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Emerging Lipid based Systems for Antifungal Delivery: A comprehensive review

Pallavi Suyal[1], Disha Dutta[*2], Ramsha Aslam[3], Manoj Bisht[4]

[1,2,3,4]Devsthali Vidyapeeth, College of Pharmacy, Lalpur, Rudrapur, Uttarakhand, India.

[*]**Corresponding author:**

Disha Dutta

Email ID: dishadas007@gmail.com

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ABSTRACT

Aim: The increasing prevalence of fungal infections and the rise of antifungal resistance necessitate innovative drug delivery strategies to enhance therapeutic efficacy and minimize toxicity. This review aims to provide a comprehensive overview of emerging lipid-based delivery systems—such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, and lipid-drug conjugates—developed for efficient antifungal drug delivery.

Methodology: A systematic literature search was conducted across databases including PubMed, Scopus, and ScienceDirect, focusing on studies published between 2005 and 2025. The selected articles were screened for relevance to lipid-based antifungal drug delivery, formulation strategies, physicochemical characteristics, in vitro/in vivo efficacy, and toxicity profiles. Comparative evaluation was performed to assess the advantages and limitations of each system.

Results: Lipid-based formulations demonstrated superior drug encapsulation, improved solubility of poorly water-soluble antifungal agents (e.g., itraconazole, amphotericin B), sustained release profiles, and enhanced skin/mucosal penetration. Among these, NLCs and liposomes showed significant promise in reducing systemic toxicity and improving site-specific delivery. Novel hybrid and surface-functionalized lipid systems further enhanced antifungal selectivity and bioavailability, especially in dermal and mucosal applications.

Conclusion: Emerging lipid-based delivery systems represent a transformative approach in antifungal therapy, overcoming the limitations of conventional formulations. Their ability to enhance pharmacokinetic profiles, target infected tissues, and reduce drug resistance makes them promising candidates for future clinical applications. However, further translational studies and regulatory validations are warranted to ensure large-scale applicability and patient safety.

Keywords: *Antifungal agents, lipid-based nanocarriers, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, drug delivery, fungal infections.*

1. INTRODUCTION

This review aims to provide a comprehensive overview of emerging lipid-based delivery systems—such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, and lipid-drug conjugates—developed for efficient antifungal drug delivery. Lipids play a pivotal role in the formulation of nanostructured lipid carriers (NLCs), serving as the primary matrix components that significantly influence drug loading, stability, and release kinetics. The strategic combination of solid and liquid lipids in NLCs creates structural imperfections within the lipid matrix, which is advantageous for encapsulating a higher amount of active pharmaceutical ingredients while enabling sustained and controlled drug release. Moreover, the physicochemical characteristics of the chosen lipids determine the degree of biocompatibility, drug-lipid interactions, and the ability to traverse biological membranes, thereby improving therapeutic efficacy (Pardeike, Hommoss, & Müller, 2009).

NLCs represent an advanced and second-generation lipid-based nanocarrier system tailored especially for poorly water-soluble antifungal drugs. These systems consist of a blend of solid and liquid lipids stabilized by surfactants, improving upon the limitations of SLNs, such as low drug loading and drug expulsion during storage. The incorporation of liquid lipids enhances formulation flexibility, increases drug solubility within the lipid matrix, and ensures better physical stability. With nanometric particle sizes typically below 200 nm, NLCs offer several benefits including improved pharmacokinetics, targeted and sustained drug release, increased bioavailability, and efficient penetration through biological barriers like the skin and blood-brain barrier.

Additionally, their ability to accommodate both hydrophilic and lipophilic drugs, high-scale manufacturability, and excellent tolerability make NLCs highly versatile for diverse routes of administration—oral, topical, parenteral, and pulmonary. These properties render NLCs promising carriers not only in antifungal therapy but also in a wide range of pharmaceutical, cosmetic, and nutraceutical applications. With ongoing advancements in formulation science and analytical characterization tools, the utility and scope of NLCs in antifungal drug delivery are poised to expand significantly (Beloqui et al., 2016). As mentioned below in **Table-1** Various type of Antifungal drugs with NLC formulations.

Table-1 Various type of Antifungal drugs with NLC formulations.

