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A Novel Strategy for Targeted Drug Administration: Nanostructured Lipid Carrier

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ABSTRACT

Nanotechnology is rapidly evolving in the development of new drug delivery systems. The second generation of solid lipid nanoparticles (SLN) are called nanostructured lipid carriers. These are the alternative carrier systems over the solid lipid nanoparticles. Combining liquid and solid lipids to create nanostructured lipid carriers produces a completely crystalline lipid system with several benefits 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. NLCs can be produced using a variety of methods that are categorized based on the amount of energy used. They can be used in different applications and by different routes such as oral, cutaneous, ocular, and pulmonary. This review explains the nanostructured lipid carriers in terms of structure, fabrication methods, characterization, future developments, wide applications, and benefits over first-generation lipid nanoparticles. Because NLCs are compatible, non-immunogenic, and biologically non-toxic, they will be extensively studied lipid nanocarrier systems. The records that have been reported show the potential of NLCs for novel therapeutic uses in the future.

INTRODUCTION

DDS (Drug Delivery System) is a well-known, well-established, and commercially viable method of producing pharmaceuticals in various dose forms (1). Professor R. H. Muller of Germany and Professor M. Gascon of Italy studied lipid nanoparticles as drug delivery devices around the turn of the nineteenth century (2). These nanoparticles are made from solid lipids or a blend of solid lipids and liquid lipids, and they are stabilized by emulsifiers. Lipid formulations, such as (Nanostructured Lipid Carriers) NLCs, necessitate the incorporation of a wide range of components. With formulations like NLCs, two crucial factors that can be enhanced for insoluble medications are their bioavailability and solubility (1). Nanostructured lipid carriers (NLCs), a second generation of lipid nanoparticles, are developed to overcome the shortcomings of SLNs. (3)

The size of nanostructured lipid carriers is usually 200–400 nm. Various methods of preparation determine the sizes of NLC. It has been shown that long-term flocculation and creaming reduce the stability of the upper nano-size range > 700 nm. Higher surfactant concentrations are required to produce diameters lower than 200 nm, which are frequently undesired in formulations. However, because they recrystallize, NLC larger than 100 nm often encounter issues. However, because of their higher capacity to penetrate the skin, NLC with a size of 100 nm are particularly interesting for some applications. Baiseng et al. (2013) created a technique for matching the necessary hydrophilic–lipophilic balance (HLB) lipid phases in order to address this. NLC's solid state can effectively immobilize medications and keep particles from clumping together.(4)(5) Consequently, the mobility of the incorporated drug molecules is greatly reduced in the solid phase. Furthermore, the solid matrix's and liquid oil droplets boost the drug's ability to load, and the lipid matrixes disordered provides for greater drug accommodation. (6)

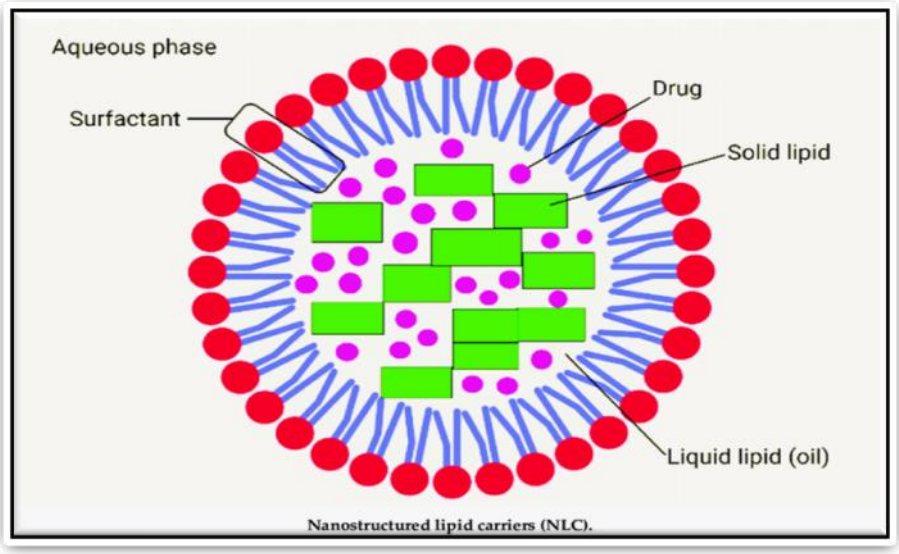

Fig 1: Nanostructured lipid carrier

2.1 Comparing solid lipid nanoparticles with nanostructured lipid carrier:

Nanostructured lipid carrier (NLC), the second-generation innovative lipid nanoparticle that acts as a bioactive carrier system, has been developed to get around a few possible solid lipid nanoparticles (SLN) restrictions.

• Payload for quantity of medications is insufficient.

• Drug expulsion during storage.

• High water content of SLN dispersion.

It is necessary to employ lipid blends that do not create a highly structured crystalline arrangement to prevent medication expulsion during storage. To accept more drug molecules than SLN, the matrix of NLCs is made up of a mixture of spatially distinct lipid molecules, typically a mixture of liquid and solid lipid. This results in more perfections in the matrix. At room temperature or body temperature, the NLC matrix is solid even when liquid lipid is present. By adjusting the amount of liquid lipids present, NLCs can absorb mixes of solid and liquid lipids and maintain their solid state. Compared to emulsions, NLCs have a stronger ability to immobilize medicines and prevent the particles from aggregating due to the solid matrix. Since NLC has a lesser chance of systemic adverse effects, it has garnered more scientific and commercial interest in recent years. (7,8). Because NLC combines the benefits

of other colloidal carriers while avoiding their drawbacks, it is a drug carrier system substitute for liposomes and polymeric nanoparticles.

