipid carriers and their specificity for various physiological affinities. Several polymers have been used in the development of nanoparticles for drug delivery research to maximize medicinal effectiveness while limiting negative effects. Because of their biological non-toxicity, non-immunogenicity, and compatibility, nanostructured lipid carriers will be the most intensively studied lipid nanocarrier systems.

Keywords: Nanostructured lipid carriers, Nanotechnology, Biocompatibility, Lipid nanocarriers.

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INTRODUCTION

Lipid nanocarriers known as Nanostructured Lipid Carriers (NLC) have a solid lipid core that is made up of a combination of solid and liquid lipids. Many varieties of NLC, including flawed, amorphous, and numerous types, are produced relying on the fabrication process and lipid mix constituents. By combining specific lipids, such as hydroxyoctacosanyl hydroxy stearate and isopropyl myristate, the lipid matrix in the amorphous type is solid rather than crystalline. The fundamental idea is to maximize the active compound payload and prevent entrapped compound expulsion during storage by giving the lipid matrix a specific nanostructure.[1] Modern pharmaceutical advance have led to the discovery of a large number of powerful novel molecules. The two most common problems with novel API compounds are their poor water solubility and low bioavailability. Consequently, there is a growing need to create a pharmaceutical carrier system that resolves these challenges. This vehicle strategy should not be poisonous, have a sufficient capacity for pharmacological loading, and be capable of pharmaceutical precise and controlled release properties. The system must ensure the included pharmaceutical's personal and chemical stability. It should be possible to access both the affordability and the viability of the production method.[2-4]

SLN has been offered as an option for dispersions, liposomes, and polymeric microparticles. Figure 1 depicts the first-generation (SLN) and second-generation (NLC) lipid nanocarriers. SLNs are made exclusively from solid lipids. The crystal lattice's defects are few as a result of this alteration's high degree of alignment, which leads to drug expulsion.[5] To overcome SLN-related problems, NLC have been created. They are suggested to be the lipid nanoparticles' second lives. NLC has a higher loading capacity for challenging compounds than SLN because it creates a slightly

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well-assembled solid lipid matrix. In other words, by combining a fluid lipid with a solid lipid, a higher element of medication layering may be accomplished. In comparison to SLN, the NLC can stack more drugs, and as a result, there is a lower chance of drug expulsion during storage.[6-8] Additionally, NLC exhibits less unexpected gelation and has a reduced water content in the element suspension.[9-10] NLC demonstrated certain advantages over other colloidal carrier techniques.[11,12] They provide additional chemical stability to the incorporated medications as well as a regulated pharmaceutical concern.[13] Furthermore, they are safe carriers that are simple to manufacture on a large scale.[14]

Advantages of NLC

NLC can be more easily verified and approved by regulatory agencies.[15]

1. NLC exhibits excellent biocompatibility NLC.[16]

2. NLC is less expensive and easier to scale up than polymeric or surfactant-based carriers.[17]

3. NLC offer control and/or targeted drug release to enhance pharmaceutical stability.[18]

4. In comparison to other carriers on the market, NLC deliver excellently and increased medication content.[19]

5. Drugs that are both lipophilic and hydrophilic can be transported simultaneously using NLC.[20,21]

6. Good physical and chemical stability as well as high encapsulation efficiency.

7. Owing to a strong matrix, offering a regulated release profile.

8. A slower rate of disintegration due to the solid matrixes less regular crystalline structure, which results in a protracted release of bioactive.

9. Made from naturally occurring, biodegradable materials with minimally harmful effects.

10. Appropriate polymers can modify the surface of NLC for a variety of purposes, such as enhancing their target ability or stability.[22]

Disadvantages of NLC

1. Shorter skin residency duration due to SLN's lower viscosity.[23]

2. Promising outcomes only for topical use; not for transdermal use.[24]

3. Reduced occlusive impact compared to SLNs.[25]

4. Because of the usage of certain surfactants, there is sensitivity and allergy.

5. Application and efficacy of protein and peptide therapeutics, as well as gene delivery technologies, still need to be improved.

Requirements

NLC, like emulsions, are composed of a lipid phase, an aqueous phase, and a surface-active agent. However, the ultimate behaviour of the created formulation might be significantly influenced by the component choices and their ratios. A versatility of lipid types, including triglycerides, partial glycerides, fatty acids, steroids, and waxes, have been employed in the creation of NLC. First, the lipids should be labelled as Generally Recognized as Safe (GRAS), meaning that they won't have any harmful effects at the current concentration. Second, the lipid's condition at room temperature will be determined by its physicochemical structure. Thirdly, the permeability of the active ingredient in the lipid should be fundamentally established prior to the manufacture of NLC.

Supplies used in the formulation of NLC

A solid lipid, a liquid lipid (if it is NLC), a surface-active agent, and water are often included in the manufacture of NLC, along with the powerful compounds that will be included.[26]

Lipids

Lipids are the prominent structural constituent of lipid nanoparticles and thus make up the majority of the lattice which has a significant impact on the features of this interfacial networks.[27-29] Typically, waxes, wax esters, free fatty acids, and fatty alcohols are employed. Additionally, it contains sphingolipids, glycolipids, and phospholipids. A few of these lipids also have a surface-active agent function that helps the formation of the particles. Table 1 represents the list of lipids used to prepare the NLC.

