Nanostructured Lipid Carriers (NLC) For Transdermal Delivery Of Antidiabetic Drug

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ABSTRACT

Lipid-based colloidal carriers, including liposomes, solid lipid nanoparticles (SLNs), microemulsions, nanocapsules, and nanostructured lipid carriers (NLCs), are the newest and most promising methods for delivering drugs because they provide a number of advantages. NLCs, which are second-generation SLNs with an unstructured matrix, provide a high drug loading capacity and long-term drug stability. SLNs and other colloidal systems have a reduced drug loading and burst release/drug expulsion during storage. This study provides information on the composition, structure, formulation processes, and characterization of NLC, which is essential for dependable drug delivery systems. NLCs have a lot of potential in the medical and cosmetics sectors since they can be absorbed by the body, they can block things, and they can keep the skin moist. This article talks about the potential of employing NLC for delivering topical medicine in order to grab the attention of readers. NLC is a potential approach for delivering drugs because of its stability, simplicity of manufacture, biocompatibility, scalability, lack of toxicity, and improved drug loading.

Keywords: *Nanostructured Lipid Carriers; Transdermal Delivery; Antidiabetic Drug*.

INTRODUCTION

Natural active chemicals have pharmacological, therapeutic, antioxidant, and antibacterial properties since they are derived from microbes, plants, and animals. These molecules might be a very effective therapy for sickness when utilized correctly. They are also less costly and have less bad side effects than traditional medications. In recent years, there has been a rise in the number of natural active substances found in skincare products. It is often used because to its ability to fight infections, heal wounds, and reduce inflammation. These compounds are often used to treat skin issues such as dryness, irritation, wrinkles, and acne. There is a growing interest among experts from across the globe in the study of nanomedicine. There are a number of polymeric nano-drug delivery systems, such as nanodiscs, nanospheres, nanofibers, and nanocapsules. Examples of lipid-based systems include liposomes, ethosomes, niosomes, phytosomes, micelles, solid lipid nanoparticles (SLNs), and nanostructured lipid carrier (NLC) systems (1,2).

Lipid nanoparticles (LNPs) were popular in the early 1990s when first-generation SLNs were released. SLNs are still a good alternative to liposomes, emulsions, and polymeric nanoparticles. They were originally recognized when various research groups started to concentrate on them during the early phases of the investigation. The selections of lipids and surfactants may have an effect on the particle size (PS), drug loading (DL), long-term storage stability, and release properties of submicron (50-1,000 nm) SLNs. Their ability to expand considerably in the industrial sector is one of their greatest assets. New-generation NLCs are trying to address a few problems, including low DL capacity, changes in the drug release profile, and drug ejection during storage, by employing SLNs (3,4).

NANOSTRUCTURED LIPID CARRIERS (NLCs)

NLCs have been shown to be a good alternative to SLNs, polymeric nanoparticles, emulsions, microparticles, liposomes, and other similar materials, according to current research by scientists. Nanocarriers may be used to deliver drugs that are both hydrophilic and lipophilic. NLCs may be useful for administering drugs via the skin, eyes, lungs,

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mouth, and injection. NLCs have recently been used in a variety of applications, including gene therapy, brain targeting, chemotherapy, the food industry, and the delivery of cosmeceuticals and nutraceuticals. Table 1 (5) shows the advantages and disadvantages of NLC.

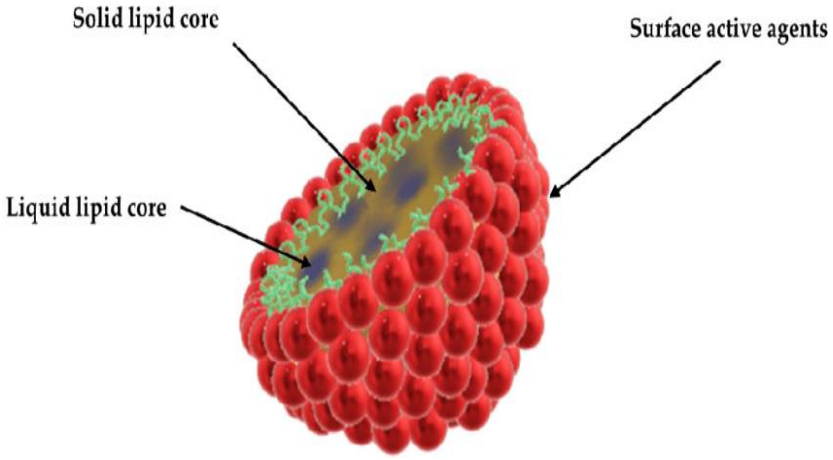

Figure 1 Nanostructured Lipid Carriers

Nanostructures, which may be anywhere from 10 to 1000 nanometers in size, have the ability to absorb or trap therapeutic compounds. NLCs work well. NLCs, which are the second generation of lipid nanocarriers, are made up of a combination of liquid and solid lipids. NLCs could be able to get around the restrictions of SLN. Nanotechnology is employed for cell development, tissue healing, and illness detection. Nanopores, liposomes, and nanoparticles (6,7) limit the usage of traditional colloidal systems.