NLCs are composed of biocompatible solid lipid matrices and liquid lipids which have different chemical structure from solid lipid (10). Liquid lipids are better solubilizers of drugs than solid lipids. (11,12). The majority of lipids that are utilized are either excipients in pharmaceutical formulations that are sold commercially or have an approved status. Regarding to topical delivery the lipid particles' small size guarantees tight contact with the stratum corneum and may enhance the quantity of medication that penetrates the skin or mucosa. These carriers provide for a regulated release because of their solid lipid matrix. When it's required to provide the medication over an extended length of time to decrease systemic absorption, and when drug produces irritation in high concentrations. (13, 14,15)

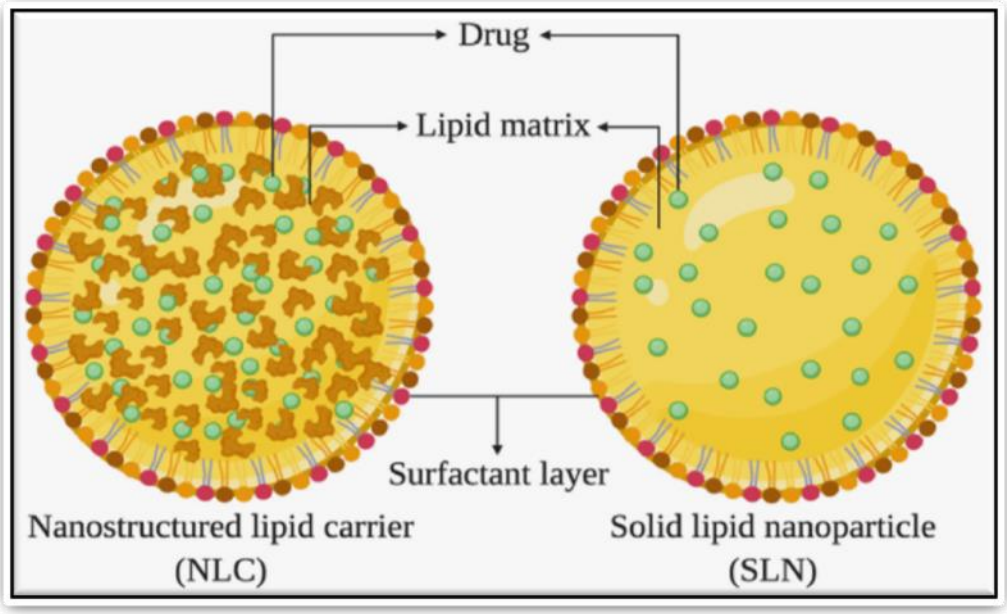

Fig 2: NLC vs SLN

2.2 Advantages of NLCs(16)

- Ease of preparation and scale-up,
- Greater ability to dissolve in an aqueous solution
- High entrapment of lipophilic drugs and hydrophilic drugs,
- Controlled particle size,
- An advanced and efficient carrier system in particular for lipophilic substances,
- Prolonged medication release,

- The stratum corneum is kept in close contact with the small lipid particles, which improves medication penetration into the skin or mucosa. Enhance the benefit-to-risk ratio.
- An increase in the suppleness and moisture of the skin
- NLC has outstanding biocompatibility.

In comparison to carriers based on polymers or surfactants, NLC is less costly and simpler to scale up.

- NLC provides targeted or controlled drug release to improve the stability of pharmaceuticals.
- NLC can be used to transport drugs that are hydrophilic and lipophilic at the same time.
- Excellent encapsulation efficiency, and good chemical and physical stability.
- Because of a robust matrix that provides a controlled release profile.
- A longer release of bioactive material is a result of a slower rate of disintegration brought on by the solid matrix's less uniform crystalline structure.
- Originated from nature

2.3 Disadvantages of NLCs (17)

- Shorter skin residency duration due to SLN’s lower viscosity.
- Not for transdermal usage; only for topical use
- less occlusive impact in comparison to SLNs.
- Sensitivity and allergy are caused by the use of specific surfactants.
- The use and effectiveness of peptide and protein therapies, as well as gene delivery technologies, still need to be improved.

2.4 Types of NLCs

Three different morphological models exist, depending on where the integrated drug moieties are located in NLC. (18)

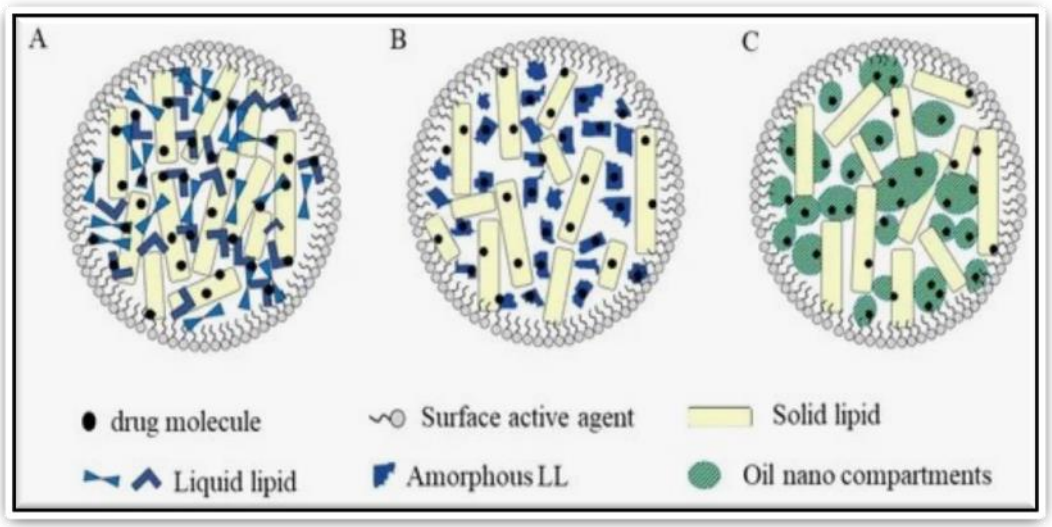

Fig 3: Types of NLCs

A) Imperfect crystal type-

NLC is made up of a highly disordered matrix with numerous gaps and holes that expand the number of medicinal molecules that can fit inside amorphous clusters. A suitable quantity of liquid lipids is combined with solid lipids to obtain these crystal-order defects (oils). The NLC matrix is unable to create a highly organized structure due to various chain lengths of fatty acids and a blend of mono-, di-, and triacylglycerols. Mixing lipids from different geographical regions increases the drug payload capacity, but this model has a low entrapment efficiency. (19, 20)