Surfactants and functions of lipids in formulation design

The characteristics and concentrations of surface-active agents have a considerable influence on the effectiveness and efficiency of nano lipid particles and nano lipid carriers. Because of their amphiphilic character, since they reduced the interfacial tension between lipid and aqueous phases, these surfactants are more regularly found in interfacial areas. In order to prevent the tiny particles in the colloidal system from aggregating, non-ionic emulsifiers, particularly Poloxamer 188, provide an extra steric stabilizing effect.[30] Table 2 represents the list of surfactants utilized in the formulation of nanostructured lipid carriers.

Other components

Other cryoprotectants utilized in lyophilized formulations include glucose, fructose, and sorbitol.[31,32] Chitosan has been employed as a coating material, and parabens or thiomersal have been used as antimicrobial preservation agents for particle dispersions.[33-35] These additives are added to the lipid components and elements of compaction used in the formulation of NLC. Several commercial preservatives, including pentylene glycol, caprylyl glycol, benzyl

alcohol, tocopherol, and potassium sorbate, have also been employed.[36]

NLC Drug Encapsulation

The lipid nanocarriers, or NLC, can include or encapsulate pharmaceuticals in one of three methods. They consist of a uniform matrix of a solid solution, a shell that is enhanced with medicines, and a core that is enhanced with therapeutics too.[37]

Solution Solid matrix that is homogeneous

The drug is evenly distributed throughout the lipid matrix of the particles as part of the encapsulation process, and the drug is released via a diffusion mechanism.

Drug-enriched shells

In this approach, the Active Pharmaceutical Ingredient (API) is directed at the nano lipid particles outermost shell. This type of nanoparticle exhibits a quick release of medication owing to a sedimentation and solubilization methodology.

Drug-enriched cores: (core enhanced with drugs)

In this approach, an extended release is seen because the drug is saturated with lipid solubility.

MATERIALS AND METHODS

According to the difference in lipid and oil mixture composition, NLC can be classed in addition to the numerous fabrication techniques which includes.

Imperfect type-I,

Amorphous type-II,

Multiple oil-in-solid fat-in-water/F/W type-II.

Imperfect type

The combination of lipids with diverse spatial properties, such as glycerides, which are made up of many fatty acids, causes defects in the crystal order in imperfect type NLC. By combining a combination of different glycerides with differing levels of

Table 1: Lipids used in earlier studies and functions.

Components	Name	Functions
Liquid lipids	Oleic acid	Increasing the oral bioavailability of carbamazepine and simvastatin. Spironolactone is delivered topically for the treatment of acne vulgaris.
	Caprylic/capric triglycerides	Vinpocetine and thymoquinone oral bioavailability improvement.
	α-tocopherol/ Vitamin E.	Enhancement of Quercetin *in vitro* anti-breast cancer activity.
	Soya bean oil	Itraconazole distribution through the lungs.
	Black cumin oil	Has a synergistic effect on the suppression of reactive free radicals when combined with marigold and carrot extract.
	Caraway essential oil	Enhances the speed of healing of infected excision wounds.
	Olive oil	Decreases the potential cytotoxicity effect of residual surfactants and produces oleuropein-loaded NLC with appropriate physicochemical stability.
	Sweet almond oil	Enhances the defenses and stability of NLC enriched with cinnamon essential oil.
	Squalene	Combination topical administration of calcipotriol and methotrexate. Improving lovastatin oral bioavailability.
	Capmul MCM C8	Enhancing the bioavailability and lymphatic dispersion of tacrolimus. Raloxifene hydrochloride sustained release with increased bioavailability.
Solid lipids	Compritol 888 ATO	Fluocinolone acetonide and clobetasol propionate skin permeating for the treatment of psoriasis, Fenofibrate's oral bioavailability is being improved.
	Precirol ATO 5	Distribution of dapsone to the skin Enhancement of rhEGF's ability to enhance healing of wounds in a full-thickness excisional wound model in pigs.
	Stearic acid	Acrylic acid distribution of tretenoin topically, Progesterone's controlled release and acid defense.
	Glyceryl monostearate	Increasing oral bioavailability Raloxifene and omega-3 fatty acids.
	Cetyl palmitate	Administration of coenzyme Q10 topically, Oral mucosal absorption of miconazole and its antifungal effects.

Table 2: List of the surface-active agents used in the manufacturing of nano lipid carriers.

Sl. No.	Surfactant type	Examples
1.	Phosphatidylcholine	Soya lecithin, Phosphatidylcholine and egg lecithin.
2.	Ethylene oxide/propylene oxide copolymers.	Poloxamer188, Poloxamer 182, poloxamer 407, Poloxamer 908.
3.	Polymers of Sorbitan ethylene oxide/propylene oxide.	Polysorbate20, polysorbate60, polysorbate80.
4.	Alkyl aryl polyether alcohol polymers	Tyloxapol.
5.	Alcohols	Ethanol, butanol.
6.	Biliary salts	Sodium cholate, sodium taurocholate sodium glycol cholate.