S. No.	Antifungal Drug	Target Fungal Infection	Advantages of NLC Formulation	Reference
1	**Terbinafine HCl**	Onychomycosis, dermatophytosis	Enhanced skin penetration, sustained release	(Patel et al., 2012)
2	**Fluconazole**	Vaginal candidiasis, systemic mycoses	Improved bioavailability, mucoadhesion, prolonged antifungal activity	(Aljaeid & Hosny, 2016)
3	**Econazole nitrate**	Superficial fungal infections	Better skin retention, high encapsulation efficiency	(De Carvalho et al., 2018)
4	**Amphotericin B**	Systemic fungal infections (e.g., candidiasis, aspergillosis)	Reduced toxicity, enhanced solubility, targeted delivery	(Cordeiro et al., 2019)
5	**Itraconazole**	Aspergillosis, histoplasmosis	Increased oral bioavailability, improved GI tolerance	(Kumar et al., 2014)
6	**Voriconazole**	Invasive aspergillosis	Better aqueous stability and tissue targeting	(Jain et al., 2021)
7	**Ketoconazole**	Topical fungal infections	Enhanced dermal delivery, reduced irritation	(Bhalekar et al., 2016)
8	**Griseofulvin**	Tinea infections	Enhanced oral absorption and therapeutic index	(Gupta et al., 2018)
9	**Miconazole nitrate**	Vaginal and cutaneous candidiasis	Improved retention and antifungal efficacy in local tissues	(Kaur & Saraf, 2011)
10	**Clotrimazole**	Vaginal and skin fungal infections	Improved residence time, increased skin permeation	(Souza et al., 2011)

1.2. Context and Rationale:

Conventional dose forms including injections, pills, and capsules frequently have issues with poor water solubility, low bioavailability, and failure to administer at a specified spot. These restrictions may lead to adverse side effects or systemic toxicity. Nanotechnology-based carriers, like NLCs, have been developed to counteract this. (Loo et al., 2013) The lipid-based platform provided by natural lipid carriers (NLCs) is compatible with the absorption pathways of a wide range of medications, including amphiphilic, hydrophobic, and hydrophilic substances. Furthermore, because their lipid components are GRAS, NLCs are increasingly being used for drug delivery through pulmonary, cutaneous, parenteral, and oral routes. They protect pharmaceuticals from enzymatic and chemical degradation, making them especially helpful for fragile biomolecules like peptides or nucleic acids.(Naseri et al., 2015)

1.3. Type of NLC

The three main structural models of NLCs can be distinguished by their interior morphology:

1.3.1. Crystal Type Imperfections

Different lipids are combined to create an uneven matrix with "imperfections" or voids. As time passes, these perforations allow for greater drug loading and decrease drug ejection.

1.3.2. Type Amorphous

utilizes lipids that are difficult to recrystallize or amorphous. In addition to increasing physical stability, this prevents the formation of ordered structures.

1.3.3. The solid lipid phase contains microscopic oil nano compartments of the Multiple (O/F/W) type: These regions function as additional drug solubilization reservoirs, especially for drugs that are extremely lipophilic..(Ghasemiyeh & Mohammadi-Samani, 2018)

1.4. Composition of NLC

There are primarily three parts to NLCs:

1.4.1. Solid Lipids

These give the carrier its structural integrity and serve as its backbone. Some such examples are:

1. Stearic acid monoglyceryl
2. 2. Aspartate of glyceryl (Compritol®)

1.4.2. Acid stearicum

2.. Coconut oil

Controlled release and medication retention are achieved by these lipids, which remain solid at room temperature and body temperature as well.