B) Amorphous type-

Lipids are carefully combined to create amorphous type NLC, which minimizes medication leakage during the crystallization process. Lipids such as hydroxyl octacosanyl, hydroxyl stearate, isopropyl myristate, and dibutyl adipate create solid yet non-crystalline particles. The nature of the lipid matrix is both amorphous and homogenous. (19).

C) Multiple type –

Compared to solid lipids, oil dissolves more readily in type II NLCs. Because the oil molecule easily diffuses at low concentrations into the lipid matrix of oil, a large amount of oil is mixed with solid lipids in type II NLCs. When more oil is injected than necessary for its solubility, different phases may separate, creating tiny, oily nano compartments that are

surrounded by the solid lipid matrix. The formulation of HLs permits controlled drug release and drug leakage from the lipid matrix. (21)

2.5 Drug release from NLCs

When it comes to NLCs, the rate of degradation and dissolution determines when pharmaceuticals can be released from a matrix. It is well described in the literature that it is compulsory to have exact and controlled release going beyond dissolution and degradation. The particle should be triggered by an impulse when a particle is administered the release (22). The drug will have to be trapped in NLC's because of their unordered and unorganized lipid structure. By applying different methods and techniques the structure of the lipid can be modified, which leads to convert the structure of lipid molecule and hence ongoing drug release can be initiated as shown in Figure 4. It was observed that this method is crucial when NLCs are added to creams intended for external use and for the management of various dermatological conditions, such as eczema and psoriasis. When these kinds of NLCs are rubbed, the temperature rises, and the water evaporation from the surface increases. They are highly beneficial. (22,23,24,25,26)

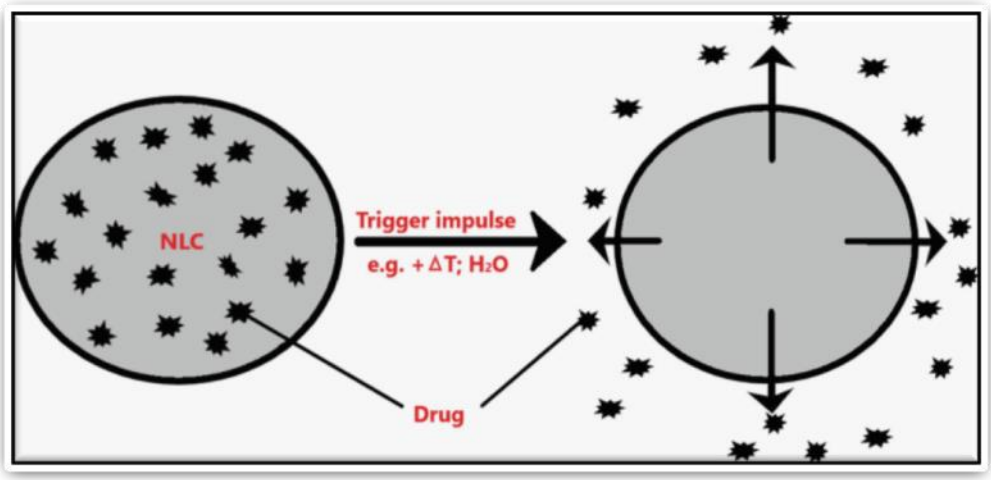

Fig 4: Drug release mechanism from NLC

2.6 Composition of NLC:

A solid lipid, a liquid lipid, a surfactant, water/solvent, and the active compounds to be integrated are the general elements for the manufacture of NLC. Surface modifiers and counter-ions are examples of additional agents that were included. The utilization of beginning materials categorized as Generally Recognized as Safe-GRAS. (27)

Lipid:

The primary component of nanostructure lipid carriers that govern drug loading capacity, and prolong action and stability of the formulations is lipid. To produce NLC, solid lipids such as fatty acids, waxes, steroids, diglycerides, and monoglycerides have been employed. Physiologically For the creation of lipid nanoparticles, acceptable, biodegradable, non-toxic, and generally recognized as safe (GRAS) lipids are preferred. Selecting the right lipids is crucial before using them to create nanoparticulate carriers. Numerous properties of nanocarriers are influenced by the kind and structure of the lipid. It has been argued that the most practical criterion for selecting an appropriate lipid is the solubility or apparent partition coefficient of the bio-actives in the lipid. Interpretation is provided by the drug molecules' solubility in lipid, which influences drug loading and encapsulation effectiveness. (28)

Surfactants:

The type and concentrations of surfactant exert influence on the quality and efficacy of NLC. It has been discovered that the choice of surfactant significantly affects the toxicity, physical stability, and crystallinity of NLC (29). Drug permeability and the degree of drug dissolution are also influenced by surfactant systems. Surfactants are selected according to their effects on particle size, lipid modification, hydrophilic-lipophilic balance (HLB) value, and mode of administration. Because of their amphipathic nature, surface active agents (emulsifiers) are adsorbed on the interface, where they lessen the tension between the lipid and aqueous phases (30). The required HLB (rHLB) is a crucial factor to consider when choosing the right kind and concentration of surfactant for NLC formulation. The number of emulsifiers to be added in the formulation is calculated using the rHLB of the lipids and the lipid matrix. The emulsifier's HLB value, or the rHLB value for lipid, is required for proper emulsification, or the lowering of interfacial tension between the oil and water phases. Additionally, this helps to achieve a stable nanosystem with small NLC particle sizes. (31,32)