saturation and carbon chain length, API loading can be improved even more by enhancing flaws. The NLC type I solid matrix, also renowned as the imperfect crystal type, is poorly structured. Glycerides are a form of fatty acid that can be utilized to strengthen and alter the structure. The overall amount of structural flaws contributes to the ability of good medicine to have an easily upgraded quality.[38] The preparation of type I NLC can involve mixing lipids that are spatially dissimilar, which can result in flaws in the crystal lattice. The drug molecules form amorphous clusters and extra-disorderly crystals in their molecular form. To avoid this, a small amount of extra liquid lipid might be added to boost the drug loading. The glycerides minor quality can be leveraged to get around this problem.[39]

Amorphous type

In the case of the amorphous kind, specific hydrophobic such as hydroxyoctacosanyl hydroxy stearate or isopropyl myristate are combined with the solid lipid to create an amorphous matrix that lacks any structure. The NLC thus takes on an amorphous structure as opposed to an organized state, preventing drug expulsion brought on by alteration during storage.[40]

Multiple O/F/W types

Various nanosized liquid oil compartments are dispersed throughout the solid matrix of the multiple O/F/W type NLC. Due to the improved drug solubility in these nanosized compartments, the drug loading is boosted. Additionally, the partitions are encircled by a thick lipid matrix, which delays the release.[41,42]

NLC preparation strategies

The strategies are represented in Figure 2.

High-energy approaches

High-Pressure Homogenization is an accurate, well-recognized, resourceful, and effective method for a wide range of production. In order to create nanoemulsions for parenteral nutrition, HPH has been employed for many years.[43]

Hot homogenization process

Hot homogenization requires carrying out the operation at temperatures exceeding the lipid's transition temperature. Here, an aqueous surfactant is mixed with melted lipids and medication at an identical temperature. The high-shear device creates a heated pre-emulsion. The pre-emulsion is typically homogenized using a Pistongap homogenizer or a jet-stream homogenizer to create a hot colloidal emulsion. In order to produce NLC, the hot colloidal emulsion must be cooled to room temperature before the droplets may be recrystallized. In some extreme circumstances, emulsions may need to undergo specific thermal treatment, such as icing to sub-zero temperatures or refrigeration settings thus generating the lipid nanoparticles of NLC which are the final products. Droplets of a few micrometers in size are required since the reliability, and excellence of the pre-emulsion considerably determine the excellence of the finished product.[44]

Cold homogenization technique

Cold HPH, like hot homogenization, involves heating a solid lipid and dissolving or dispersing drug molecules in molten lipids to incorporate them into the matrix. By cooling the drug-containing lipid melt with dry ice or liquid nitrogen, it quickly solidifies. The homogeneous accumulation of the medication within the lipid substance is favoured by quick cooling. The solid is subsequently milled into tiny particles to create a fine powder. Then, a cold aqueous surface-active agent solution is used to disperse the microparticles. To create SLNs, the dispersion is commodified at high pressure. In contrast to hot homogenization, which includes a lipid melt, cold homogenization involves homogenizing solid lipids. High energy input is needed for this solid lipid dispersion, which in turn necessitates difficult homogenization circumstances. In the heated instance, homogenization is therefore more effective, and the smaller particles that arise are more monodisperse.[45]

Ultrasonication or high-shear homogenization techniques

Dispersion procedures include ultrasonication and high-shear homogenization. Lipid nanoparticle suspensions are created

Table 3: List of Patents on Nanostructured lipid carriers.

Publication /patent no.	Title	References
US20080020058A1	Compositions and methods for delivering physiologically active chemicals utilizing lipid nanoparticles.	100
EP2229936 A1	Nanotechnology is being used in testosterone preparations to boost accessibility.	101
US20090238878 A1	Medicinal compounds in a solid nanoparticle formulation with reduced Ostwald ripening that is insoluble in water.	102
US20100047297 A1	Nanocrystals for topical cosmetic compositions and their manufacturing processes.	103
US20100247619 A1 WO2008000448 A3	Pharmaceutical formulations containing solid particles and nanostructured lipid carriers containing riluzole.	104
US20110059157 A1	Anionic lipids, lipid nanostructures, techniques for making and utilizing them.	105
US20110097392 A1	Delivering chemicals to the central and peripheral neural systems via antibody-bound synthetic vesicles.	106
WO2011116963 A2	Capsules with lipid nanoparticles.	107
US20130035279 A1	A methodology and approach for producing thermally unstable nanoparticles with particular characteristics, as well as the resulting nanoparticle matrices.	108
WO2007028421 A1	The production method for nanoparticles.	108
US20080102127 A1	Composition for hybrid lipid-polymer nanoparticulate delivery.	108
US20080286365 A1	Create solid-lipid composite drug particles using this technique.	108
US20090214633 A1	Pharmaceutical formulations that can be used to treat ocular illnesses.	108

by high-shear homogenization of melting lipids in a warm, surfactant-containing aqueous phase, followed by ultrasonication. The main step in this process is to heat a solid lipid to a temperature that is roughly 5-10°C over its melting point. To create an emulsion, the lipid melt is mixed quickly at an identical temperature with an aqueous wetting agent solution. The size of the emulsion's droplets is decreased by further sonication. Slow settling of the heated emulsion underneath the crystallization temperature of the lipid results in lipid nanoparticle dispersion. Ultracentrifugation can be utilized to make a composition of lipid nanomaterials dispersions.[46]

