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A Comprehensive Review on Nano Structured Lipid Carriers (NLCs)

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ABSTRACT :

Nanostructured Lipid Carriers (NLC) are Nano-sized colloidal drug delivery systems containing a mixture of solid and liquid lipids in their core. As a biocompatible, nontoxic, and safe nano-drug delivery system compared to polymeric or metallic nanoparticles, this Lipid-Based Nanosystem has been introduced. With higher drug loading capacity and improved stability and safety over other lipid-based nanocarriers, NLC has gained researchers' attention for formulating safe and effective drug carriers. Encapsulating drugs in a lipid shell while increasing their solubility and permeability makes NLC an ideal carrier for delivering drugs through difficult routes. Surface modification of NLC and various additives enable drug targeting and increased residence time. With these qualities, NLCs can treat diseases like cancer, infections, neurodegenerative diseases, hypertension, diabetes, and pain. This review focuses on advantages, applications of NLCs, different types of NLCs, composition, NLCs preparation methods and evaluation tests.

Key words: NLCs, Lipid-Based Nanosystem, Biocompatible.

1. Introduction :

The oral route is the most often used method of drug absorption since it is the safest, easiest to use, and provides patient compliance. It is chosen as the intake route for typical treatments, including the long-term therapy of several chronic diseases including diabetes, hypertension, cardiovascular problems, and cancer, since it provides systemic effects through absorption in the gastrointestinal tract. On the other hand, oral administration could have a delayed onset of action and low absorption. Furthermore, poor absorption and insufficient therapeutic activity in the target site result from the physiochemical character of medicines with low solubility and/or low permeability in the gastrointestinal obstacles arise from the physiology of GIT-challenging medications (Aldemar Gordillo-Galeano *et al*., 2018).

Safe and efficient drug delivery necessitates an efficient drug delivery system. While many different carrier systems are being investigated, the goal is to find a stable, biocompatible, and biodegradable system that can target particular organs. These characteristics are the result of the carrier system's fabrication materials. Biocompatibility and biodegradability, which are challenging to accomplish with other materials, are provided by lipids. These lipid-based systems offer qualities that are hard to achieve in their bulk equivalents when they are employed as nanoscale carriers. The development of nanostructured lipid carriers (NLCs) as a potential medication delivery vehicle

NLC is a nanocarrier that, in addition to having a higher drug loading capacity and greater stability than SLN, possesses the benefits of earlier lipidic nanoparticles. Because of the qualities they provided, NLCs entered the cosmetics industry in 2005, and as of right now, the market has about 40 cosmetic goods. The effective encapsulation capacity and intrinsic features of NLC have prevented this system from being introduced to the market as a medication delivery device. Includes a variety of lipid-based nanocarrier types

As the name implies, NLCs are multiparticulate systems that are nanoscale, ranging in size from 50 nm to 500 nm. The content and method of nanoparticle manufacture determine the NLC particle size dispersion. This particle is colloidal in nature and has a structure similar to SLN, with the primary difference being in the core.14 NLC has lipid liquid in addition to a solid lipid core, forming a disorganized drug matrix, in contrast to SLN, which has a solid lipid core with highly organized lipid arrangement. In addition to stability problems seen during long-term storage of SLN due to crystallization and drug expulsion, this disorganized character allows for the loading of more pharmaceuticals into the core, which can then be corrected by NLC.11 The foundation of NLC is made (Saba khan *et al*., 2015).

Advantages

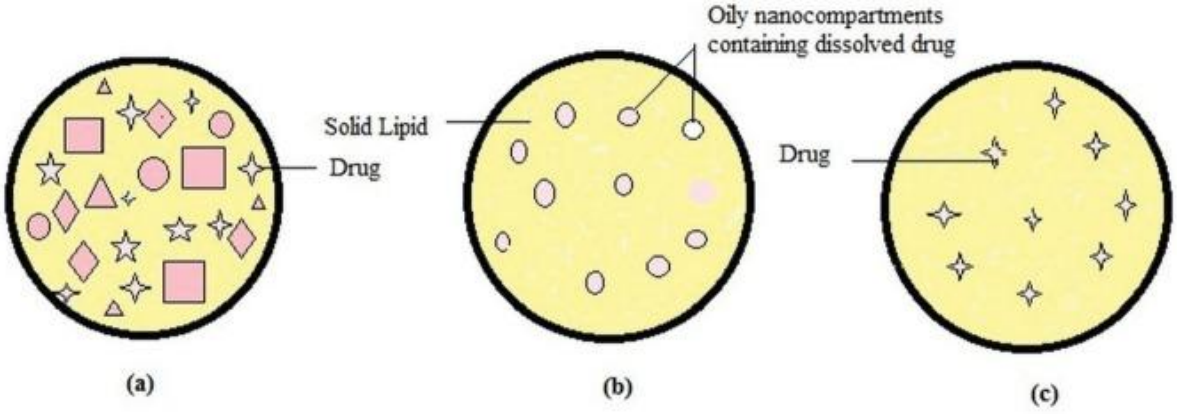
- Extended the duration of the drug's release
- Increased likelihood of drug loading and entrapment
- Greater physical stability
- Minimum surfactant concentration for maximal medication loading capacity
- NLC exhibits superior biocompatibility

1.2 Disadvantages

- The erosion mechanism causes the drug to release quickly.
- Inadequate comprehensive clinical research.
- The amount of drug payload in hydrophilic medicines is restricted (Saba khan *et al*., 2015).