1.4.3. Oils and Other Liquid Lipids

In order to improve drug loading and decrease the likelihood of drug expulsion during storage, these oils cause cracks to form in the solid lipids' crystalline structure. Here are several examples:

1. Olive acid

2.Oil containing medium-chain triglycerides

3. Propylene glycol

4. A product of Capryol®

c. Solubilizers

Emulsion stabilization and prevention of aggregation and sedimentation are achieved by these. They may exhibit ionic, non-ionic, or amphiphilic properties:

1. Polysorbate 80, or Tween 80,

2. Anhydropoloxamer 188

3. Soybean gelatin

4. Chloride salt

Particle stability, surface charge, and surfactant concentration are affected by the surfactant choice and concentration.(Naseri et al., 2015)

1.5. The function of lipids and surfactants in formulation development:

The quality and effectiveness of lipid nanoparticles and nanolipid carriers are significantly influenced by the characteristics and concentrations of surfactant. Because of their amphiphilic character, these surface active agents are preferentially found in interfacial regions where they reduce the interfacial tension between lipid and aqueous phases. The ionic surfactant sodium deoxycholate, which has a low emulsification efficiency, can be used to boost the charge of the nanoparticles. This is linked to an improvement in electrostatic repulsion, which improves the colloidal system's physical stability. Non-ionic emulsifiers, particularly Poloxamer 188, provide an extra steric stabilizing effect that prevents the tiny particles in the colloidal system from aggregating. (Lombardi Borgia S, 2005) (Kovacevic A, 2011)

1.6. Advantages of NLC

1.6.1. Greater drug loading: One significant benefit of NLCs over SLNs is their capacity to load more medication. Combining solid and liquid lipids results in a weak crystalline structure in the lipid matrix. These flaws make it possible for more drug molecules to fill the voids in the lipid core. This is advantageous for medications with high lipid or low water solubility.

1.6.2. As the lipids recrystallize into more stable polymorphism forms, the highly organized crystalline structure of SLNs frequently prevents medication molecules from being expelled during storage. On the other hand, full crystallization is prevented by the partial disorder in the NLC matrix, maintaining formulation integrity and minimizing drug leakage.

1.6.3. Preserving Drug Release Based on lipids and surfactants, NLCs can modify the release of medications. Lipids, both liquid and solid, delay the release of drugs by preventing their diffusion out of the matrix. Particularly for chronic illnesses, this feature lowers dose frequency and enhances patient compliance.

1. Better Bioavailability: NLCs increase oral medication bioavailability in numerous ways:

a. Improved gastric solubility.

b. Anti-enzymatic protection.

c. Improved lymphatic transport,

2. Bypassing hepatic first-pass metabolism.

They also boost intestinal epithelial cell adhesion and absorption due to their nano size.

3. Regulatory agencies typically classify NLC lipids and surfactants as GRAS due to their biocompatibility and biodegradability. They lessen cytotoxicity by being biodegradable and changing into non-toxic metabolites. This makes NLCs safe to administer intravenously, pulmonaryly, topically, and orally.

Labile Drug Protection: Enzymatic activity, heat, and light break down bioactive materials like proteins, peptides, and nucleic acids. The drug's shelf life and in vivo stability are increased by the lipid matrix of NLCs, which shields it from environmental deterioration. (Araújo et al., 2010)

Crossing Bio-barriers: The nanoscale and lipophilic characteristics of NLCs allow them to overcome biological barriers like:

Transdermal medication administration stratum corneum.

The BBB for CNS medication delivery.

Intestinal mucosa improves oral absorption. (Souto et al., 2020)

This opens up NLCs for diseases that need tailored delivery to hard-to-reach locations.

NLC surfaces can be altered by antibodies, peptides, and polymers (such as PEGylation) to target particular tissues or cells. This allows for surface customization and targeted administration. This improves therapeutic results by concentrating the drug at the site of action and lowering off-target effects.

The ability to be mass-produced through the use of high-pressure homogenization or ultrasonication sets NLCs apart from liposomes or polymeric nanoparticles. They facilitate the translation from laboratory to market because they are reasonably priced and compatible with pharmaceutical production processes.

Minimal Use of Organic Solvents: A lot of NLC preparation techniques avoid using organic solvents, which makes scaling up safer and more environmentally friendly. The residual solvent risk in the finished formulation is decreased.