Low-energy approaches

Microemulsion technique

The initial step involves combining melted lipids with a heated surfactant solution. Until the microemulsion forms, gentle stirring is used. The second stage involves swirling moderately while a large amount of hot microemulsion is distributed in chilled water (2°C to 3°C). This results in the solidification of the liquid droplets. The ease of production stages is a benefit of this method, but it also needs a lot of co surfactant and surfactant to stabilize created nanoparticles.[47] This approach produces spherical NLC with a limited size distribution. The resulting dispersion is considerably diluted (varies from 1:25 to 1:50 in comparison to the hot emulsion), which is one of the methods many flaws. This can call for additional concentration through lyophilization, ultra-filtering, or other techniques.[48]

Membrane contractor technique

This method makes use of a barrel-shaped biofilm component. The water phase with a surface-active agent is supplied across the biofilms interior channel, and melted lipid is forced into the internal water flow through membrane pores, permitting the creation of tiny globules that are swept away by the aqueous phase. The preparation is then brought to room temperature in order to generate NLC. The process is scalable, and by utilizing membranes with various pore sizes, the particle size may be adjusted.

Phase Inversion Technique (PIT)

This technique involves swirling lipid, drug, water, and surfactant while performing three heating and cooling cycles before diluting the emulsion with cold water, which causes the emulsion to split and cause phase inversion, producing NLC. Phase inversion, which occurs when an o/w category of emulsion transforms into a W/O kind of emulsion, is brought about by altering temperature, and the temperature at which the reversal takes place is known as the PIT.[49] This method primarily relies on how polyoxyethylated surfactants characteristics change as a function of temperature.

Coacervation technique

A standard supramolecular stabilization solution is produced in warm water before forming lipid nanoparticles. A sodium salt of the lipidic acid is uniformly mixed into an inventory solution of the polymeric stabilizer to produce a "transparent" solution. This solution is then repeatedly agitated even when being heated far

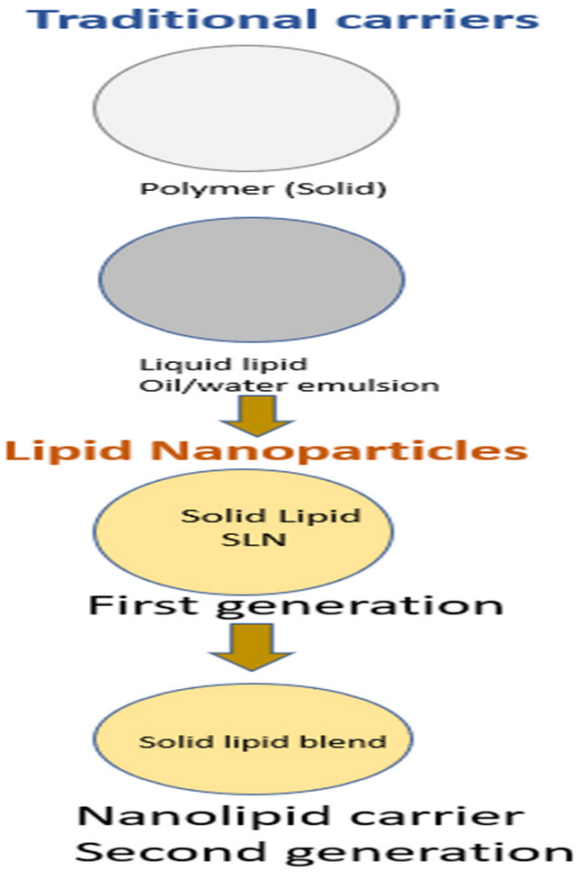

Figure 1: A diagrammatic representation of Nanostructured lipid Carriers.

above the sodium salt of the fatty acids Krafft point. Later, the medication (hydrolyzed in ethanol) is integrated into the evident solution while agitating constantly to create a single phase. This mixture produces a suspension when a coacervating solution is gradually added. The suspension is further cooled in a water bath while being constantly stirred; producing drug-loaded nanoparticles that are evenly spread.[50] The procedure of particle formation is a drop in the pH of a dilute solution of alkaline salts of fatty acids due to acidity (coacervating solution) in the involvement of a polymeric coacervation.

Double emulsion technique

For the yield of SLN and NLC, the double emulsion method is appropriate for peptides and active medicinal components that are hydrophilic. This technique involves emulsifying a drugs liquid solution in a melting lipid blend to create a primary W/O emulsion that is stabilized with appropriate excipients. To create a double W/O/W emulsion, the aqueous phase of a hydrophilic emulsify is appended to the initial W/O emulsion. To separate the double emulsion, it is agitated and filtered. This procedure generates large particles, but it also allows for surface modification, such as using PEGs, in addition to the insertion of hydrophilic molecules. The particle formation mechanism is lipid crystallization as a result of emulsion solidification.

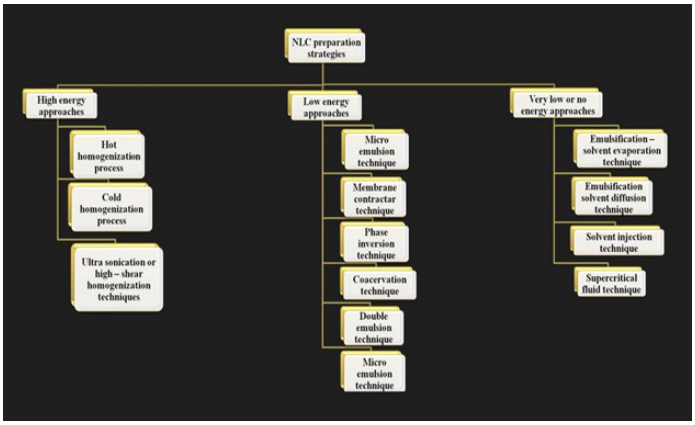

Figure 2: Strategies of NLC preparation.