Other ingredients:

Organic salts and ionic polymers may be employed as counter-ions in formulation of nanostructure carriers to overcome the challenge of encapsulating water-soluble drug molecules. Another class of excipients utilized in NLC formulation is surface-modifiers, which reduce the phagocytic absorption of the particles by the macrophages in the reticuloendothelial system (RES). To extend the duration of therapeutic molecules' residency

in the systemic circulation, hydrophilic polymers such as PEG, poloxamines, or poloxamers are applied to lipid particles. Surface modification leads to increase physical stability and biocompatibility, drug targeting, increased transport across epithelium. (33)

Table 1: Composition of NLC

Sr. no	Ingredients	Materials
1	Solid lipid	Tristearin, stearic acid, cetyl palmitate, cholesterol, Precirol® ATO 5, Compritol® 888 ATO, Dynasan®116, Dynasan® 118, Softisan® 154, Cutina® CP, Imwitor® 900 P, Geleol®, Gelot® 64, Emulcire® 61
2	Liquid lipid	Medium chain triglycerides, paraffin oil, 2-octyl dodecanol, oleic acid, squalene, isopropyl myristate, vitamin E, Miglyol® 812, Transcutol® HP, Labrafil Lipofile® WL 1349, Labrafac® PG, Lauroglycol® FCC, Capryol® 90
3	Hydrophilic emulsifier	Pluronic® F68 (poloxamer 188), Pluronic® F127 (poloxamer 407), Tween 20, Tween 40, Tween 80, polyvinyl alcohol, Solutol® HS15, trehalose, sodium deoxycholate, sodium glycocholate, sodium oleate, polyglycerol methyl glucose distearate
4	Lipophilic emulsifier	Myverol® 18-04K, span 20, span 40, span 60
5	Amphiphilic emulsifier	Egg lecithin, soya lecithin, phosphatidylcholines, phosphatidylethanolamines, Gelucire® 50/13

1. METHODS OF PREPARATION

Generally speaking, the lipophilic phase's nano emulsification in an aqueous solution comprising a mixture of liquid and solid lipids and water-soluble surfactants/emulsifiers is used to make NLCs. The methods used for the production of NLCs are based on the energy requirement, they are categorized into three types.

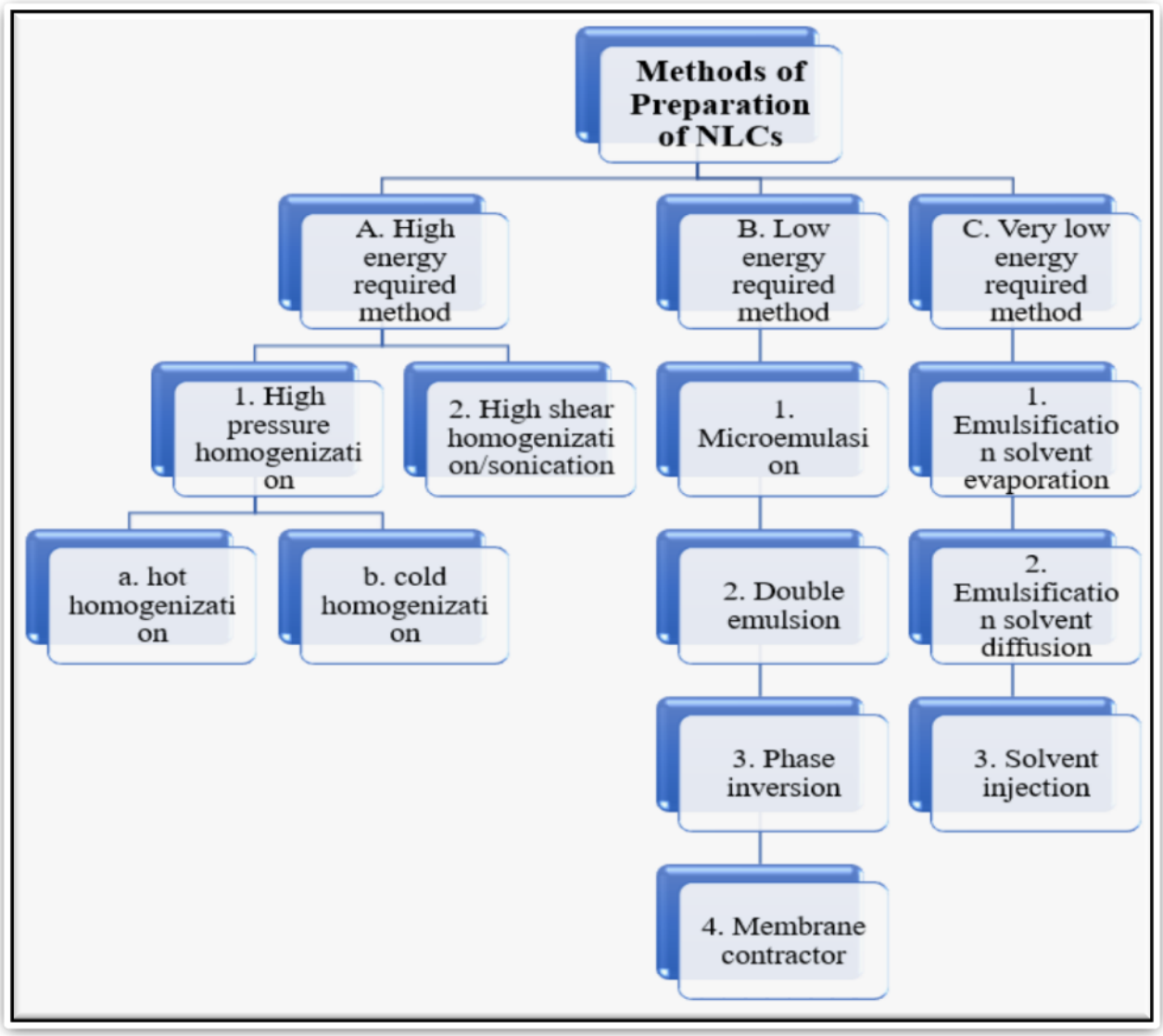

Fig 5: Method of preparation of NLC

3.1 High energy-required methods

3.1.1 High-pressure homogenization

The high-pressure homogenization method is considered as among the most widely preferred method, because while preparation solvents are not added, as it formulates highly stable particles and also required no organic solvent addition. It is regarded as a potent technique for producing NLCs on a big scale. This method is further divided into hot homogenization and cold homogenization. (34,35)

i. Hot homogenization:

This approach involves mixing a molten lipid combination with a hot aqueous surfactant solution at high speed before adding the drug. A high-pressure homogenizer is then used to completely homogenize the pre-emulsion. At normal temperature, nanoemulsions are formed once they recrystallize. Some disadvantages of this approach include the heat-induced breakdown of thermolabile actives, the reduction emulsification power of Some surfactants may partition in both lipid and aqueous surfactant solution at higher temperatures, resulting in low drug encapsulation efficiencies at high temperature, which encourages drug escape into aqueous phase. (36,37)

ii. Cold homogenization:

This process solidifies the medication and molten lipid combination by rapidly cooling it while subjecting it to liquid nitrogen or dry ice. After that, it is pulverized and mixed with a chilled aqueous surfactant solution. High pressure homogenizer is used to complete the final processing of the produced dispersion. The drawbacks of hot procedures, such as avoiding the heating of medications and surfactants, can be somewhat resolved by this technique. Controlling the crystallization process is another way to get the desired crystal structure. (38)

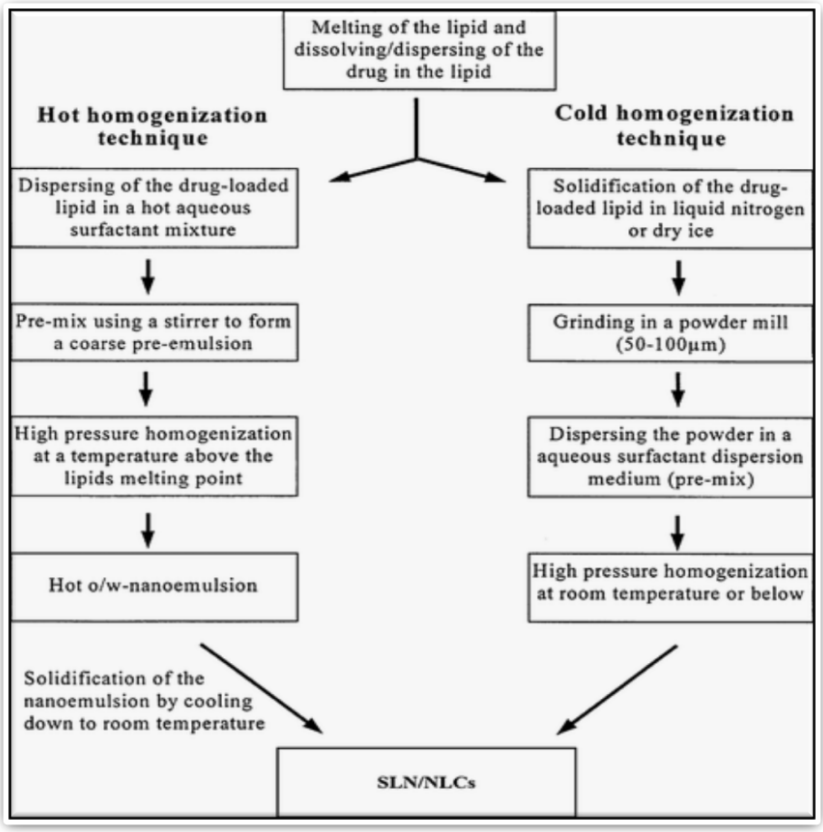

Fig 6: Hot and cold homogenization

3.1.2 High shear homogenization/sonication

Using this method, a lipophilic drug is dissolved or dispersed in a molten blend of liquid and solid lipids. The temperature used should be 10 C above the melting point of solid lipid to make recrystallization problematic. Pre-microemulsion is created by adding the aqueous surfactant solution to the lipid phase at the same temperature and stirring it vigorously. After being treated with a probe sonicator, the High-shear homogenizers are used to further homogenize the pre-emulsion. (39,40)