Table 1 Advantages and disadvantages of Nanostructured Lipid Carriers (8)

Advantages	**Disadvantages**
More loading capacity for some drugs	Cytotoxic effects related to the nature of lipid matrix and concentration
Less water in the dispersion	Irritation and sensitizing action of surfactants
Prevent or minimize the drug expulsion during storage	Application and efficiency in case of protein and peptide drugs and gene delivery systems still need to be exploited
Control and targeted drug release	Stability of Lipids
Feasibilities of loading both lipophilic and hydrophilic drugs	-
Use of biodegradable and biocompatible lipids	-
Avoid organic solvents	-
More affordable (less expensive than polymeric/surfactant based carriers	-
Easier to qualify, validate and gain regulatory approval	-
Better physical stability	-
Ease of preparation and scale-up	-
Improve benefit/risk ratio	-
Increase of skin hydration and elasticity	-
Small size ensures close contact with the stratum corneum	-
Enhanced stability of drugs	-

This paper provides a summary of the manufacture, characteristics, and biological uses of NLC. The report also discusses existing patents, regulatory difficulties, and the toxicity of NLC (9).

Types of NLCs

NLCs may be imperfect, amorphous, or show variable O/F/W (10) due to their changing lipid and oil content.

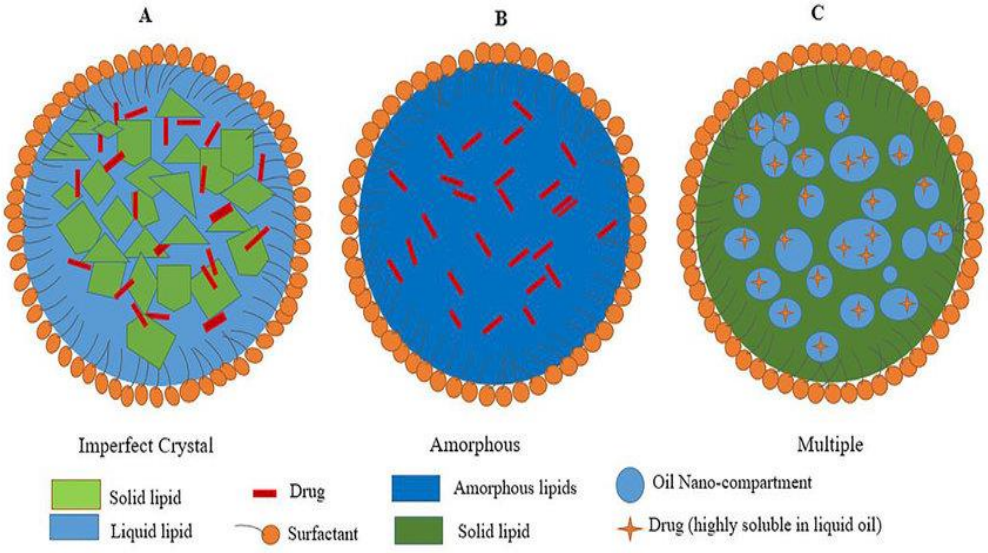

Figure 2 Types of NLCs

Imperfect NLCs

Synthetic imperfect NLCs are made by combining lipids of diverse structures, such as fatty acids and glycerides. As a result, the order of the crystal is changed (11).

Amorphous NLCs

Lipids are combined in NLCs to form a matrix that is amorphous and does not have a definite structure. This is done in order to prevent crystallization from occurring. Combine the solid lipid with either hydroxyoctacosanyl hydroxystearate or isopropyl myristate. As a result, NLCs stay amorphous, which prevents medicine from being excluded from β modifications while it is being stored (12).

Multiple O/F/W NLCs

In many O/F/W-type NLCs, the solid matrix includes occasional nanosized liquid oil pockets that increase the drug's solubility and DL. These lipid particles can only hold small amounts of hydrophilic medicines due to their lipophilicity. Lipid conjugates that are insoluble in water may be generated by forming salts or covalent connections between lipids and drugs that are soluble in water. When lipid conjugates are converted into nanoparticles for medications that dissolve in water, there may be a 30–50% loss of solubility (DL) (13).

Components of NLCS

NLCs are made up of surfactants, surface modifiers, liquid and solid lipids, and other components. The matrix is made up of the core lipids of solid NLC. Table 2 (14) 13 displays the melting points and compositions of the solid lipids that are used in NLC formulations.