Micro-emulsion cooling technique

This technique involves creating an o/w microemulsion by melting an emulsifying wax between 37°C and 55°C and adding water warmed to an identical temperature while stirring infrequently to create uniform milky slurry. After the injection of a suitable polymeric surface-active agent in the amounts recommended, a steady and unambiguous o/w microemulsion in the form of a lattice of solvents is also created. This o/w microemulsion is subsequently refrigerated at ambient temperature or 4°C to precipitate SLN. This approach is repeatable, uncomplicated, and convenient to build.[51]

Very low (or) no energy approaches

Emulsification-solvent evaporation technique

There are three steps in the setup for this technique,

(a) To prepare the organic phase, magnetic stirring is used to dissolve the lipophilic substance in the required volume of the organic solvent. (b) Pre emulsification step: Employing a high-speed homogenizer, to make a coarse pre-emulsion, a lipid-incorporating organic phase is scattered in significant quantities of an aqueous solution. The obtained coarse pre-emulsion is instantly put through a high-pressure homogenizer at a maximum generating pressure to achieve nanodispersion. (c) To alleviate the organic solvent, The resultant nanodispersion is then left overnight on the mechanical stirring.[52]

Lipid precipitation in the aqueous medium causes the formation of nanodispersion after the solvent evaporates. To get rid of lipid and medication agglomerates, a sintered glass filter is then utilized to filter the solidified nanodispersion. This technique produces tiny, monodisperse nanoparticles with great encapsulation effectiveness. For the synthesis of many nanoparticles, the procedure can be scaled up and automated.[53] Lipid crystallization as a result of anti-solvent solvent evaporation is the particle formation mechanism.

Emulsification solvent diffusion technique

To attain the initial thermodynamic equilibrium for the formation of NLC using this technique, the solvent and water must be simultaneously saturated. Then, bioactive and lipidic components are dissolved in corresponding solvents that are saturated with oil and water. A high-speed rotor-stator homogenizer emulsifies the solvent containing lipids and bioactive compounds in an aqueous emulsifier solution to create an O/W emulsion. The emulsion is created in this step by adding water in a specific amount, and the nanoparticles are created by solvent diffusion in the aqueous phase.[54] The mechanism of particle production is lipid crystallization as a result of solvent migration from the interior organic phase to the external aqueous phase.

Solvent-injection technique

The solvent injection technique and the solvent diffusion technique have a similar fundamental idea. Employing an injection needle, lipids are quickly administered into an aqueous solution of wetting agents after being solubilized in a water-miscible solvent or a combination of water-miscible solvents. To effectively generate NLC, two concurrent events must occur. Lipid crystallization results from rapid solvent diffusion from the interior organic phase to the external aqueous phase, which is the particle creation mechanism.

Supercritical fluid technique

The technique of "Supercritical Fluid Extraction of Emulsions" (SFEE) is used to create lipid nanoparticles from emulsions.[55] To make an organic solution, the medication and lipid material is disseminated in an organic solvent such as chloroform with the introduction of an accurate surface-active agent. To make an o/w emulsion, an organic solution is combined with an aqueous suspension using a high-pressure homogenizer. The supercritical fluid is delivered at a counter-current and permanent flow rate, while the O/W emulsion is initiated from one edge of the extraction column (typically the top). Lipid nanoparticle dispersions are created by continuously extracting solvents from oil/water emulsions.[56] The process by which particles are composed by the expansion of the organic phase causes lipid crystallization.

Characterization of NLC

Particle size

The most effective techniques for regular measurement are laser diffraction and Photon Correlation Spectroscopy (PCS) for the size of the particles. Another name for PCS is dynamic light scattering. It gauges the intensity variation of dispersed light created by the motion of particles. This method addresses the sizes that were determined to range from a few nm to 3 µm. Laser diffraction can be used to identify bigger sizes. This conclusion is based on the diffraction angle's reliance on an area of a particle. While adding multiple emulsifiers always promotes deeper emulsification and a stronger rigid structure, size inclusion can be minimized.[57,58] The preparation process affects the particle size of NLC formulations.

Zeta potential

Zeta potential can be analyzed by the Zetasizer/PCS. Surface charge is measured in order to ascertain the Particle stability in use is affected by aggregation and dispersion mechanisms. In general, charged particles have a lower likelihood of aggregation or fusion due to electrostatic opposition. An electrically positive surface of NLC has a high rate of Blood-Brain Barrier entry (BBB) because it adheres to BBB's paracellular region, an abundant in anionic sites region.[59] The zeta potential can be determined by checking if the cationic surface is useful for formulation design. To stabilize the nanoparticulate systems during certain processes, particle surfaces may occasionally need to be negatively charged during storage. The zeta potential, or particle's surface charge, is a measure of a system's stability during storage. The endurance of NLC formulations stabilized by charged wetting agents during storage requires a zeta potential of at least 30 mv.

