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NANOSTRUCTURED LIPID CARRIERS: THE ADVANCED LIPID CARRIERS AND THEIR APPLICATIONS

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ABSTRACT: Nanostructured Lipid Carriers (NLCs) is a novel type of drug-delivery system. They are binary system which is stable in a different environment. Nanostructured Lipid Carrier (NLC) comprises a blend of solid and liquid lipids as a core matrix. NLCs have aggravated the incessant impulsion for developing safe and valuable drug delivery systems due to their exceptional physicochemical and biocompatible characteristics. Additional utilization NLCs is crucial because of overcoming barriers enclosed by the technological procedure of lipid-based nanocarriers' formulation and raised data on the core mechanisms of their transport via numerous routes of administration. NLC it can be easily used as a carrier for drugs *via* different routes of administration such as oral, parenteral, ocular, and nasal. Nanostructured lipid carriers (NLCs) have been reported to be an alternative system and are considered superior to many other traditional lipid-based nanocarriers such as emulsions, nanoemulsion, liposome, microparticle, and solid lipid nanoparticle (SLNs). It imparts many advantages over SLN's such as increased solubility and stability, improved permeability and bioavailability, enhanced drug loading capacity, drug release modulation flexibility, reduced adverse effects, prolonged half-life, and tissue-targeted delivery. This review highlights the NLC with a focus on the structure, preparation methods, characterization of NLCs, formulations, pharmaceutical and therapeutic applications towards targeted drug delivery of NLC in delivery systems.

INTRODUCTION: Nanotechnology has developed exponentially. Nano-technology has practically made its influence in all technical fields, including pharmaceutics. Nanoparticulate systems such as liposomes were described for the first time in the 1960s by Bangham *et al.*

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In 1990s, solid lipid nanoparticles (SLN) were firstly developed by Muller and Gasco by avoiding organic solvents which were involved in the preparations of polymeric nanoparticles. SLNs are sub micronic colloidal nanocarriers containing solids ranging from 1 to 1000 nm.

SLN's use only solid lipids. Recently, SLNs based on a mixture of solid lipid and liquid lipids called nanostructured lipid carriers studied a size range of 1-100nm [1]. NLC's minimized many problems like drug expulsion during storage which are associated with SLN formulation for many drugs due to its high water content.

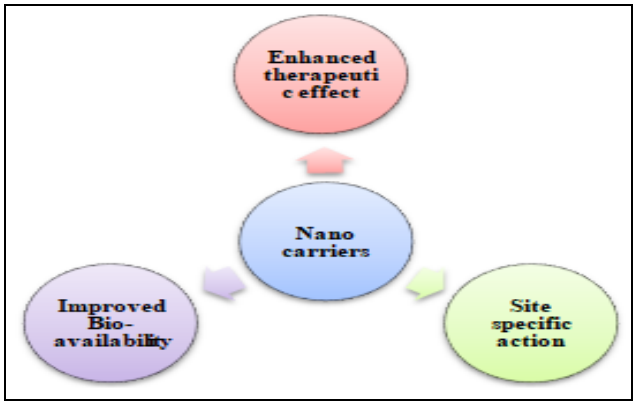

FIG. 1: IMPORTANT ASPECTS OF NANO CARRIERS[1]

Lipid nanoformulations build dispersions of fairly soluble drugs. They might decrease the characteristic restrictions of slow and imperfect dissolution of fairly water-soluble drugs like Biopharmaceutics Classification System (BCS) class II and change the formation of solubilized phases from that drug absorption happens easily.

In any other vehicle mediate delivery system like an emulsion, liposome the degree and mode of drug release from the system are vital to the movement of the delivery system *in-vivo* [2].

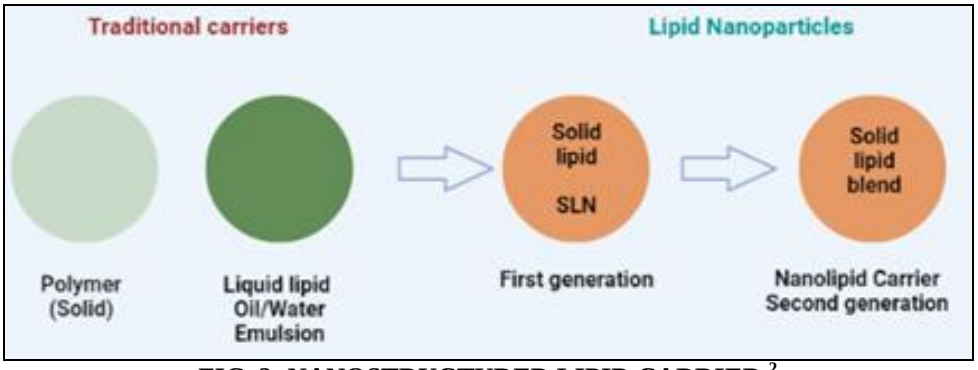

FIG. 2: NANOSTRUCTURED LIPID CARRIER [2]

Advantages of NLC's:

1. Improve physical stability.
2. Controlled particle size and targeted drug release.
3. High entrapment of lipophilic drug and feasibility of carrying both lipophilic and hydrophilic drug.
4. Easier to validate.
5. Superior drug loading when compared with SLNs.
6. As it is water-based methods, organic solvents can be avoided.
7. Delivers great and higher drug content as related to other carrier.
8. Most lipids are biocompatible and biodegradable.[3]

Limitations with Nanoparticles:

1. Cytotoxic effects due to concentration of matrix and nature.
2. Irritative and sensitizing action of some surfactants.
3. Lack of sufficient pre-clinical and clinical studies of these nanocarriers in case of bone repair.