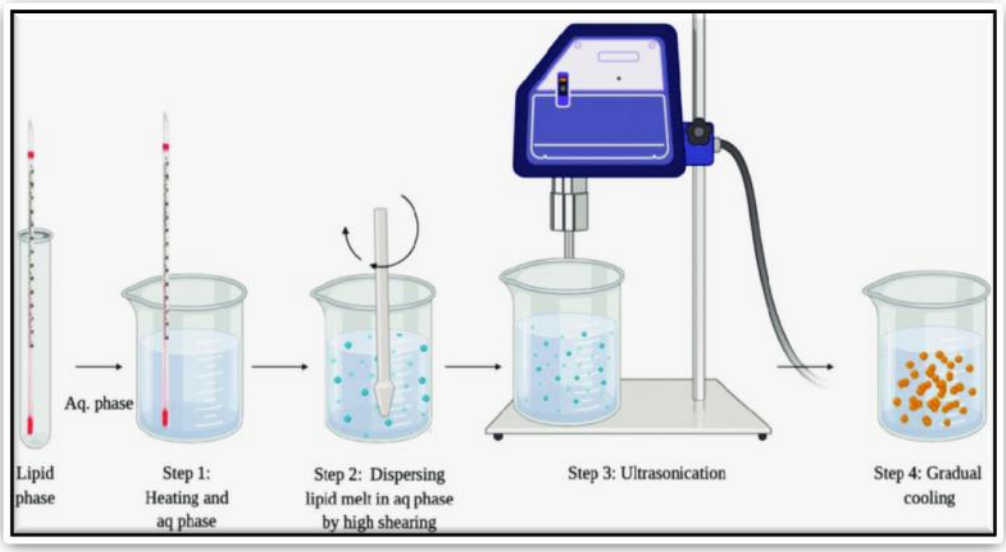

Fig 7: High shear homogenization process

3.2 Low energy required methods

3.2.1 Microemulsion

By applying a technique known as microemulsion, the lipid carrier is warmed and softened, and after that drugs, emulsifier assistant emulsifier, and deionized water are added to yield a blend with a straightforward appearance and a thermodynamic strength like that of oil-in-water (O/W)- type microemulsion. The microemulsion is immediately dispersed in ice water (4°C), shaping an NLC dispersion system. The sizes of the nanoparticles and particles from microemulsion and weakening are amazingly near the temperature distinction between the cold water and the microemulsion, which is a key factor in planning little molecule size NLCs. Quick cooling and solidification can keep the collection of a few particles. This strategy's minimal drug content is one of its advantages and it is effortlessness, while the weaknesses are the plenitude of assistant emulsifier and emulsifier required. (41)

3.2.2 Double emulsion

This process is mostly utilized to create lipid nanoparticles that contain hydrophilic medications. This method resolves the issue of the water-soluble moiety's escape from the oily phase into the aqueous phase, as shown in the microemulsion method (42). This approach involves dispersing the medication in the lipid phase after it has been dissolved in an aqueous solvent (the inner aqueous phase) (Molten solid lipid + liquid lipid+ lipophilic surfactant+ lipophilic active moiety) to produce primary emulsion (w/o). The aqueous phase and the lipid are kept at the same temperature. Drug loss to the external phase during solvent evaporation is prevented by the stabilizer. Subsequently, the primary emulsion is mixed with a significant amount of surfactant aqueous solution and sonicated to create a double emulsion (w/o/w). The lipid nanoparticles are then purified by ultrafiltration or solvent evaporation. (43)

3.2.3 Phase inversion

Three cycles of heating and cooling are required to combine all the components in this procedure. Phase inversion leads to the development of NLCs after the hot mixture is shocked by being diluted with cold water.

3.2.4 Membrane contractor

The term "membrane contactor" refers to the identification of membrane systems utilized for "keeping in contact" between two phases. The lipid phase is put in a pressured tank at a temperature higher than its melting point. Under applied pressure, it is let to infiltrate through ceramic membrane holes to create tiny droplets. The aqueous phase flows tangentially inside the membrane module while being continuously stirred, brushing away the droplets that have formed at the pore outlets. Lipid particles arise when the preparation is cooled to room temperature. The process parameters influencing the size of lipid nanocarriers include the temperature of the lipid and aqueous phases, the tangential-flow velocity of the aqueous phase, the pressure of the lipid phase, and the size of the membrane pore. Commercial scalability is one of the advantages of this novel membrane emulsification technique. (44)

3.3 Very low energy required methods

3.3.1 Emulsification solvent evaporation

This method involves dissolving the medication and the lipids (solid and liquid) in an organic solvent that is water-immiscible (cyclohexane, chloroform). An o/w emulsion is created by dispersing the resulting mixture into an aqueous emulsifier solution. The solvent is extracted from the emulsion via reduced pressure evaporation. Because of lipid precipitation in the aqueous medium, evaporation causes nanoparticles to disperse in the aqueous phase. This process eliminates any heat stress, but the usage of organic solvent is a disadvantage. Particle size can vary from 30-100 nm according to the solid lipid and surfactant. (45)

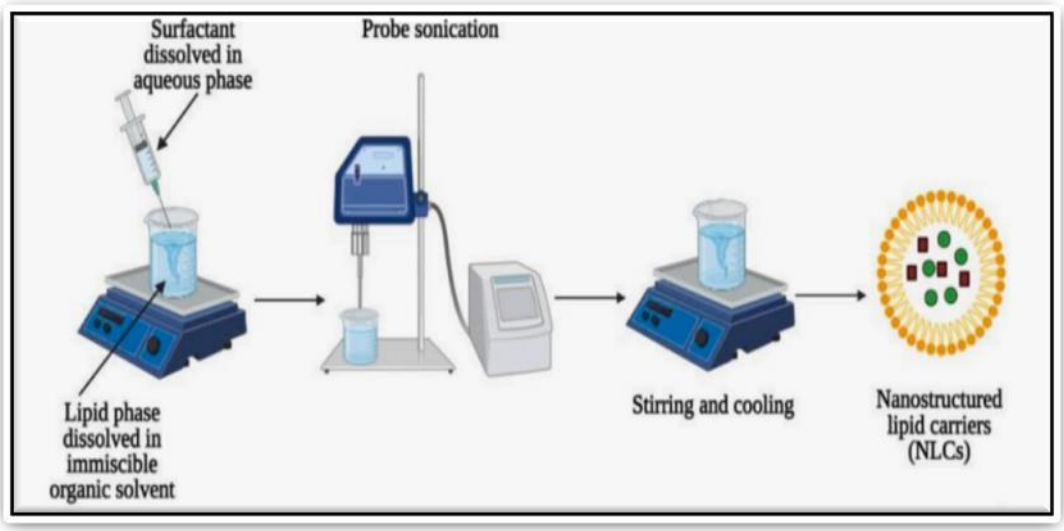

Fig 8: Emulsification solvent evaporation process

3.3.2 Emulsification Solvent diffusion

In this method, the initial thermodynamic equilibrium is maintained by mutual saturation between the solvent and the water. Subsequently, the medication and lipids dissolve in the solvent that is saturated with water. To create an o/w emulsion, a homogenizer emulsifies a solvent-containing medication and lipids in an aqueous emulsifier solution that is saturated with solvent. Following dilution with excess water (ratio: 1:5–1:10), the lipid nanoparticles precipitate as a result of the organic solvent diffusing from the emulsion droplets into the continuous phase. Lyophilization or ultrafiltration are two methods for removing the solvent. When compared to volatile solvents, solvent diffusion is more inventive and the majority of the solvents used have higher safety profiles.