Electron microscopy

SEM and TEM can also be utilized to estimate the particle radius and allocation of the size of NLC (TEM). The electron microscope is also useful for monitoring the morphology and form of the particles. While TEM utilizes electrons passed by means of the specimen, SEM uses electrons transmitted from the sample's contact area. High resolution and simple sample preparation are two benefits of SEM. After freezing or thawing, nanoparticles can be seen under a TEM.

Atomic force microscopy

AFM is the most effective technology for assessing incredibly fine morphological and surface properties. Instead of photons or electrons, AFM employs a tiny, sharp-tipped probe at the free end of a cantilever that is pushed by inter-atomic forces between its tip and perhaps the specimen's surface.[60]

Surface tension

Using the Wilhelmy plate method, the surface tension of lipid nanoparticles is regularly studied. The contact angle is also another technique for evaluating the surface tension of nanoparticles.[61]

Differential scanning calorimetry

DSC sheds light on the solid lipids from NLC' behavior during melting and recrystallization. The assertion that different lipid alterations have various melting points and enthalpies is used in DSC determination. The percentage of NLC enthalpy to bulk lipid enthalpy, calculated using the gross capacity collected, characterizes the extent of crystallinity of NLC.[62,63] With an

increase in the ratio of liquid to lipid in the particles, the crystallinity degree of nanoparticles drops.

X-ray diffraction

The state of lipids is frequently studied using both DSC and X-ray diffraction. Polymorphism has been observed in lipid molecules with extended hydrocarbon chains.[64] With the use of wide-angle X-ray diffraction, NLC' crystalline organization can be better understood. The polymorphism status of the nanoparticles discovered by X-ray might be employed to validate DSC outcomes.[65] The length of the lipid lattice's long and short spacing can be determined using X-ray scattering.

Parelectric spectroscopy

The foundation of parelectric spectroscopy is the intensity dependence of dipole density and mobility under an electromagnetic field modification. This strategy is used to comprehend the dynamics and structure of NLC. The versatility of parelectric spectroscopy has been demonstrated by providing details on the experimental design and operation of open-ended coaxial probes that can be utilized to analyze liquid dispersions and even test live things material used to aid in medical diagnosis.[66]

Nuclear magnetic resonance

To look into the mobility of the materials found in NLC's internal structure, proton NMR spectroscopy is used. The spacing at half amplitude of the indications is correlated with the movement of the solid and liquid lipids.[67] Molecules with limited mobility and significant affinities exhibit broad signals and tiny amplitudes.[68]

Raman spectroscopy

After a powerful laser beam has excited molecules, Raman spectroscopy may detect their vibrations. At 3500 cm^{-1}, water only produces broad peaks. The bands denoting the sequence of lipid chains are of relevance in relation to the feature of oil filled in a crystalline lattice.[69] The methylene group bending vibration modes at 2840 cm^{-1} and the prominent bands of the non-symmetric stretching mode at 2880 cm^{-1} demonstrate that NLC have a high degree of hydrocarbon chain structural organization.[70]

Molecular surroundings

Nile red, a lipophilic fluorescent dye, can be utilized to construct a fluorometric spectroscopy-identified indicator. The solvatochromism of Nile red helps to clarify the molecular surroundings or polarity of NLC.[71] A lipophilic benzo phenoxazine known as Nile red exhibits intense fluorescence in lipid and organic solvent environments. The Nile red emission maximum is close to 600 nm, which is consistent with high lipophilicity. Nile red's emission spectra can change to shorter wavelengths when the polarity of the surroundings becomes less. On the other hand, when accessed to more hydrophilic conditions, such as a liquid media or a nanoparticulate shell, the maximum emission wavelength switches to a higher wavelength and the emission intensity diminishes. Nile red is typically found in the aqueous lipid phase of NLC.[72]

Drug encapsulation efficiency

The ability to incorporate active molecules is a critical characteristic of an efficient DDS. The ultra filtration-centrifugation method was used to assess the Encapsulation Efficiency (%EE) of the most effective formulations. For NLC, determining drug-loading efficiency is crucial because it affects the release characteristics. Encapsulation Efficiency (EE) is a significant characteristic that must be addressed during processing design since it affects both drug release and formulation cost-effectiveness. It is the amount of medicine that is encapsulated in the nanoparticle and shows the NLC formulation's efficiency. Entrapment is excellent for lipophilic medications because the substance is homogeneously solubilized within the lipid. Consequently, the medication is kept entrapped within the lipid system due to the creation of a stiff solid lipid particle after freezing. Lipids having flaws in their crystal structure have a greater EE. The inclusion of liquid lipids in NLC enhances crystal structural defects, hence raising Encapsulation efficiency.[73]

Crystallinity

The degree of lipid crystallinity and polymorphic forms are two others prominent NLC properties that have a significant effect on the rates of bioactive incorporation and release. The lipids used in the manufacture of the NLC have a substantial impact on these behaviors. The three primary polymorphic types of glycerides are hexagonal, orthorhombic, and triclinic, with the latter having a totally packed structure and a fast rate of release.[74] The lipid crystallization pattern is specifically correlated to the polymorphism phenomenon, which is influenced by both intrinsic variables like molecular organization and defects and environmental variables like temperature, pressure, and cooling phases. Colloidal instabilities are then exacerbated by polymorphism by increasing surface and hydrophobic contacts.[75,76]