Structure of NLC's: The structure of NLCs is similar to SLN's. The three types of NLC can be summarized based on the location the drug will be integrated and on variation in the lipid composition [5-8].

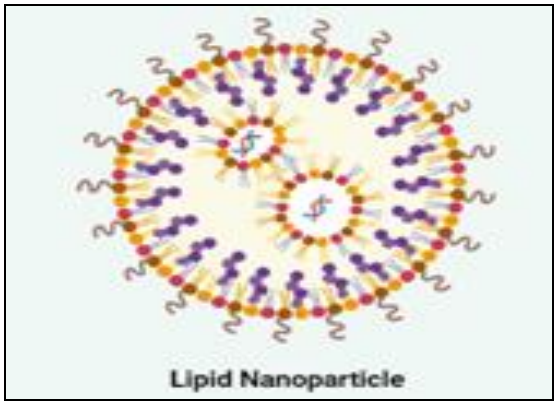

FIG. 3: STRUCTURE OF NANOPARTICLES

- NLC type I or Imperfect crystal.
- NLC type Π or multiple types.
- NLC type ш or amorphous type.

NLC type I or Imperfect Crystal:

- In type, I low concentration of liquid lipid is used as compared to solid lipid. The imperfect crystal type has a mixing of spatially different lipids such as glycerides which are used to improve the structure [5].

NLC type Π or multiple types:

- NLC type Π or multiple types, also called oil-lipid-in-water type. The drug's solubility is higher than solid lipids' solubility. It contains numerous nano compartments distributed in a solid lipid matrix. The release of drug is prolonged and permits controlled drug release [9, 10].

NLC type ш or amorphous type:

- A structureless amorphous matrix is formed by mixing solid lipids with special lipids such as hydroxyl stearate, MCT or iso-propyl myristate [11]. The lipid matrix is solid, but in an amorphous state non-crystalline, NLC is formed [2, 12].

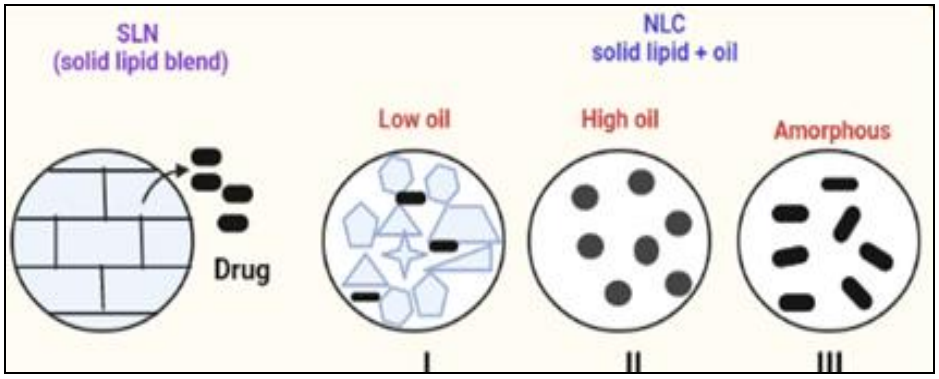

FIG. 4: (A) IMPERFECT CRYSTAL, (B) MULTIPLE TYPE, (C) AMORPHOUS TYPE OR MODEL OF NLC'S [3]

Drug Release: The release of the drugs from a matrix depends upon the rate of degradation and diffusion just in case of NLC's. The literature well documented that it's required to possess precise and controlled release going on the far side diffusion and degradation. An impulse should trigger the particle once a particle is administered the release. The drug can have to be compelled to trap in NLC's due to their unordered and unorganized lipid structure. By applying different strategies and techniques, the lipid structure is often modified, which converts the lipid molecule's structure, and therefore, current drug release can be initiated as shown in **Fig. 4** [2].

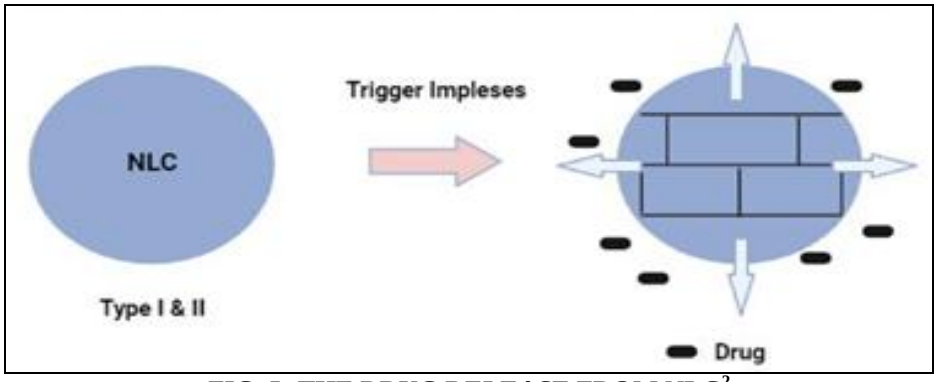

FIG. 5: THE DRUG RELEASE FROM NLC[2]

Components and formulation Attributes: Basically, lipid, itself, is the main ingredient of NLC that influences their drug loading capacity, their stability, and the sustained release behaviour of the formulation. Generally the selection of lipids relies on physicochemical structure, drug solubility, physiological tolerance and solid /liquid lipid miscibility. The concentration of lipids used should be categorized as Generally Recognized as Safe (GRAS) which could not produce significant toxic effects [5].