More volatile, sensitive, and stable medications: Essential oils and antioxidants are examples of volatile or oxidizable medications that can be encapsulated to prolong their therapeutic effects and product shelf life by preventing evaporation or deterioration.(Viegas et al., 2023)

1.7. Disadvantages of NLC

Despite their promising potential in drug delivery systems, Nanostructured Lipid Carriers (NLCs) exhibit several limitations that can hinder their wide-scale application. One of the primary drawbacks is the complexity of their formulation and optimization process, which requires a careful selection of solid and liquid lipid ratios, surfactants, and production techniques (Mehnert & Mäder, 2012). This complexity may lead to issues in reproducibility and scalability for industrial production. Additionally, NLCs may encounter physical instability over time, such as particle aggregation, lipid crystallization, and drug expulsion, especially under fluctuating storage conditions (Wissing et al., 2004). The potential for burst drug release due to imperfect drug entrapment can also compromise sustained delivery profiles, leading to suboptimal therapeutic outcomes (Doktorovova et al., 2014). Furthermore, the use of surfactants and excipients, while essential for stabilization, may provoke cytotoxicity or immunogenic responses in certain formulations, limiting their biocompatibility and safety (Mukherjee et al., 2009). Therefore, although NLCs offer considerable advantages over traditional carriers, a careful evaluation of their disadvantages is necessary for future clinical translation.

1.8. Limitations with lipid nanoparticles:

NLCs have a lot of promise for targeted distribution, yet they have some drawbacks, such as:

1. cytotoxic consequences associated with matrix composition and concentration,
2. Some surfactants have an irritating and sensitizing effect.
3. Gene delivery techniques and the use and effectiveness of protein and peptide medications still require further investigation.
4. These nanoparticles have not been thoroughly studied in preclinical and clinical settings for bone healing. (Schäfer-Korting M, 2007)

2. MECHANISM OF DRUG ENCAPSULATION

When liquid lipids are added to the NLC matrix, a rather disorganized structure is created. Gaps created by the aforementioned "imperfection" allow medications to be accommodated inside the matrix. During the encapsulation procedure, the medication may either be dissolved in the lipid phase or adsorbed onto the surface. Drugs that are lipophilic will usually embed in the core, while amphiphilic substances may live close to the interface. NLCs can deliver medications in a number of ways, such as the following: The term diffusion-controlled describes the method by which the medication subtly diffuses out of the lipid matrix. Erosion regulates the lipids' breakdown in vivo through metabolic activities. It is common to see the combination mechanism in biodegradable lipid systems. The size of the particle, the kind of surfactant, the lipid makeup, and the medication's compatibility with the lipids all affect release.

2.1 Method of Preparation of NLC

1. **High-pressure homogenization:** Most large-scale production uses this strategy. The solid and liquid lipids are heated above their melting point and the medication is added. High-speed stirring forms a pre-emulsion from the lipid melt in a hot aqueous surfactant solution. This emulsion is homogenized multiple times at 500–1500 bar. NLCs form from lipid droplets when cooled. It suits lipophilic medicines but not heat-sensitive ones.
2. **Cold-High-Pressure Homogenization:** The hot HPH method for thermolabile pharmaceuticals is modified. After mixing the medication into the melting lipid phase, liquid nitrogen or dry ice immediately solidifies it. Microparticles of the solid mass are distributed in a cold aqueous surfactant solution. NLCs form from high-pressure homogenization of this dispersion at room temperature. Particle sizes may increase, but thermal deterioration is minimized.
3. **Solvent Evaporation-Emulsification:** The medication and lipids are dissolved in chloroform or dichloromethane and emulsified into an aqueous surfactant solution to generate an oil-in-water emulsion. Under lower pressure, solvent evaporates, precipitating lipids and NLC. Organic solvents must be removed safely, although this procedure works for poorly water-soluble medicines.
4. **Injection or diffusion of solvent:** The drug-lipid mixture is dissolved in ethanol or acetone and immediately injected into an aqueous phase under stirring. Lipid precipitation and NLC arise when solvent diffuses quickly into water. For heat-sensitive medications, this procedure is mild and easy. It is not suitable for large-scale production due to solvent recovery and batch consistency issues.
5. **Micro-emulsion:** A heated micro-emulsion is made from melted lipids, surfactants, and surfactant and the medication. Lipids harden as nanoparticles when this combination is rapidly disseminated in cold water under agitation. It's fast and easy to use, but formulation components make it sensitive and unscalable.
6. **Ultrasound/High-Shear Homogenization:** This lab-scale approach emulsifies the medication with melting lipids in a heated aqueous phase utilizing high-speed stirring. Ultrasonication with a probe sonicator reduces particle size in the emulsion. NLCs form from lipid droplets when cooled. It is cost-effective for research, but scalability and particle size