2. Types of NLCs :

- NLC Type I, also known as the imperfect type
- NLC Type II, also known as the multiple types
- NLC Type III, also known as the amorphous type.



NLC Type I, also known as the imperfect type

These crystal types are commonly referred to as imperfect due to their lack of structure. However, it is precisely these imperfections that offer significant opportunities for drug integration and result in high entrapment efficiency. This is achieved by utilizing a smaller amount of liquid lipid compared to solid lipids. Through careful mixing and blending of solid lipids with oils, an oil/water (o/w) nanoemulsion is developed, which upon cooling to room temperature produces lipid particles.

2.2 NLC Type II, also known as the multiple types

Type II nanostructured lipid carriers (NLCs) utilize significantly higher concentrations of oils compared to solid lipids. This results in a miscibility gap between the two components during the formulation process. Upon cooling, phase separation occurs as small oily nano-compartments precipitate and become surrounded by the solid lipid matrix. These type II NLCs are particularly beneficial for achieving controlled drug release from the matrix.

2.3 NLC Type III, also known as the amorphous type

In type III NLCs, the central matrix remains amorphous to avoid drug expulsion caused by crystallization. The matrix is a blend of oils and solid lipids that inhibits crystallization. Special lipids like hydroxyoctacosanyl hydroxy stearate, isopropyl myristate, and dibutyl adipate are used because they do not crystallize during homogenization and cooling of the nanoemulsion. This amorphous matrix prevents drug expulsion and leakage that can occur when crystallization takes place (Iti Chauhan *et al*., 2020).

3. COMPOSITIONS OF NLCs :

Generally speaking, NLCs include of multiple constituents, including as solid and liquid lipids, surfactants, organic solvents, surface-modifying agents, and counter-ions, as presented in a tabular format (Bhargavi CH and Sampathi S, 2021).

The components used in the creation of NLCs

S.No	Components	Examples
1	Solid lipids	Cholesterol,Stearicacid, palmitic acid

2	Liquid lipids	Squalene, Labrafil, Paraffin oil
3	Lipophilic emulsifiers	Span 20, Span 40, Span 60
4	Hydrophilic emulsifiers	Sodium glycocholate,Sodium deoxycholate, Sodium oleate,
5	Amphiphilic emulsifiers	Phosphatidylethanolamines, Phasphotidylcholines

4. Applications :

- Because oral medication administration has high patient compliance, it is frequently used and favored.
- NLCs, also known as nanostructured lipid carriers, are employed in cosmetic formulations for efficient delivery of active components likesun screen,anti-acne **(**Neda Naseri *et al.*, 2015**).**

5. Methods of Preparation:-

1. Hot high-pressure homogenization technique
2. Cold high-pressure homogenization technique
3. High speed/shear homogenization technique
4. Microemulsion
5. Solvent diffusion and evaporation technique
6. Hot melt extrusion
7. Solvent injection technique

Hot high-pressure homogenization technique

An energy-intensive and scalable method for creating nano-sized colloidal systems (NLC, SLN, and nanoemulsions) is high-pressure homogenization. With the use of applied pressure, it employs a top-down method to reduce microemulsion particles to nanoscale size.This method created a hot lipid phase by melting solid lipid and then adding liquid lipid. To create an aqueous phase, surfactants—with or without cosurfactants—are added to water. To make a microemulsion, the heated aqueous phase and the preheated lipid phase are combined while being constantly stirred. A high-pressure homogenizer is used to reduce the size of this heated microemulsion. Different cycles of homogenization might be used according to the target particle size. To transform this nanoemulsion into NLC, it is cooled. At a moderate pressure of 1000 bar**.**

Cold high-pressure homogenization technique

This method, which is similar to hot high-pressure homogenization, combines a lipid phase with a cold aqueous solution that is constantly stirred and kept at a temperature between roughly 2 and 6 degrees Celsius. At low temperatures, a high-pressure homogenizer is used to homogenize this coarse NLC suspension. This method works well with medications and materials that shouldn't be exposed to extreme heat **(**Neda Naseri *et al.*, 2015).