The physicochemical structure will determine the state of lipid at room temperature. The solubility of

the drug in lipids should be essentially determined. It is preferred to blend solid lipid and liquid lipid in a ratio of 70:30up to 99.9:0.1; depending upon formulation attributes, the ratio may vary [3].

If higher the liquid lipid content, then faster drug release was observed. The NLCs may be stabilized by a single surfactant or a combination of more than one surfactant. The type and concentration of surfactant play an important role in designing NLCs. Generally higher the concentration of surfactant, the smaller the particle size.

Solid Lipids: A combination of numerous chemical compounds with a melting point higher than 40 °C.

These solid lipids are well tolerated.

- Accepted for human use.
- Also *in-vivo* biodegradable [13-15].

TABLE 1: SOLID LIPIDS USED FOR PREPARATION OF NLCS [5, 65]

Ingredients	Examples
Solid lipids	
Fatty acids / Hard fats	Stearic acid [42,43], Palmitic acid , Myristic acid
Mono, Di, Tri-glycerides	Glyceryl monostearate[44-48], Glyceryl behenate[49,50], Glyceryl palmitostearate[51-55], Glyceryl dibehenate, Caprate and Caprylate Triglycerides[56]
Waxes	Beeswax, Cetyl palmitate[57-59], Carnauba wax[60]
Triglycerides	Tristearin, Tripalmitin, Trimyristin

Liquid Lipids: These oils or lipids typically used for NLCs. These are well tolerated and accepted for human use [2].

TABLE 2: LIQUID LIPIDS USED FOR PREPARATION OF NLCS [5, 65]

Liquid lipids	
Natural oils	Soya bean oil, Palm oil, Coconut oil, Olive oil, Almond oil, Corn oil [61], Peppermint oil
Synthetic lipids	Medium chain triglycerides, Paraffin oil, Oleic acid [62], Squalene [52, 53], Isopropyl myristate [63], Transcutol, Labrafac PG, Capryol 90, α-tocopherol

Emulsifying agents - Surfactants: The surfactant or emulsifiers are used to stabilize the liquid dispersion.

These are the compounds that reduce the surface tension between two phases. The properties of the NLCs are really influenced by the type of surfactant used in the formulation. It has been found that a combination of emulsifiers can prevent particle aggregation more efficiently.

Required HLB (rHLB) value plays a very significant role while selecting the suitable type and amount of surfactant for NLC formulation [41].

TABLE 3: SURFACTANT USED FOR PREPARATION OF NLCS [16]

Emulsifiers	
Hydrophilic emulsifier	Pluronic®F68, Pluronic®F127, Tween 20 [64], Tween 40, Tween 80 [49, 50], Sodium oleate [66, 67], Polyvinyl alcohol
Lipophilic emulsifier	Span 20, Span 60 [66, 67]
Amphiphilic emulsifier	Egg lecithin, Soya lecithin

Methods of Preparation of NLCs: There are several methods for preparing colloidal carries or NLCs. These are as follows:

- High-pressure homogenization.
- Microemulsion techniques.
- Emulsification solvent diffusion method.
- Multiple emulsion techniques.
- Phase inversion method.
- Ultrasonication.
- Membrane contractor technique.
- Solvent injection or displacement method [2, 3, 17, 18].