Table 2 List of solid lipids, their melting points, and compositions used in the NLC formulations (15, 16)

Solid lipids	**Melting point (±5°C)**	**Compositions used**
Stearic acid/octadecanoic acid/cetylacetic acid	69.6	Stearic acid + palmitic acid + small concentration of oleic acid (HLB value = 15)
Glyceryl monostearate (GMS)	57–65	Monoglycerides + diglycerides of fatty acids (HLB value = 3.8)

Glyceryl monostearate polyoxylethylene stearates (Gelot™ 64)	55–62	Mixture of glycerol monostearate and PEG-75 (MW 3,500) stearate (C18) (HLB value = 10)
Carnauba wax	82	Hydroxy acid aliphatic ester + p-methoxy cinnamic acid aliphatic ester + p-hydroxy cinnamic acid aliphatic diester + oxy-polyhydric alcohol (HLB value = 12)
Cetyl palmitate	54	Ester derived from hexadecanoic acid and hexadecanol (HLB value = 10)
Glyceryl palmitostearate (Precirol® ATO 5)/glyceryl distearate	50–60	Mono- + di- + triglycerides of C16 and C18 fatty acids (HLB value = 2)
Glyceryl behenate (Compritol® 888 ATO)/glycerol dibehenate	65–77	Mono- + di- + triesters of behenic acid (HLB value = 2)
Compritol® HD5 ATO/behenoyl polyoxyl-8 glycerides	60–67	Mono- + di- + triglycerides of PEG8 and mono- + diesters of behenic acid (HLB value = 5)
Geleol™ mono- and diglycerides NF/mono- and diglycerides	54–64	Mono- + di- + triesters of palmitic acid (C16) and stearic acid (C18) (HLB value = 3)

Interactions with liquid lipids (oils), which are lipophilic, may cause the solid lipid core to become less crystalline. Natural and synthetic oils may both be used to create NLCs, and the majority of medicines dissolve in synthetic oils. Table 3 (17) has a list of several natural and synthetic oils that are utilized in NLC formulations, along with samples of each kind of oil.

Table 3 Synthetic and natural oils used for the formulation of NLCs and their examples (18)

Types of oil used Synthetic oils	**Examples**
Medium-chain mono- and diglycerides of caprylic/capric acid	Capmul MCM
	Imwitor
Propylene glycol (PG) fatty acid esters including PG monolaurate	Lauroglycol FCC
	Capmul PG-12
	Lauroglycol 90
PG diester of caprylic/capric acid	Labrafac PG
PG dicaprylate	Miglyol 840
Medium-chain triglycerides and their esters including capric/caprylic triglycerides	Akomed R, Akomed E, Miglyol 810, Captex 355, Crodamol GTCC, Neobee M5
Fractionated coconut oil	Miglyol 812, Triacetin, Labrafac CC, Captex 300
Long-chain monoglycerides, such as glyceryl monolinoleate	Maisine 35
Glyceryl monooleate	Peceol, Capmul GMO
Capric/caprylic/diglyceryl succinate	Miglyol 829
Fatty acids, such as oleic acid and caprylic acid	Crossential O94
Fatty acid esters	Ethyl butyrate, ethyl oleate (Cardamol EO), isopropyl myristate, ethyl butyrate, isopropyl palmitate
Mineral oil	Liquid paraffin
Vitamins	Vitamin E/α-tocopherol
Diethylene glycol monoethyl ether	Transcutol HP
Natural oils	
Fixed oils	Sunflower oil, shark liver oil, palm oil, sesame oil, olive oil, rice bran oil, margosa oil, mustard oil, jojoba oil, cod liver oil, cottonseed oil, arachis/peanut oil, castor oil, soyabean oil, chaulmoogra oil
Essential oils	Pumpkin seed oil, lemon grass oil, cinnamon oil, peppermint oil, citronella oil, lavender oil, clove oil, garlic oil, geranium oil

Lipids have an impact on several characteristics of NLC formulations, including as stability, drug-loading capacity, controlled release, and entrapment efficiency. It is well recognized that these lipids are both safe and easy for the

human body to absorb. When selecting drugs, one of the factors to consider is the drug's solubility in lipids, even if there are no strict guidelines. Third-component polymeric surfactants help to prevent particle development, disperse PS, and suspend lipid crystals. Surfactants are important for developing formulations because they change the solubility of NLC in water and have an impact on its viscosity. They stop particles from staying together and not dispersing, which makes the formulation more stable (19).

Excipients used in formulating NLC

NLCs are typically made up of lipids (which may be either liquid or solid), organic solvents, surfactants, counter-ions, and surface modifiers. Table 2 shows a list of some of the excipients in the NLC.