3.3.3 Solvent injection

It is a workable new method for producing lipid nanoparticles. Using this method, lipids are dissolved in a mixture of water-soluble and water-miscible solvents, such as acetone, methanol, ethanol, and isopropyl alcohol. And then rapidly injected into an aqueous surfactant solution under continuous stirring. The additional lipid is filtered out of the resulting dispersion. The method depends on the solvent diffusing quickly over the solvent lipid that interfaces with the aqueous phase. The rate at which the organic solvent diffuses affects the size of the nanocarrier particles through the lipid-solvent interface. This method offers the advantage of easy handling, efficiency, versatility, no employment of technical equipment (e.g., high-pressure homogenizer), and use of approved organic solvents.

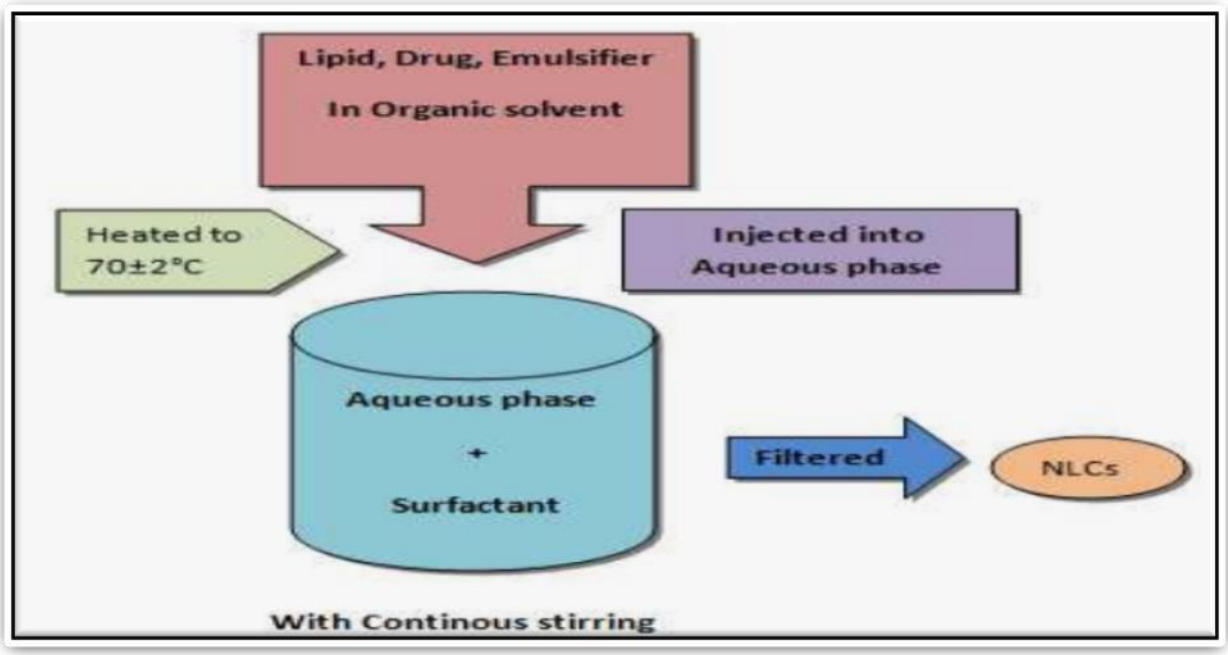

Fig 9: Solvent Injection Process

4 CHARACTERIZATION OF NLC

4.1 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

according to the diffraction angle's reliance on the area of a particle. While adding multiple emulsifiers always promotes deeper emulsification and a stronger rigid structure, size inclusion can be minimized. (46,47) The preparation process affects the particle size of NLC formulations.

4.2 Zeta potential

Zeta potential can be analyzed by the Zetasizer/PCS. Surface charge is measured to ascertain whether 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 (48). 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.

4.3 Morphological studies:

The morphological study of the NLCs can be done using

- transmission electron microscopy (TEM)
- scanning electron microscopy (SEM)
- atomic force microscopy (AFM)

For examining microscopy of the NLCs, TEM is generally used. Using this method, the carbon-coated copper grids are covered with a little drop of the NLC formulation diluted in water. These have uranyl acetate or phosphotungstic acid staining them. The drop is allowed to dry and then analyzed. The dark spots seen on the surface of NLCs are the liquid lipid sticked over the surface. The particles observed are generally of spherical or elliptical shape. (49)

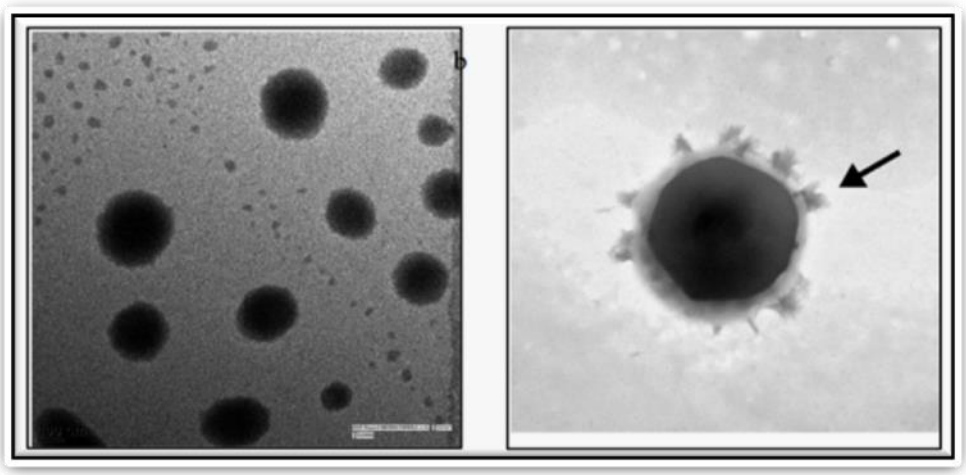

Fig 10: TEM of NLC

4.4 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. With an increase in the ratio of liquid to lipid in the particles, the crystallinity degree of nanoparticles drops (50,51).