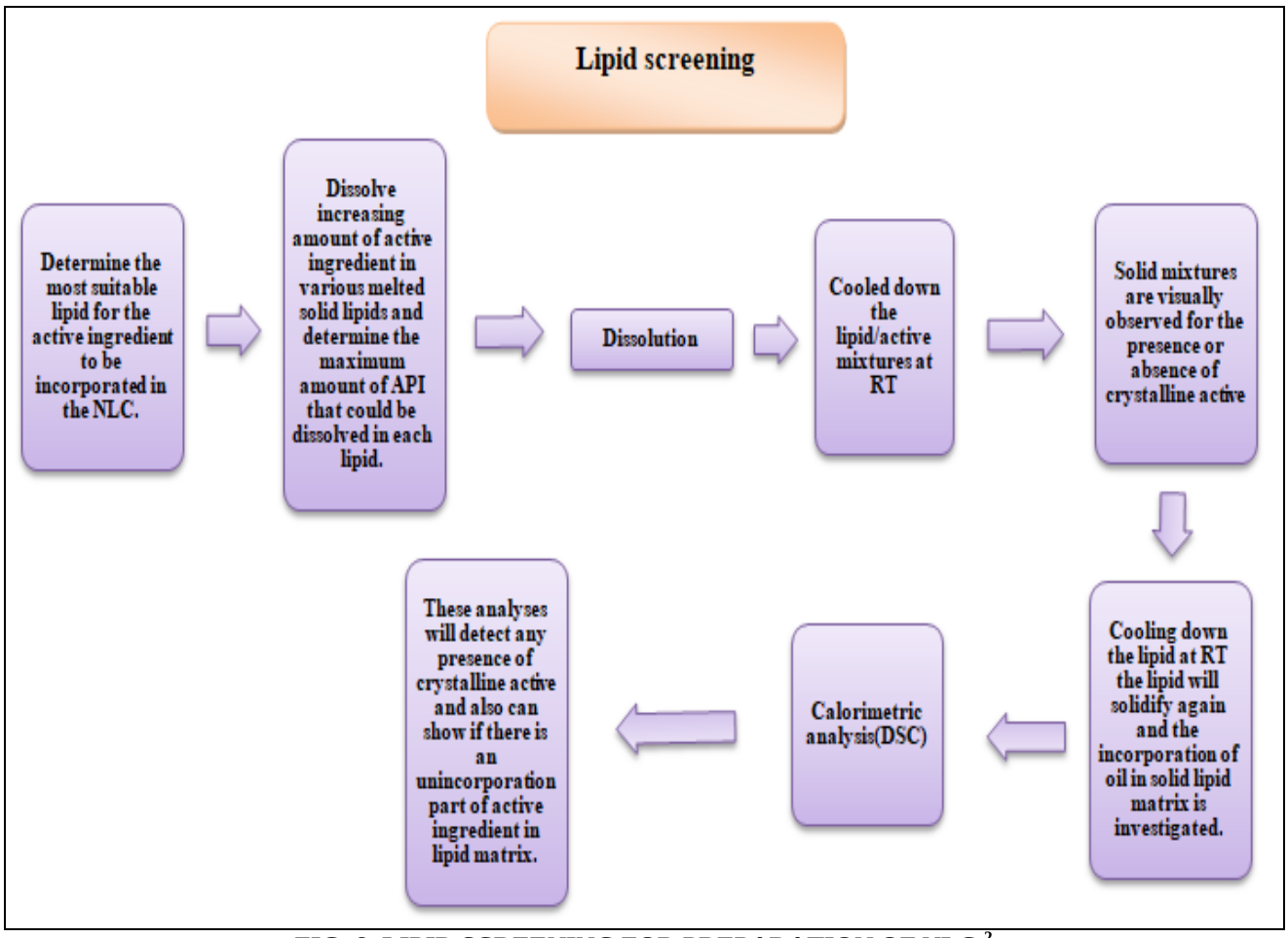

FIG. 6: LIPID SCREENING FOR PREPARATION OF NLC [2]

1. High-Pressure Homogenization: During this procedure, a stable emulsion will be created that involves the division of particles into Nano size. Within the market, 2 forms of homogenizers are accessible a) jet-stream homogenizers b) piston-gap homogenizers [19, 20]. HPH has been used as a reliable and vital approach for the large-scale production of NLCs, lipid drug conjugate, SLNs and parenteral emulsions. The lipid is pushed with high pressure (100 – 2000bars) through veritably high shear stress, performing in dislocation of particles all the way down to the sub-micrometer or nanometre vary. Usually, the lipid contents are within the vary of 5-10% [1, 3]. In contrast to alternative medication strategies, high-pressure homogenization does not show up bother. Homogenization is also achieved either at raised temperature (hot homogenization) or below room temperature (cold homogenization).

❖ **Advantages:**

- Wisely utilized in the food and dairy farm industries and cosmetic trade.
- It increased the product shelf life, stability, digestion.
- It increased the taste of the formulation.
- It considerably reduces the amount of additives.
- Important for quality and stability of the product within the cosmetic business.
- By homogenization bioavailability of the formulation will be increased.
- Economical.
- Microbiological contamination is clearly less.[2]

1.1. Hot homogenization Technique: In this technique the drug together with molten lipid is dispersed below steady stirring by a high shear device within the aqueous surface-active agent solution of even temperature. The pre-emulsion acquired is homogenized by using a piston gap homogenizer. The earned nanoemulsion is cooled all the way down to temperature wherever the lipid

recrystallizes and results in the formation of nanoparticles [1].

❖ **Merits:**

1. Science lab scale and huge scale relevance.
2. Narrow particle size distribution.
3. Low polydispersity index.

❖ **Demerits:**

1. Sample remains in supercooled melt state for months rather than solid-state.
2. Increasing the rate of homogenization results in an increase in particle size cause coalescence thanks to the high kinetic energy of particles [3].

1.2. Cold Homogenization Technique: Cold homogenization is dispensed with the solid lipid-bearing drug. Cold homogenization has been developed to overmatch the difficulties of the hot homogenization technique analogous as temperature mediate accelerated degradation of the drug load, partitioning, and therefore loss of drug into the aqueous phase throughout homogenization.

The primary step of each the cold and hot homogenization strategies is that the same. Within the posterior step, the melt containing drug is cooled quickly using ice or liquid nitrogen for distribution of drug within the lipid matrix. Cold homogenization minimizes the thermal exposure of the sampling [1].