Table 4 Excipients used in formulating NLC

Ingredient	Examples
Solid lipid	Bees wax, Caranauba wax 2442, Stearic acid, Cetyl Palmitate, Apifil®, Cutina CP®, Dynasan® 116, Dynasan®118,Precifac ATO, Compritol®888 ATO, Elfacos® C 26, Imwitor 900®,Precirol® ATO 5, tristearin, cholesterol, Palmitic acid
Liquid lipids (oils)	Cetiol V, Miglyol® 812, Castor oil, oleic acid, Davana oil, Palm oil, Olive oil, Isodecyl oleate, Paraffin oil, propylene glycol dicaprylocaprate, linoleic acid, decanoic acid, Argan oil, coconut oil
Emulsifying agents	Pluronic® F68 (poloxamer 188), Pluronic® F127 (poloxamer 407), Tween 20, Tween 40, Tween 80,polyvinyl alcohol, Solutol® HS15, trehalose, sodium deoxycholate, Sodium glycocholate, sodium oleate,polyglycerol methyl glucose distearate, Tego®Care 450, Tween™80, Maquat® SC 18Maquat® BTMC-85%, Egg lecithin, soya lecithin, phosphatidylcholines, phosphatidylethanolamines, Gelucire® 50/13, Miranol ultra 32
Counter-ions	Sodium hexadecyl phosphate, Monodecyl phosphate, Mono hexadecyl phosphate, Mono octyl phosphate, Dextran sulphate sodium salt, Hydrolysed and polymerized epoxidised soybean oil

Lipids

Nanostructure lipid carriers are made up mostly of lipids, which help to stabilize formulations, prolong the duration of action, and control the maximum amount of medicine that may be loaded. Solid lipids, including waxes, fatty acids, diglycerides, monoglycerides, triglycerides, and steroid hormones, are the components that make up NLC. The best lipids to utilize in the production of lipid nanoparticles are those that are safe, biodegradable, non-toxic, and acceptable for human physiological usage (GRAS). Before producing nanoparticle carriers, it is important to choose the right lipids. Nanocarriers are influenced by the kind and structure of lipids. When choosing a lipid, it is important to take into account its partition coefficient or bioactive solubility. The solubility of medicinal compounds in lipids has an impact on how efficiently they can be loaded and encapsulated. The lipid crystallization process has an impact on a number of factors, including drug entrapment, loading, size, charge, and efficacy. The average particle size rises due to the viscosity of the dispersed phase and the melting lipids that are present in nano dispersion. The quality of NLC may be influenced by the amount of lipid crystals, their hydrophilicity, and their form. When lipids increase by 5-10%, the size of the particles increases by the same amount (21).

Surfactants

The quality and effectiveness of NLC are affected by the kind and concentration of the surfactant. The surfactant that is utilized has a major impact on the toxicity, physical stability, and crystallinity of NLCs. The permeability and solubility of the drug are influenced by surfactant systems. The use of surfactants is affected by particle size, lipid modification, distribution strategy, and HLB value. By using interface adsorption, amphipathic compounds that are surface active may reduce lipid-aqueous tension. The particles in the colloid crystallize and harden when NLC is formed, but their surface areas increase significantly, which causes the system to become unstable. This indicates that surfactant improves the surface quality of nanoparticles, which in turn increases their stability. Changing the composition of the surfactant system might have an effect on the stability and chemical miscibility of NLC. The kind and amount of NLC surfactant needed is determined by the required HLB (rHLB). The amount of emulsifier that is needed for formulation is determined by the rHLB of the lipids and lipid matrix. Lipid rHLB is the emulsifier HLB value that is required to decrease oil-water interfacial tension. This helps in the formation of small NLC particles and the consistent development of nanosystems. By determining the rHLB, the formulation may be able to employ the best emulsifiers at the lowest practicable concentration. By dispersing surfactant blends with different HLB values in

an experiment, it is possible to measure the rHLB of lipids (both liquid and solid) and lipid matrix. After high-pressure homogenization, the liquid is checked for the presence of small particles (22).

Other ingredients

Therapeutic chemicals that dissolve in water may be encapsulated in nanostructure carriers using organic salts and ionic polymers as counter-ions. Surface modifiers are another kind of excipient that is included in the formulation of NLC. They work by decreasing the amount of phagocytic absorption that macrophages in the reticuloendothelial system perform. Hydrophilic polymers such as PEG, poloxamines, and poloxamers are used on lipid particles to extend the amount of time that the medicine remains in circulation. Surface alterations may lead to improvements in physical stability, biocompatibility, medicine targeting, and transport across epithelial cells.