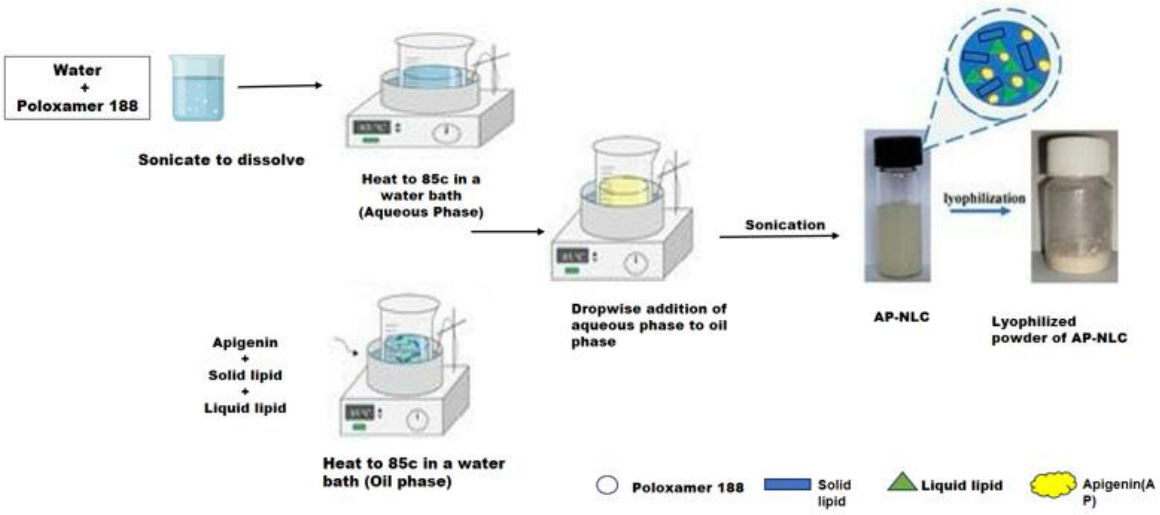
homogeneity are its key drawbacks.

7. **W/O/W Double Emulsion:** This method is for hydrophilic medicines predominantly. To make a water-in-oil (W/O) emulsion, the medication is dissolved in water and emulsified in lipid. To create a W/O/W system, this main emulsion is re-emulsified in an external aqueous phase. Chilling or solvent removal hardens lipids into NLCs. The approach works for protein or peptide medications, but is complicated and hard to scale.

2.2 Formulation of Solid Nanoparticles

To create Luliconazole-loaded nanoparticles via the solid lipid nanoparticle (SLN) method, commence with the preparation of the lipid phase. Precisely measure the necessary quantity of solid lipid, such as stearic acid or glyceryl monostearate, and transfer it to a clean, dry beaker. Heat this lipid to approximately 70–75°C using a water bath or heating mantle until completely liquefied. Dissolve the requisite quantity of Luliconazole in the liquefied lipid separately. The step by step process for Preparation of NLCs are as mentioned below in **Fig-1.**

Fig-1. The step by step process for Preparation of NLCs.



If the drug is challenging to dissolve directly, it may first be solubilized in a minimal volume of ethanol, after which this solution can be included into the molten lipid while stirring to ensure thorough mixing. Concurrently, formulate the aqueous phase by dissolving a surfactant, such as Poloxamer 188 or Tween 80, along with a co-surfactant, such as soy lecithin or Span 20, in distilled water. The aqueous phase must be heated to the same temperature as the lipid phase (70–75°C) to avert early solidification during mixing. Upon achieving readiness and uniform temperature in both phases, the molten lipid phase containing the drug is gradually introduced into the aqueous phase while subjecting the mixture to high-speed homogenization at 10,000 to 15,000 rpm for approximately 10 to 15 minutes. This procedure generates a heated pre-emulsion. The resultant heated emulsion is subsequently exposed to ultrasonication with a probe sonicator for 3 to 5 minutes in pulse mode. This process diminishes the particle size to the nanometer scale, generally under 200 nm, and stabilizes the formulation. Subsequent to sonication, the nanoemulsion is permitted to cool gradually to ambient temperature while being continuously stirred gently. As the temperature decreases, the lipid component solidifies, resulting in the creation of solid lipid nanoparticles (SLNs) that encapsulate Luliconazole. As mentioned below in **Table-2** Various type of NLC loaded plant phytoconstituents with their therapeutic uses.