❖ **Merits:**

1. Prevents temperature-induced degradation of thermolabile drugs and lipids.
2. Prevents the complexity of the crystallization step of nanoemulsion, leading to modification in supercooled melts.
3. High cooling rate favors higher distribution of the drug in a very lipid matrix.

❖ **Demerits:**

1. Larger particle size and larger particle size distribution compared to hot homogenization.
2. Effective temperature control and regulation are needed to confirm the unmolten state of lipid.
3. Costly [3]

2. Microemulsion Techniques: Melted lipid-containing drug is mixed with a surface-active agent Co-surfactant containing aqueous phase is ready at an equivalent temperature because the lipid in such a proportion to make a small emulsion. The hot microemulsion is additionally diluted by more than cold water. The unexpected reduction in temperature causes the breaking of the microemulsion, converting into a nanoemulsion, which upon recrystallization of the lipid part produces lipid molecules.[40]

3. Emulsification Solvent Diffusion Method: In this method, an o/ w emulsion consists of an organic phase with partially water-miscible solvents (e.g., benzyl alcohol, tetrahydrofuran) saturated with water to assure the original thermodynamical stabilization of both liquids. Particles with a mean diameter of 30-100 nm may be attained by this technique. Rejection of heat throughout preparation is the most important advantage of this method.

4. Multiple Emulsion Techniques: This is a changed solvent emulsification-evaporation technique predicated on a w/ o/ w double emulsion. The drug is dissolved in an aqueous solution and emulsified within the molten lipid. The stabilizing agents stabilize this primary emulsion.

The double emulsion technique avoids the condition of melting the lipid for the preparation of peptide-loaded lipid nanoparticles. Therefore, the surface of the nanoparticles might be changed to stabilize them using the manifestation of lipid-PEG derivates.

5. Phase Inversion Method: It involves adding formulation components with magnetic stirring and posterior heating and cooling cycles with dilution below cooling conditions. 3 cycles of heating and cooling from room temperature to 85 ºC and back to 60 ºC are thereafter applied at a rate of 4 ºC/ min. This heating treatment causes the inversion of the emulsion.

❖ **Merits:** Suitable for thermosensitive medicine and avoids the use of organic solvents.

❖ **Demerits:** Tedious method [11].

6. Ultrasonication: Ultrasonication relies on the mechanism of cavitation. In the beginning, the drug is added to already molten solid lipids. Within another step, the heated aqueous phase (heated to an equal temperature) is added to the melted lipid and emulsified by using high- a speed stirrer. The aqueous phase drops to the lipid phase with magnetic stirring. The attained emulsion is ultrasonicated using a probe sonicator. To prevent crystallization throughout the method, the product temperature is kept a minimum of 5 ºC higher than the lipid melting point.

7. Solvent Injection or Displacement Method: A lipid solution in an exceedingly very water-miscible solvent or a mixture of solvents is injected into an aqueous phase with or without a surface-active agent. During this procedure, an o/ w emulsion is made by injecting the organic phase into the aqueous phase under magnetic stir to make a Nanoemulsion.

8. Membrane Contractor Technique: Small lipid globules are acquired by pressing the melted lipid against the porous membrane. Coincidentally, they are circulated within the membrane module and sweep far from the opening. NLCs are formed after cooled at room temperature [17].

Stability of Nanostructured Lipid Dispersions: NLC may contain various colloidal structures, such as micelles, mixed micelles, liposomes, and nanoemulsions which impact the stability of the formulation. In highly concentrated NLC dispersions, the pearl-like network of particles is observed; thus, the formation of a network leads to the prevention of collision and perikinetic flocculation. Physical instability of NLC in terms of aggregation and shell formation during storage is a major concern [1]. Preservatives are used to maintain physical stability, especially in products that mainly contain fluid or semisolid preparations containing water as the dispersion media.

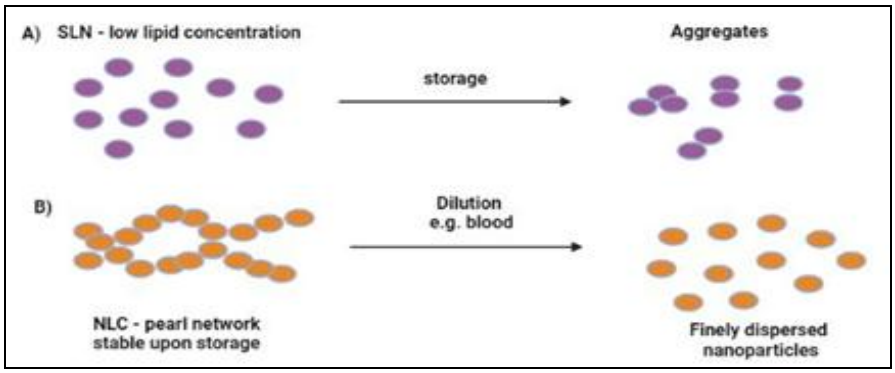

FIG. 7: STABILIZATION EFFECT A) AGGREGATE FORMATION FROM LIPID PARTICLE B) PERL-LIKE NETWORK FORMATION IN NLC'S DISPERSION [11]

Strategies to Overcome Stability Issue of NLCs:

1. Polyethylene Glycol:

- Providing good dispersibility and physical stability of colloids.
- Improves colloidal presence in blood circulation for systemic use.
- Increase the stability of colloids in gastrointestinal fluid,
- Decreasing thrombogenicity of drug carriers.
- Increasing biocompatibility.