NLC PREPARATION METHODS

There are several different methods and technologies that may be used to load natural compounds onto nanolipid carriers. These methods and technologies might lead to the development of improved product compositions. Some examples are phase inversion (separation), membrane contactors, solvent emulsification/evaporation, microemulsion, microsonication, high-shear homogenization (HPH), and coacervation (23).

High-pressure homogenization (HPH)

High-pressure homogenizers (HPHs) employ a micro-nozzle to transmit excipients at pressures between 100 and 2000 bar. When excipients are put under mechanical and thermodynamic stress, the pressure in the nozzle goes down and the shear stress goes up a lot. The shear stress is caused by cavitation forces and turbulent eddies. HPH breaks down the lipid matrix and emulsifies natural components into nanosized droplets in order to enhance the development of NLC. The main problem with HPH (24) is that it produces particles that are smaller than a millimeter.

High-shear homogenization (HSH) and ultrasonication

NLCs are readily dispersed by adopting high-shear homogeneity. The two main processes in making an emulsion are quickly melting solid lipid at a temperature of 5 to 10 °C and mixing it with an aqueous phase at the same temperature. After the mixture has been homogenized, it is treated with ultrasound in order to reduce the size of the droplets. The lipids turn into nanosized dispersions when the heated emulsion is allowed to cool down slowly. After that, an ultracentrifuge is employed to concentrate the lipids. Lipid nanoparticles with beneficial biological and physicochemical characteristics are well-suited for topical application. On the other hand, this approach creates microparticles, which causes the nanocarriers to break apart. Ultrasonication may introduce metal pollutants, which is one of the potential dangers of the process (25).

Microemulsion

Microemulsion makes it easier to create NLC, even if organic solvents are not recommended. Thermolabile compounds may have issues when active drugs are heated. The drug dissolves when the bulk lipid is melted at a temperature that is 10 °C higher than its melting point. To create an oil-in-water (o/w) microemulsion, the melting phase is added to the heated water phase, and the resulting liquid is stirred to mix the surfactant and co-surfactant together. The microemulsion may then be rapidly cooled in an ice-water bath until it reaches a temperature of 2 to 3 °C. It may then be introduced to the cool aqueous phase drop by drop or mixed together with it. When there are sudden fluctuations in temperature, lipids crystallize, which leads to the production of NLCs (26).

Solvent emulsification/evaporation

In order to make NLCs, the solvent emulsification/evaporation process needs an o/w emulsion to precipitate in water. To make nanoparticles, bulk lipids need to be dissolved in an organic solvent that prevents water from flowing through. After that, the emulsion that is formed must be precipitated. When natural components are dissolved in a solvent and then evaporated, nanosized lipid particles are formed. On the other hand, microemulsion causes heat stress. One of the disadvantages of this method is that the final product contains organic solvents such as acetone, dichloromethane, ethyl acetate, and acetic acid (27).

Membrane contactors

When melted lipids are pushed through tiny pores in a cylindrical membrane contactor, minute droplets are formed. The surfactants in the membrane module are the ones that pull these droplets out of the aqueous phase. The water phase keeps the lipid melting point stable. If you cool nanoparticles to room temperature at their pore outputs, they may turn into NLCs. By changing the size of the membrane holes (28), this approach produces a variety of particle sizes.

Phase inversion temperature (PIT)

When the temperature approaches the phase inversion temperature (PIT), thermal changes lead water-in-oil (w/o) emulsions and oil-in-water (o/w) emulsions to turn into one another. This method produces nanoparticles (29) by applying irreversible thermal shocks that break emulsions and cause spontaneous inversion during cycles of freezing and heating.

Coacervation

Nanoparticles are created when lipids and naturally occurring chemicals with opposite charges are mixed together. Coacervation is the term we use to describe this process. Micelles that contain alkali fatty acid salts may produce NLCs when they are acidified. This occurs via a process called coacervation. Before the solution is acidified, a polymeric stabilizer is heated in water to form a stock solution. To clear the stock solution, it must be heated above the Krafft temperature and continuously stirred. Before heating, make sure that the fatty acid sodium salts are distributed uniformly. The medicine should be added to the clear liquid with a spoon and mixed well until a distinct phase appears. A suspension is created with the gradual addition of coacervate, with the assistance of acidity. The solution is stirred and cooled in a water bath in order to create nanoparticles that are well-dispersed and loaded with drugs. Due to its energy efficiency, sustainability, environmental friendliness, and cooling technology, many NLCs (30) have been built and tested utilizing HPH.

NLC CHARACTERIZATION

It is essential to do a physicochemical characterization in order to determine the purity and stability of the NLC. Understanding the physical and chemical features (31) may be helpful in improving the design for safety, stability, and effectiveness. The following list shows some of the most common methods that are used to describe NLCs:

Particle size analysis.