Drug release

The Franz cell and dialysis are two techniques for estimating *in vitro* drug distribution profiles from nanoparticles. By altering the kind and concentration of Liquid lipids, Solid Lipids, and surfactants, as well as the production parameters, drug molecules can be released from NLC under certain conditions.[77,78] Faster release rates are produced by lipids with shorter fatty acid chains because they are enhanced permeability and break down more quickly than those with longer fatty acid chains. owing to their increased contact area and shorter necessary path for drug diffusion, NLC with tiny particle sizes indicated the quicker release of the drug.[79]

Applications

Topical delivery

For the delivery of drugs to cutaneous areas, the topical route has been extensively used with lipid-based nanoparticles. The topical use of NLC for their special features has been the subject of numerous investigations and experiments in recent years NLC are used to apply many categories of medications topically for improved penetration and prolonged release.[80]

Acitretin NLC impregnated gel is widely used in the management of psoriasis on the skin. Miconazole nitrate-loaded NLC used for the management of antifungal therapy.[81,82]

Oral delivery

NLC have been demonstrated to be one of the significant processes for the oral administration of medicines with limited bioavailability and poor water solubility. Because NLC are dispersive, they have a vast defined contact area for enzymatic assault by intestinal lipases. Additional benefits of ingesting NLC encompass enhanced medication loading, enhanced drug accumulation, patient compliance, relatively superior particulate concentration, and a cream-like substance texture.[83,84]

Parenteral delivery

NLC of artemether (Nanoject), which significantly improve anti-malarial efficacy and action duration in comparison to the traditional injectable formulation, is another case that has been described. The existing injectable intramuscular formulation can be effectively replaced by nanoject.[85,86]

Ocular drug delivery

Ibuprofen is a lipophilic medication, and recent research suggested that NLC could boost its ocular bioavailability. Another strategy is to promote drug transcorneal passage by adding permeation enhancers to formulations such as Gelucire 44/14, a type of solid lipid, and Transcutol IP, which may elevate drug corneal permeability to some level while stearyl amine may increase drug pre-corneal retention. The preparation of an NLC ocular medication delivery was optimized using all three materials, and the preparation demonstrated greater bioavailability as compared to eye drops. The *in vivo* distribution study discovered that thiolated NLC may intensify the period of pre-corneal residency and transport substantial amounts of cyclosporine to the ocular surface and anterior chamber tissues.[87]

Pulmonary drug delivery

Inhalation medication delivery has various merits over traditional (parenteral and oral) dose modalities, including avoiding first-pass metabolism and pervasive hazard, minimizing dosage on a regular basis, and increasing local drug concentrations by immediately approaching the lung epithelium. There have been rare attempts to use nanoparticles and liposomes to deliver anti-cancer drugs through inhalation, but the main drawbacks are instability during nebulization, biodegradability, drug leakage, and unfavorable consequences. The majority of the nebulized nanoparticles were capable to accumulate in the alveolar region of the mucus lungs, extending the duration of celecoxib lung occupancy. Celecoxib, a lipophilic COX-2 inhibitor, was convincingly fabricated in NLC nanoparticles utilizing a perfect blend of solid and liquid lipids.[88]

Drug delivery to the brain

In comparison to oral delivery, this method has the benefits of preventing first-pass metabolism and having a rapid onset of effect. Because of their quick absorption by the brain, bioacceptability, and biodegradability, LNC (for example, NLC) of this generation is taken into account as one of the frontier techniques for drug delivery without any alteration to the active ingredient. NLC improved duloxetine intranasal medication administration to the brain for the management of severe depression. Bromocriptine, a dopamine activator of a binding site, has also been included in NLC for active targeting medicine administration in an effort to provide protracted medicinal value and maybe lengthen the BC half-life *in vivo* for Parkinson's disease therapy.[89,90]

Other applications

Cosmetics

NLC were created using the regulated nanostructured formation of the particle-matrix, which offers considerable benefits in terms of load-bearing capability and long-term stability. NLC dispersions come in a range of formulations, including gels, creams, lotions, and ointments. The advantages of using these NLC in cosmetics include improving the skin's absorption of active ingredients, controlling occlusion and film formation, UV protection, enhanced permeation, transdermal targeting enhanced physical and chemical stability, and hydration of the skin *in vivo* are all benefits of this product.[91]

Chemotherapy

Various nanosystems have been created in conjunction with anti-cancer medications, such as albumin-paclitaxel nanoparticles, which were endorsed for use in radiation therapy for propagated breast cancer in early 2005; etoposide NLC, which were discovered to be cytotoxic against human epithelial-like lung carcinoma cells; and topotecan NLC stabilization and prolonged release, which were developed for the treatment of refractory ovarian and mild-cell lung cancer. High drug loading efficiency, longer transmit potential, enhanced chemical stabilization, and increased cytotoxicity are benefits of using anti-cancer medications in NLC.[92]

Gene delivery and gene therapy

The two main categories of gene delivery technologies are viral and non-viral vectors. Although gene therapy that is not viral has the profits of reduced antigenicity and simplicity of fabrication, viral vectors have garnered a lot of attention due to their high transfection effectiveness. Their effectiveness, though, could be improved. Lipopolyplexes are employed as nanomedicines to deliver genes successfully and effectively. These are made by combining lipids, polycations, and genes (RNA/DNA). The ability of PNLC combined with triolein to transfer genes *in vitro* in human lung adenocarcinoma emphasized the relevance of NLC in gene transport.[93] Recently, the improved efficacy of NLC for tumor-localized distribution of anti-cancer medications via inhalation, as well as a combination of siRNAs for treating pulmonary cancer with effective tumor growth lowering and the avoidance of undesirable consequences on sensitive organs, has been proven.[94]