2. Spray Drying:

- The NLCs dispersion can be spray dried, to increase their stability.
- The lipids having melting point more than 70℃ are recommended.

3. Lyophilization:

- Another efficient way for the long-term stability of a product containing hydrolysable drugs is lyophilization.
- When SLN/NLC is lyophilized without cryoprotectant, the final product commonly results in the aggregation of particles. Examples of cryoprotectants are glucose, sucrose, maltose, mannose, sorbitol, and trehalose [39].

Factors Affecting Drug Release: Several factors affect the release of drugs from the NLC system.

1. Particle size: It is a crucial factor of a colloidal system for the release of the drug incorporated inside the matrix and affects the stability, solubility and biological performance of NLC dispersion. Usually NLC has a diameter in a range of 10-1000 nm. A 50-300 nm range for site-specific delivery is preferred for CNS disorders. The size above 300 nm provides sustained drug delivery.

2. Lipid Matrix: Lipids' different crystal order, melting points, and HLB values lead to different release profiles. The drug's affinity to be entrapped inside the lipid matrix varies from one lipid to another.

3. Surfactant: The surfactant influences the physicochemical properties of NLCs. Surfactants used to stabilize particles in dispersion media. The affinity of surfactant for lipid differs depending upon HLB value and molecular weight of surfactant molecules.

4. Drug Loading: It might affect the release profile of drug. It depends on the affinity of drug to mix the lipid.

5. Drug type: It affects the release of profile because, with different drug compositions, there are different affinities to lipid.

6. Bioavailability and Bioequivalence: The bioequivalence appraisal of the test and reference product is based on studies with pharmaco-dynamic measurements [3].

7. Entrapment Efficiency (EE): Entrapment efficiency is a critical factor which needs to be optimized during formulation design as it has an impact on the release of drug. The entrapment of drug is increased by the formation of a rigid solid lipid after cooling.

The imperfection in lipid crystal structure of lipid show higher entrapment efficiency (EE). Therefore, in NLC, the presence of liquid lipid increases the imperfections in the lipid crystal structure, thereby further increasing in EE [22].

8. *In-vitro* Release: The drug release actions of NLC is dependent on the type of solid lipid used, proportion of oil, production temperature and emulsifier concentration.

In utmost of the cases, release of the drug is controlled by slow dissolution rate in the aqueous environment and the degradation rate of the lipids.

The release profile is generally biphasic with an original burst release due to the drug present on the surface of the nanoparticles followed by a prolonged release of the drug from the core [21, 22, 23].

9. Zeta Potential: Zeta potential is the electric potential of a particle at a location away from the particle surface, nearly in the diffuse layer. This location, related to particle movement in liquid, is called the slipping or shear plane.

The potential measured at this plane is called zeta potential, a truly important parameter for colloids or nanoparticles in suspension. Its value is nearly bonded to suspension stability and particle surface morphology [24].

Applications in Drug Delivery:

1. Oral Delivery: The oral route is the most preferred route owing to its painlessness, accurate dosing, ease of administration, and patient compliance [17]. NLCs have been proved as one of the beneficent systems for peroral administration of poorly water-soluble drugs owning low bioavailability.

Thus, novel drug delivery systems are needed to overcome these limitations and enhance therapeutic efficiency leading to dose reduction and relief of side effects.

NLC has been particularly used for oral administration to improve oral bioavailability by enhancing the uptake of drugs by lymphatic complex *via* micro fold cell (M cells) in the intestinal membrane and bypassing the first pass metabolism.

Inside the GIT, the lipids in the NLC are digested incompletely in the stomach and also in the small intestines into diglycerides and free fatty acids.

Lipids also decrease transit and therefore increase the residence time in stomach and upper small intestine, directing to enhanced absorption [11, 25].

To resolve insolubility concerns, NLCs can entrap lipophilic drugs.

TABLE 4: NLC FORMULATION FOR ORAL DELIVER

Active Ingredient	Method of preparation	Research highlights	References
Docetaxel	Emulsification-ultrasonication	The DNLCs achieved excellent drug entrapment, a satisfactory particle size and good GI stability. Results indicate that the NLCs are very promising method for enhancing the oral absorption of anticancer drugs	68
Carvedilol	Emulsification-ultrasonication	NLC formulation remarkably improved the oral bioavailability of CAR. The promising findings in this investigation suggest the practicability of these systems for the enhancement of bioavailability of CAR	69
Hydrochlorothiazide	Homogenization-ultrasonication (HU) and Microemulsion (ME),	HCT-loaded NLC formulations showed higher stability than the corresponding SLNs	70
Nimodipine	High-pressure homogenization	NMP-NLC shared a spherical shape of ~70 nm. High encapsulation efficiency of 86.8%±2.1%	71
Simvastatin	Emulsification-solvent evaporation technique	A single dose of SIM-NLC, 4-fold increase in bioavailability was observed, as compared to the SIM suspension	72
Candesartan Cilexetil	Hot homogenization-ultrasonication	The oral bioavailability of candesartan cilexetile was remarkably improved above 2-fold after encapsulation into nanostructured lipid carriers	73
Quercetin	High-pressure homogenization	The optimized QT-NLC, the average particle size, the zeta potential and the average entrapment efficiency were 129 ± 12.13 nm, −26 ± 4 mV and 93.50 ± 0.35%, respectively	74