The stability, bioavailability, and cellular absorption of natural liposomes are all greatly affected by the size of the particles. DLS and NTA may be used to assess the size distribution. The sizes of the submicron particles in nanostructured lipid carriers (NLCs), which are designed for transdermal medicinal administration, range from 40 to 1000 nm, depending on their lipid content (32).

Zeta potential analysis.

The zeta potential (ZP) of a nanodispersion is an important element that affects its stability and surface charge properties. Furthermore, ZP is determined by measuring the electrophoretic mobility of particles in water. When there are bigger amounts of particles, electrostatic repulsion is more likely to occur, which reduces the chances of the particles coming together. When the ZP is not enough, dispersions are more likely to clump together or form particles, which makes them less stable. In order for an NLC to be electrostatically stable, the dispersion ZP must be either -30 mV or +30 mV. Electrophoretic light scattering (33) is a method for calculating ZP.

Morphology analysis.

We utilize transmission electron microscopy (TEM), scanning electron microscopy (SEM), and atomic force microscopy (AFM) to investigate the surface morphology of NLC. These methods are effective in explaining the structural and dimensional features of NLC. It may be possible to study the morphology and architecture of NLC by using high-resolution transmission electron microscopy (TEM) in combination with other advanced imaging methods. This might offer information on the distribution, size, and structural features of lipid nanoparticles. The scanning electron microscope (SEM) is used to examine the shape and surface roughness of NLC particles. The sample is placed on a grid made of copper or gold that is the size of a mesh. It is then stained with a solution that contains heavy metal

salts in order to prepare it for electron microscopy. Nanoparticles will seem white on a black backdrop when they are dried out and looked viewed under an electron microscope. The shape of the nanocarrier may change as a result of dehydration that occurs during the sample preparation procedure (34). Nanoscale AFM is used to determine the height and irregularity of NLC particles by evaluating their mechanical properties and surface topography. This simple and non-invasive technology allows for the effective monitoring of lipid nanoparticles, as well as the ability to change their size and structure. When atomic force microscopy (AFM) samples are prepared without water, it may help to reduce lipid polymorphism and the phase transitions of emulsifiers. Instead than using beams or radiation, this method uses a scanning device that has a sharp tip and is attached to a cantilever that looks like a spring. One way to evaluate how well the specimen tip is making contact with the surface is to measure the change in resonance frequency, oscillation, or deflection that occurs as a consequence of the cantilever's movement (35).

Entrapment efficiency

Entrapment efficiency, or EE for short, is the ratio of the amount of a drug that is still encapsulated after it has been dispersed to the total amount of the medication. Ultrafiltration-centrifugation methods may be used to determine the amount of medicine that is encapsulated in relation to the weight of the nanostructured lipid carriers (NLC). Put a known NLC dispersion in a tube that has been lined with an ultrafilter and spin it in a centrifuge. After the medicine has been diluted properly, the amount of the drug that has been released in the supernatant is measured (36).

***In vitro* release studies**

The kinetics of drug release from NLCs are examined in vitro under physiological settings. This technology makes it easier to distribute medications to the epidermal layer by using nanostructured lipid carriers (NLCs) to target the distribution of the drugs. NLCs may help to extend the therapeutic advantages of pharmacological drugs by providing a continuous supply of medication. The release of the pharmacological drug is controlled by changes to the lipid matrix (37).

Crystallinity and polymorphism

The regulated release, stability, and efficacy of the medication are all affected by the lipid polymorphism and crystallinity of NLC. Differential scanning calorimetry (DSC) may be used to study the melting point, solid lipid state, and crystallization processes of nanostructures. Differential Scanning Calorimetry (DSC) is used to undertake a complete analysis of medicines, lipids, and nanoparticles. Differential scanning calorimetry (DSC) might be used to determine the composition of NLCs, which includes the combination of solid and liquid lipids. When the concentration of liquid lipids increases, the highly ordered structure of nanostructured lipid carriers (NLCs) is improved, which leads to a decrease in crystallinity. Differential Scanning Calorimetry (DSC) uses measurements of enthalpy and melting temperature for different lipid modifications in order to create Nanostructured Lipid Carriers (NLCs) that are smaller in size but have a larger surface area and more surfactant. X-ray diffraction (XRD) analysis is an important technique for detecting compounds that have experienced changes in their polymorphic structure. The monochromatic X-ray beam is refracted to different degrees depending on the surface area of the crystal, the atomic composition of the crystal, and the arrangement of the atoms that make up the crystal. Lipid arraying may produce a wide variety of results, such as micelles, lamellar phases, tubular structures, and cubic phases. In addition to their organizational properties, wide-angle and small-angle X-ray scattering methods may be used to explore the crystalline structure, phase behavior, and polymorphism of lipid and drug molecule layers. In addition to measuring both the long and short lipid lattice spacings, Wide-Angle X-ray Scattering (WAXS) and Small-Angle X-ray Scattering (SAXS) patterns (38) may be used to determine the position of the active component.