High speed/shear homogenization technique

The process of preparing NLC using high shear rate homogenization is similar to hot high-pressure homogenization. The lipid phase is created by mixing liquid lipid with melted solid lipid, while the aqueous phase is made by mixing surfactant with water. The heated lipid and aqueous phases are then homogenized at high rpm for 10-30 minutes. The resulting solution is cooled to room temperature to form NLC. The speed of homogenization directly impacts the particle size of the nanocarriers. Additionally, the liquid nanoemulsion can be sonicated for 5 minutes before cooling to further reduce particle size. Some studies have used a melt emulsification method with low-speed homogenization and increased sonication time. See Figure 4 for a flowchart of the steps involved in formulating NLC through high-speed homogenization (Van-An Duong *et al*., 2020).

5.4 Microemulsion

Liquid lipid is added to molten solid lipid in the microemulsion process. To create a microemulsion, the final solution is combined with an aqueous phase. The NLC dispersion system is created by quickly cooling this microemulsion with cold water. The NLC particle size is determined by the difference between the microemulsion and water. Although this method of preparing NLC is straightforward, a significant quantity of surfactant and cosurfactant is needed (Jivesh Garg *et al*., 2022).

5.5 Solvent diffusion and evaporation technique

This method involves adding liquid lipid to molten solid lipid that has been dissolved at a high temperature in one or more organic solvents. After that, this lipid solution is stirred into an aqueous solution containing surfactant. This generated dispersion is ultrasonically agitated to create an oil in water nanoemulsion, which is then cooled while being gently stirred to remove the remaining organic solvent.This method uses less energy and prevents physical stress from shear or high pressure, but it requires an extra step to get rid of the leftover hazardous solvent because it uses an organic solvent. demonstrates the method of solvent evaporation or diffusion used to prepare NLC.

5.6 Hot melt extrusion

The process of hot melt extrusion involves pumping raw materials into a barrel and then using sonication to create NLC. In this method, a mixture of drug and solid lipid is fed into an extruder barrel using a volumetric feeder. Liquid lipid and aqueous solutions are added through a peristaltic pump at the extrusion temperature. The mixture is then extruded at the melt temperature of the components to form a pre-emulsion. The hot pre-emulsion is then sonicated to reduce the particle size of the NLC. This process outlines the steps for preparing NLC using the hot melt extrusion technique (Saba khan *et al*., 2015).

Solvent injection technique

This method involves dissolving the lipid phase in a water-miscible solvent or a combination of solvents with the help of heat to melt the solid lipid. The resulting organic phase is quickly injected into an aqueous phase that contains a surfactant or buffer solution while being stirred constantly. The solvent diffuses as the lipid precipitates, leading to the formation of lipid nanocarriers. The size of the particles is determined by the diffusion of the solvent and the amount of emulsifier present. The steps for preparing NLC using the hot melt extrusion technique are illustrated (Jivesh Garg *et al*., 2022).

6. Evaluation and characterization of NLCs :

6.1 Determination of zeta potential, and polydispersity index (PDI)

The NLCs were analyzed using zeta potential, particle size, and polydispersity index (PDI). The PDI is crucial for determining the particle size distribution and identifying whether the nanoparticles are monodisperse or polydisperse and also zeta potential use to identify the charge.

Transmission electron microscopy (TEM)

To measure the size and morphology of NLCs, a TEM can be used. A small amount of the appropriately diluted formulation was applied onto a gold-glazed copper grid with a mesh size of 400. The sample was then air-dried at room temperature using vacuum for 24 hours before examination (Min-Hwan Kim *et al.*, 2019).

Determination of entrapment efficiency and drug loading

The centrifugation/filtration method is used to evaluate the percentage of drug encapsulated into NLC and its loading ability (Ganesh R *et al*., 2019).

6.4 Characterization of prepared formulation

6.4.1 Fourier Transform Infrared Spectroscopy (FT-IR)

FTIR is used to analyze the physical interactions between the drug and chosen excipients. The sample was finely ground with potassium bromide in a glass mortar, then placed in a sample holder and scanned in the wave number range of 4000 – 600 cm -1 (Bhargavi CH and Sampathi S, 2021).

6.4.2 X-ray diffraction (XRD):-

X-ray diffraction (XRD) is employed for examining the physical characteristics of the drug in its original state and when incorporated into a lipid matrix. To verify the drug's crystalline structure, X-ray powder diffraction experiments were carried out on both the pure and freeze-dried forms. The samples were scanned over a range of 2θ values spanning from 10° to 40°, with a step size of 0.01° at each interval (Min-Hwan Kim et al., 2019).

Differential scanning calorimetry (DSC)

The thermal characteristics of the drug and lyophilized -NLC will be examined using Mettler-Toledo DSC (Mettler-Toledo, Viroflay, France) (Bhargavi CH and Sampathi S, 2021).

Conclusion :

The development of NLCs has been largely driven by efforts to address formulation challenges associated with SLNs. The main goal of NLC formulation is to create a stable product that can be successfully marketed. NLCs are biocompatible, biodegradable, non-irritating, and non-sensitizing, with no reported toxicity due to the use of safe lipids and excipients. Despite their advantages, NLCs face challenges in creating cost-effective formulations with improved therapeutic profiles compared to traditional dosage forms.

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