2. Topical Delivery: Topical delivery is preferable for skin diseases. Compared to other administration routes such as oral and parenteral, the topical delivery reduced systemic side effects. It also bypasses the first pass metabolism and maintains the drug concentration at the site of action for longer periods. The challenging part of this delivery system is the low drug uptake owing to the stratum corneum, which acts as a barrier for both therapeutic and toxic molecules. Recently, lipid nanoparticles have acquired attention as novel colloidal carriers for topical delivery.

NLCs have various advantages and unique properties of providing control release, protection of the active component, enhanced permeability into the skin, and minimal skin irritation [11].

TABLE 5: NLC FORMULATION FOR TOPICAL DELIVERY

Active Ingredient	Method of preparation	Research highlights	References
Aceclofenac	Melt-emulsification	NLC gel showed a rapid onset of action and prolonged duration of action as compared with the marketed gel	75
Terbinafine hydrochloride	High-pressure homogenization	NLC formulation showed better permeation into the skin and reduced fungal burden in a shorter duration of time as compared to marketed gel preparation	76
Clotrimazole	High-pressure homogenization	NLC showed a faster release	77
Apremilast	Cold homogenization technique	Nanostructured lipid form of poorly water-soluble drug increased drug deposition in the skin.	78
Diacerein	Hot homogenization-ultrasonication	NLC-based gel showed quicker start and sustained operation for up to 24 hours	79

3. Intranasal Delivery: Intranasal drug delivery is a safe and noninvasive alternative way to the parenteral route of administration. This route offers so many advantages, such as, rapid absorption because of high surface area, porous endothelium of nasal mucosa having rich blood supply, and avoids hepatic as well as GI metabolism. This route shows lesser side effects which give better patient compliance. NLC formulation by intranasal route has been analyzed thoroughly for enhanced drug delivery to the brain [26]. There are various pathways involved in intranasal drug delivery to the brain, including: **the** first one is a systemic pathway in which drug is absorbed across the nasal cavity into the systemic circulation and then crosses BBB into the brain.

The second one is an olfactory pathway in which drug passes through the olfactory epithelium (paracellularly and extracellularly) into the olfactory bulb and further into brain tissue. The third one is a trigeminal pathway; in this pathway, the drug is transported through this nerve system. The olfactory nerve pathway is a major component of intranasal delivery [27].

TABLE 6: NLC FORMULATION FOR INTRANASAL DELIVERY

Active Ingredient	Method of preparation	Research highlights	References
Artemether	Microemulsion method	ARM-NLC showed the highest drug targeting efficiency and drug transport percentage	80
Phenytoin	Melt emulsification	NLC Formulation strategies can enhance olfactory uptake	81
Asenapine maleate	High shear homogenization and sonication	The results of behaviour studies showed a significant decrease in extra-pyramidal side effects with increasing antipsychotic effect after 1–2 week(s) of treatment	82
Carbamazepine	Microemulsion followed by probe sonication	Improved anticonvulsant activity	83
Curcumin	Hot high pressure homogenization	CRMNLC with improved drug incorporation and release properties	84
Venlafaxine	High shear homogenization method	Full factorial 32 design was applied	85

4. Ocular Delivery: Topical administration is noninvasive and the most desired route of administration, especially to the anterior eye segment. Nevertheless, the ocular bioavailability of the medicine is very low, mainly due to low residence time at the target tissue. Alternative routes like intravitreal and sub-conjunctival infections are affiliated with risks such as bleeding, eye infection, and loss of vision [28, 29]. Usually, NLCs can overcome the ocular barrier by various mechanisms;

- Prolongation of drug release and enhanced residence time of the encapsulated drug.
- Development of ocular bioavailability of the encapsulated drug by way of both transcellular and paracellular mechanisms.
- Overcome ocular blood barriers.
- Strengthen the encapsulated drugs against inactivation by lacrimal enzymes.
- Upraise the patient compliance by decreasing the dosing frequency [17].

TABLE 7: NLC FORMULATION FOR OCULAR DELIVERY

Active Ingredient	Method of preparation	Research highlights	References
Lactoferrin	double emulsion/solvent evaporation	High EE and LC values were obtained (up to 75%)	86
Celecoxib	Microemulsion template technique	Study showed faster onset and elicited prolonged activity until 24 h	87
Ciprofloxacin	Hot homogenization	It prolongs the residence time on the ocular surface after topical administration, improves ocular bioavailability	88
Curcumin	Hot-melt emulsification and ultrasonication	The formulation enhanced curcumin permeation across excised corneas	89
Natamycin	Emulsification-ultrasonication	improved corneal penetration, increased antifungal activity without cytotoxic effects on corneal tissues	90
Dexamethasone	Ultrasonication	For the stability and the entrapment efficacy of NLCs; lower surfactant and lipid concentrations could be beneficial	91
Propranolol	Cold homogenization	NLC formulations improved propranolol hydrochloride permeation	92

5. Delivery to the Brain: The brain is highly defended by diffusion, preventing the blood-brain barrier (BBB). Drug delivery to the brain is a great challenge as nearly 98% of the newly discovered medicine are unable to cross BBB [31, 32]. NLCs of this generation is considered to be one of the major strategies for drug delivery without any modification to the drug molecule due to their rapid

uptake by the brain, acceptability and biodegradability. The major advantages of this route are;

- Avoid hepatic first-pass metabolism.
- Fast onset of action as compared to oral route.
- Reduces the dosing frequency. The NLCs of Asenapine (ANS) maleate were found to have enhanced uptake of ANS to the brain and show improved bioavailability [33].