APPLICATIONS

NLCs for cancer therapy

NLCs may include pharmaceutical compounds that are used to treat cancer. When anticancer drugs are added, the chemical stability and cytotoxicity of NLCs are improved. Nanoliposomes that contain camptothecin and topotecan have been shown to be more effective in killing melanoma and leukemia cells. They have better cytotoxicity and cellular absorption. Docetaxel is used to treat lung, ovarian, breast, and other types of cancer. Duopafei® and NLCs were used to target lung cancer cells with cytotoxicity. Docetaxel-encapsulated VEGFR-2 antibody-modified nanoliposomes showed better cytotoxicity and tolerance than Duopafei in mouse models of cancer. VEGFR-2 antibody-modified nanoliposomes have been shown to have cytotoxic characteristics in the setting of melanoma (38, 39).

Paclitaxel (PTX) and indocyanine green (ICG) for laser-triggered synergetic therapy of cancer

Biocompatible NLCs and PTX have been created for the goal of chemotherapy and photodynamic treatment, primarily targeting malignant tumors. ICG helps in the release of medication and acts as an imaging agent when it is exposed to laser stimulation. NLC was shown to be effective in targeting cancers in mouse models. The NLC-based PTX was produced using GMS, oleic acid, folic acid, Hoechst 33342, indocyanine green (ICG), 2′,7′-dichlorofluorescein diacetate, methylthiazolyldiphenyl-tetrazolium bromide (MTT), 1,3-diphenylisobenzofuran, stearic acid-PEG, and stearic acid-PEG-folate. NLCs helped to protect and manage the delivery of medications to neoplastic cells. As a result, the delivery of tumor-targeted paclitaxel (PTX) and indocyanine green (ICG) using nanostructured lipid carriers (NLC) may be an effective treatment for cancer (37).

NLCs for topical drug delivery

Nanostructured lipid carriers (NLCs) for the skin will focus on medicinal formulations and enhance transdermal absorption. Cyproterone acetate has been shown to decrease the number of acne lesions and the amount of sebum that is produced. Nanoparticles make it easier to transfer acne medicine to the follicles, which increases the effectiveness of the therapy. NLCs improved the absorption of topical medicines by two to three times. Acitretin has been shown to be effective in treating psoriasis. Compritol 255 and 45 mg of Miglyol were the NLC formulations that showed the most promise. NLC was used for the transdermal administration of medications. Calcipotriol and methotrexate may be used to help treat psoriasis. Quercetin, an anti-inflammatory medicine, was utilized in conjunction with NLCs to improve the substance's ability to penetrate and its antioxidant impact. In conclusion, NLCs might be a reasonable option for delivering topical QT. Flurbiprofen, which is a non-steroidal anti-inflammatory medicine (NSAID), is included in NLCs for tropical diseases such as gout, dermatitis, and rheumatoid arthritis. It is used to treat inflammatory skin disorders such as atopic dermatitis and psoriasis. Lidocaine is a local anesthetic that works quickly and has a modest impact. Lidocaine-encapsulated nanostructured lipid carrier (NLC) hydrogels were applied to the dermal surface (37, 38).

NLCs for brain targeting

Nanostructured lipid carriers (NLCs) that are loaded with curcuminoids have been shown to be effective in treating Alzheimer's disease and other illnesses that are connected to aging. Researchers used the rat electroshock paradigm to study how intranasal valproic acid is transported to the brain. Cetyl palmitate is the lipid matrix, while squalene is the cationic surfactant. Furthermore, Pluronic F68, polysorbate 80, and polyethylene glycol (PEG) are used as interfacial additives in the formulation of nanostructured lipid carriers (NLCs). A comparative investigation was performed on SLNs and lipid emulsions. Apomorphine, a medication used to treat Parkinson's disease, was the paradigm that was used. Baicalein-NLC is a drug that is meant to be injected into the brain. The formulation that NLC used was made up of tripalmitin, Gelucire, vitamin E, phospholipids, and poloxamer 188. Bromocriptine is delivered to the brain with the help of Plumronic F68 carriers. Bromocriptine has been used to treat Parkinson's disease and neuroleptic diseases. Apomorphine, which is a dopamine receptor agonist, has been used to treat Parkinson's disease. The encapsulation efficiency of NLC Apomorphine was found to be 60%. Biacalein has antioxidant and anti-inflammatory characteristics that help protect against ischemia damage. NLC shows a 7.5-fold increase in the brain compared to the control group (39).