4.5 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 (52). 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 (53). The length of the lipid lattice's long and short spacing can be determined using X-ray scattering.

4.6 Drug entrapment 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 Entrapment Efficiency (%EE) of the most effective formulations. For NLC determining drug-loading efficiency is crucial because it affects the release characteristics. Entrapment 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 Entrapment efficiency (54). EE can be calculated using following formula:

$$\text{Entrapment efficiency (EE)} = \left(\frac{\text{amount of encapsulated drug}}{\text{total drug added}} \right) \times 100$$

4.7 In vitro 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. Faster release rates are produced by lipids with shorter fatty acid chains because they have 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 (55).

5 APPLICATIONS(56-70)

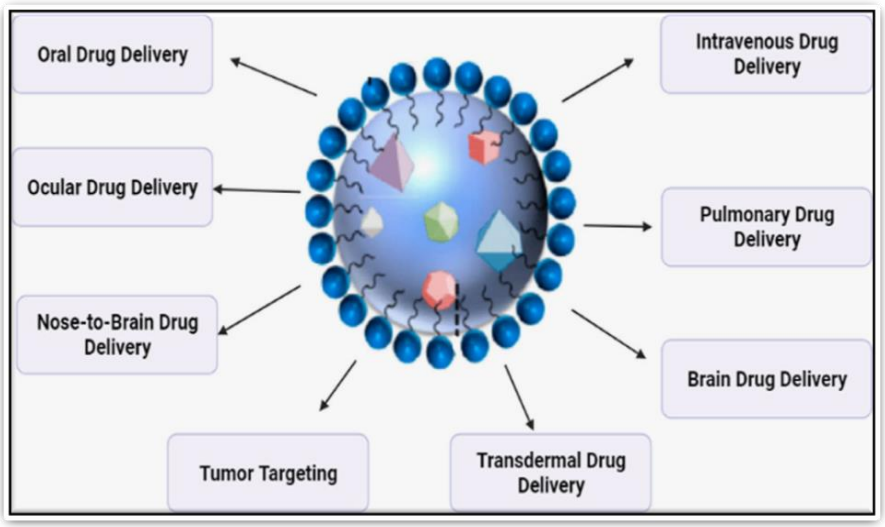

Fig 11: Applications of NLC

5.1 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 its special features has been the subject of numerous investigations and experiments in recent years NLC is used to apply many categories of medications topically for improved penetration and prolonged release. 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.

5.2 Oral delivery

NLC are 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.

5.3 Parenteral delivery

NLC of artemether (Nanoject), which significantly improves 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.

5.4 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 class 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.

5.5 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 regularly, 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 unfavourable consequences. The majority of the nebulized nanoparticles were capable of accumulating in the alveolar region of the mucus lungs, extending the duration of celecoxib lung occupancy. A precise combination of liquid and solid lipids was used to persuasively construct celecoxib, a lipophilic COX-2 inhibitor, in NLC nanoparticles.

5.6 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, bio acceptability, 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 to provide protracted medicinal value and maybe lengthen the BC half-life in vivo for Parkinson's disease therapy.

5.7 Other applications

5.7.1 Cosmetics

NLCs 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.

5.7.2 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.

5.7.3 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. Lip polyplexes are employed as nanomedicines to deliver genes successfully and effectively. These are made by combining lipids, polycations, and genes (RNA/DNA). The significance of NLC in gene transport was highlighted by its capacity to transmit genes in vitro in human lung cancer when coupled with triolein. Recently, the improved efficacy of NLC for tumour-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.

8. 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 has become one of them and has garnered a lot of interest recently. Topical and oral routes as well as intravenous administration are potential means of drug delivery from NLC. Nanoparticles of lipid 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. Even though 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. In spite of this, 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. To incorporate high molecular weight medicines like peptides, proteins, and nucleic acids utilized in cancer therapy, The range of their applications must be expanded. 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 (71,72). The number of research organizations working with NLC, as well as the number of publications in this field, has expanded dramatically during the last five years. It reflects the fact that an increasing number of academic scientists have recognized the NLCs' potential and are working to develop it. Not just in Germany, Canada, and China, but also in Slovenia and Poland, research organizations have been established all over the world. If only academic research groups are working on a delivery system, there will be no breakthrough Success is feasible if the pharmaceutical business also invests in research and development to ensure that a carrier system is widely used.

In vivo experiments are needed to properly build the tolerances and criteria that should be incorporated as specifications for NLC design. Finally, greater research on NLC absorption, distribution, metabolism, and excretion, as well as techniques to scale up their manufacturing, and their use in clinical trials in the near future, could provide an alternative for a safer and more efficient delivery route for chemotherapeutic medicines.

9. CONCLUSION

In the 20th century, Paul Ehrlich envisioned his magic bullet concept; the idea that drugs reach the right site in the body, at the right time, at the right concentration. The aim has been to develop therapeutic nanotechnology undertakings, particularly for targeted drug therapy. As the new generation, the smart NLCs offer far more adaptability in medication loading, release modulation and improved performance in producing final dosage forms such as

creams, tablets, capsules and injectables. Extending their applications should continue the effort to develop alternative routes and treat other diseases with NLCs. Permeation via the gastrointestinal tract and BBB could be a trend of the future. Another consideration for future development is the combination of the two therapeutically active agents to be included in a single nano-system.

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