Nutraceuticals

Nutraceuticals are bioactive substances that give pharmacological or health profits, such as the ability to treat and prevent disease. Hesperetin, a flavanone, was also directly incorporated in NLC, which displayed acceptable acceptability, uniformity, superior flavor, and improved medicinal qualities. Hesperetin has been shown to be effective in chemically induced breast malignancy, colon carcinogenesis, cardiac arrest, and hypertension.[95]

Present and upcoming developments of NLC

The choice of choosing the appropriate carrier for drug delivery plays a crucial role.

To load medications for therapy, some innovative nanocarriers are being researched. Because of their potency and safety as a medication carrier, NLC have become one of them and have attracted a lot of attention recently. Topical and oral routes as well as intravenous administration are potential means of drug delivery from NLC. Lipid nanoparticles can be utilized to fix problems with clinically used vehicles. As new medicines for conditions like cancer, neurodegenerative illness, and inflammation become urgently needed, it is anticipated that the use of NLC in fundamental research and therapeutic settings will rise. Despite the fact that the majority of the components used to manufacture NLC are recyclable, the attainable detoxification of nanoparticles must be taken into account when generating NLC. Owing to their small size and correspondingly enhanced contact areas, nanomaterials are thought to be more harmful to organisms than materials of a larger size. There is still little knowledge available about the potential dangers of nanomaterials to human health. Two primary drug delivery methods used by NLC are intravenous injection and topical application. Another factor for future progress is the incorporation of two medically effective medicines to be contained in a unified polymeric matrix.

Despite the fact that NLC for drug delivery has advantages, it is not quite clear how these advantages are achieved. Low molecular weight medications have been the main focus of exploration on NLC as delivery of drug systems for chemotherapeutic treatments. In order to incorporate high molecular weight medicines like peptides, proteins, and nucleic acids utilized in cancer therapy, it is necessary to broaden the scope of their applications. This might make it easier to treat a larger range of cancers. In fact, it has been claimed that NLC can act as a promising vector in lung cancer gene therapy.[96,97] In reality, very few researchers have focused on safety concerns related to the usage of NLC. Farther than *in vivo* experiments are needed to properly build the tolerances and criteria that should be incorporated as specifications for NLC design. The potential of NLC can also be further explored through additional research on their upscaling of production, and kinetics as well as their use in clinical trials in the near future.

Patents

It is clear that there aren't many patents related to NLC. The phrase "nanostructured lipid carriers" appears in the caption of just one patent. Due to two restrictions, the cellular transport of medicinal substances is frequently hampered. First off, a lot of the medications have poor selectivity. Second, the sophisticated membrane systems of live cells prohibit chemical transportation. Researchers have developed novel particle delivery systems to transmit various substances to cells, including cationic lipids, microparticles, and nanoparticles.[98,99] Table 3 represents the list of patents of NLC.

CONCLUSION

The pharmaceutical sector is keen to develop a delivery method that can be used for a variety of administration modern amenities. NLC are a form of O/W emulsion system that contains both liquid and solid lipids in its matrix, as well as sufficient thickeners in the exterior phase to achieve an extreme distribution of these lipids in an aqueous environment. NLC appear to be appropriate drug delivery vehicles for local, oral, pulmonary, ophthalmoscopically, and parenterally. The active ingredients utilized have either been registered by legislator bodies and are GRAS-compliant, or they have been extensively utilized in pharmaceuticals or food commodities. Excipients, on the other hand, must be utilized at specific compositions. If larger quantities are needed for NLC production, a toxicological analysis should be performed to determine the excipients' tolerability at those concentrations. These (Nanocarriers) may enhance the sustainability of liposoluble health supplements. NLC may combine the benefits of several colloidal delivery techniques while addressing a few of their drawbacks (poor LC, depletion of phytochemical constituents owing to storage expulsion, particle agglomeration, and deterioration). This nanocarrier has also been identified as a potential method for improving the biodistribution and rigidity of hydrophobic bioactive chemicals, as well as controlling

bioactive ingredient release to their locations of action. The ability to easily scale up the formulation technology is another appealing characteristic of NLC formation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

NLC: Nanostructured lipid carriers; **TDDS:** Targeted drug delivery systems; **SLN:** Solid lipid nanoparticles; **GRAS:** Generally recognized as safe; **SEM:** Scanning Electron microscopy; **TEM:** Transmission Electron microscopy; **PCS:** Photon correlation spectroscopy; **AFM:** Atomic force microscopy; **DSC:** Differential scanning calorimetry; **HPH:** High pressure Homogenization; **CPH:** Cold pressure Homogenization; **BBB:** Blood brain barrier; **BC:** Bromocriptine; **PCS:** Photon correlation spectroscopy; **PIT:** Phase inversion technique; **SCF:** Super critical fluid technique; **SFEE:** Super critical fluid extraction of emulsions; **COX:** Cyclooxygenase; **PNLC:** Poly cationic nanostructured lipid carriers.

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