TABLE 8: NLC FORMULATION FOR DELIVERY TO THE BRAIN

Active Ingredient	Method of preparation	Research highlights	References
Artemisinin	solvent evaporation method	ART-loaded NLCs can be successfully achieved high entrapment efficiency and a controlled drug release profile suitable for brain administration	93
Atazanavir	Melt emulsification	Greater Cmax in the brain and 4-fold improvement in brain bioavailability	94
Flibanserin	Hot emulsification–ultrasonication	To improve the drug bioavailability	95
Itraconazole	Hot and high-pressure homogenization	An in vivo study showed that ITZ-NLCs could increase the ITZ concentration in the brain by almost twofold.	96
Rivastigmine	High-pressure homogenization, ultrasound technique	HPH was selected as the most suitable production method, although the ultrasound technique has also shown effectiveness	97
Temozolomide	High-pressure homogenization	Improved delivery of the chemotherapeutic agent to the brain with the potential of lesser side effects	98

6. Parenteral Delivery: The Nano drug delivery systems, namely nanoemulsion, nano-micelles, and nanoparticles have revealed great potential in the improved parenteral delivery of hydrophobic agents over the time of last two decades. NLC has been assessed as an alternative to liposomes and emulsions because of advanced properties like the ease in manufacturing, high drug loading aqueous nature, and biocompatibility of excipients has empowered intravenous drug delivery with passive targeting ability. NLCs of artemether (Nanoject) significantly improve anti-malarial activity and duration of action compared to the conventional injectable formulation [34].

TABLE 9: NLC FORMULATION FOR PARENTERAL DELIVERY

Active Ingredient	Method of preparation	Research highlights	References
Articaine	Emulsification-ultrasonication	The developed formulation showed average particle sizes of 237.6 ± 3.3 nm, low polydispersity (PDI=0.169 ±0.015) and negative zeta potentials (-42.1 ± 0.5 mV), suitable for parenteral application	99
Buparvaquone	High-pressure homogenization	To improve the availability of affordable medicines	100, 101
Carvacro	Warm microemulsion	increasing its *in-vitro* leishmanicidal efficacy in the amastigote form	102
All-trans retinoic acid	Ultrasonication technique.	All ATRA-loaded NLC formulations exhibited a photoprotective property and higher anticancer activity than the free drug on human carcinoma cell lines.	103
Silybin	Emulsion evaporation	The resultant NLC had a mean size 232.1 nm and a zeta potential of −20.7 mV, Silybin-NLC showed higher AUC values and a prolonged residence time of drug in the blood circulation	104

Other Applications:

Cosmetic: Recently, NLCs have been developed based on the controlled nanostructuring of particle-matrix, providing enormous advantages concerning loading capacity and long-term stability. NLC dispersions can be given in various forms: gel, cream, lotion, and ointment.

Chemotherapy: Different nano-systems have been developed with anti-cancer drugs. Their studies have shown that NLCs reduce the side effects of many cytotoxic drugs and enhance efficacy and stability.

Nutraceuticals: These are bioactive compounds that give medicinal or health benefits. It includes prevention and treatment of the diseases. The carotenoids are one of the most important among the group of natural pigments. Carotene-LNC with enhanced antioxidant and significant antibacterial activities were effectively produced by using natural oils [1].

TABLE 10: NLC FORMULATION FOR NUTRACEUTICALS

Active Ingredient	Method of preparation	Research highlights	References
Conjugated linoleic acid	Hot high-shear homogenization	Nanostructured lipid carriers system is an appropriate and stable nanocarrier system for the delivery of nutraceuticals in foods and can be used to protect them against oxidation, heating, and other processes in order to fortify foods and beverages	105

CONCLUSION: The lipid Nanoparticulate delivery systems like SLN, NLC, LNC, *etc.*, have been potential carrier systems with good therapeutic applications and are extensively used in the biomedical field. This work aimed to highlight the role of NLCs as a novel drug delivery system for efficient delivery of various categories of drugs by various routes of administration like intranasal, oral, ocular, and parenteral routes. They are 'Smart, new generation system which offers much more flexibility in drug loading, modulation release and improved performance in producing final dosage forms like tablets, capsules, creams, and injectables. The impact of this carrier system (NLCs) continuously increases due to their rapid uptake, bioacceptability, and biodegradability. The lipid carriers have the property to improve the bioavailability of lipophilic drugs with low water solubility. The lipid nanocarriers (LNC) offer an economical and patient-friendly device for drug administration.

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