Ocular delivery

NLC coated with COS for the administration of eye medications. After the melt-ultrasonic processing of flurbiprofen nanostructured lipid carriers (NLCs), the next step was to apply a coating made of chitosan oligosaccharides (COS) with a molecular weight between 3000 and 6000 kDa. Nanocarrier for administering cyclosporine to the eye. A thiolated NLC, which is a cysteine-PEG monostearate conjugation, was provided. Acyclovir that is manufactured as nanostructured lipid carriers (NLC) showed a quicker penetration into the cornea, suggesting that it penetrated more deeply into the ocular tissue. Triamcinolone acetonide is a corticosteroid that is used to treat inflammatory, edematous, and angiogenic diseases of the eye. NLC medicines have a high level of bioavailability. Triamcinolone may be given via the cornea or by other means. Flurbiprofen-loaded nanostructured lipid carriers (NLCs) with stearic acid as a solid lipid (40) are utilized for anti-inflammatory treatment of the eyes.

NLCs for cosmetics

The Nano-Cutanova Repair Q10 cream was made available for use in cosmetic formulations in October 2005. A comparison was made between the o/w cream that did not include NLC and the o/w cream that did contain NLC. The

study focused on particle size, dissolving behavior, and rheological qualities. The Cutanova Nano Repair Q10 cream was tested using an epicutaneous patch test, which showed that it has gentle effects on the skin. The Valdecoxib-NLC topical gel was created to provide a quicker and longer-lasting therapeutic impact for the treatment of inflammation. Microemulsion templates have been used to create nanostructured lipid carriers (NLCs). Fluticasone propionate-NLC was developed with the goal of minimizing negative side effects and improving safety. The formulation used glyceryl palmitostearate, which is a blend of polysorbate 80, medium-chain triglycerides (MCT) that include PEG, and soybean phosphatidylcholine. NLCs that showed sunscreen qualities were able to efficiently reduce UV light. Dr. Kurt Ric invented Nano Lipid Restore CLR® in 2006. It was the first NLC in the cosmetics industry. Topical lutein protects the epidermis from UV damage since it has antioxidant and anti-stress qualities. NLC-loaded octyl-methoxy cinnamate was created by Puglia et al. in order to improve percutaneous absorption and photostability. Octyl-methoxycinnamate absorbs UVB energy and filters blue light. When carnauba wax is combined with lipophilic filters, the sun protection factor (SPF) is more than 45%. This is in contrast to beeswax nanostructured lipid carriers (NLCs), which have an SPF of 39.

Analgesia

Buprenorphine was used to treat chronic pain and dependence on narcotics. The liver and intestines make extensive use of the drug for first-pass metabolism. As a result, it is given as a sublingual tablet and as a parental injection. Buprenorphine has a half-life of around 2.75 hours. Wang et al. used linseed oil and cetyl palmitate as the liquid and solid lipid components, respectively, to create buprenorphine-loaded nanostructured lipid carriers (NLCs). Nanoparticles have a diameter that falls between 180 and 200 nanometers. Continuous NLC release was achieved using buprenorphine ester prodrugs that had different alkyl chains. When buprenorphine was given to rats by an intravenous injection, the analgesic effects lasted for up to 10 hours, according to tail-flick evaluations. When erythrocyte hemolysis occurs, it shows that nanocarriers have a low degree of toxicity. The combination of prodrugs and nanostructured lipid carriers (NLCs) was shown to be beneficial in promoting analgesic effects (40).

CONCLUSION AND FUTURE PERSPECTIVE

Large bars are an important part of a dependable drug delivery system, and NLC has a major impact on them. The use of nanocarriers for topical medication delivery has led to the emergence of a new area of research. Nano- and micro-layered conjugates (NLCs) are chemically and physically stable, and they help with drug incorporation and bioavailability. Recently, lipid carrier systems have gained a lot of interest from the industry. There are more than 30 NLC formulations (41) available for those who are interested in obtaining medicinal or cosmetic chemicals. NLC and other advanced lipid nanoparticles show potential in the areas of skin targeting, occlusive effect, and delayed release. Lipid nanocarriers are beginning to attract attention from the industry due to their ease of large-scale production, their status as generally recognized as safe (GRAS) excipients, and their proven scale-up technology. Future NLC formulations may improve the lipid carrier system since they provide many benefits compared to first-generation systems. One of the potential dangers of nanostructures is that they might be harmful to people's health. More preclinical and clinical research is necessary to confirm that nano-lipid structures are beneficial. It is possible that the pharmaceutical industry may embrace academic research on this carrier system for medicinal and cosmetic compounds, which might lead to its successful development (42).

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