Table-2 Various type of NLC loaded plant phytoconstituents with their therapeutic uses.

Sr. No.	Phytoconstituent (Plant source)	Therapeutic focus in the cited NLC study	Key advantages reported for the NLC formulation	Reference
1	**Curcumin** (Turmeric, *Curcuma longa*)	Brain-tumour therapy (also ocular)	6.4-fold higher systemic AUC and markedly enhanced brain/tumour targeting vs. free curcumin	(Y. Chen et al., 2015)

2	**Resveratrol** (Grapes, *Vitis vinifera*)	Breast-cancer targeting	~9-fold AUC increase; folate-decorated NLCs showed higher cytotoxicity toward MCF-7 cells	(Poonia et al., 2019)
3	**Quercetin** (Onion/Apple skins, various)	Topical treatment of bacterial skin infections	>99 % encapsulation efficiency; stronger anti-*Staphylococcus aureus* activity, reduced cytotoxicity	(De Barros et al., 2022)
4	**Thymoquinone** (*Nigella sativa* seeds)	Gastro-protection & pharmacokinetics	Improved ulcer protection, favourable PK profile, low hepatic cytotoxicity vs. free drug	(Abdelwahab et al., 2013)
5	**Silymarin** (Milk-thistle, *Silybum marianum*)	Oral hepatoprotective therapy	2.5–3.1 × higher relative bioavailability in beagle dogs vs. commercial Legalon®	(Shangguan et al., 2013)
6	**Berberine** (*Coptis chinensis* / *Berberis* spp.)	Alzheimer's-disease model	Optimised NLCs (≈186 nm) improved cognitive/behavioural endpoints in vivo	(Raju et al., 2021)
7	**Ursolic acid** (Apple peel, *Rosmarinus* spp., etc.)	Visceral leishmaniasis	NLCs (≈104–143 nm) cut parasite burden by ≈ 99 % and showed 88 % entrapment efficiency	(Das et al., 2017)

If intended for topical use, the nanoparticle dispersion may be integrated into a gel matrix. To accomplish this, suspend 1–2% Carbopol 934 in distilled water and permit it to hydrate for a minimum of 4 to 5 hours. The chilled SLN dispersion is thereafter added gradually to the hydrated Carbopol gel while maintaining continuous agitation. Finally, modify the pH of the formulation to 6.5–7.0 with triethanolamine to achieve a smooth and stable Luliconazole nanogel, prepared for topical application.(Zheng et al., 2013)

3. CHARACTERIZATION PARAMETERS:

3.1 Particle Size and Polydispersity Index (PDI)

Particle size is a crucial factor in the characterization of NLCs, as it directly affects the drug release rate, skin penetration, and physical stability of the formulation. The polydispersity index (PDI) reflects the uniformity of the particle size distribution. A lower PDI (preferably below 0.3) indicates a homogenous formulation, whereas a higher PDI suggests a broader size distribution that may compromise stability. Both particle size and PDI are typically determined using Dynamic Light Scattering (DLS), also known as Photon Correlation Spectroscopy (PCS). The sample is diluted with distilled water and analyzed using a Zetasizer. Smaller nanoparticles with uniform distribution facilitate better dermal penetration and controlled drug release.(Andonova & Peneva, 2018)

3.2 Zeta Potential

Zeta potential is a measure of the surface charge of nanoparticles and is an important indicator of the physical stability of colloidal dispersions like NLCs. It helps predict the degree of electrostatic repulsion between adjacent, similarly charged particles in dispersion. A zeta potential value greater than +30 mV or less than –30 mV is generally considered stable, as it suggests strong repulsive forces that prevent particle aggregation. Zeta potential is measured using Electrophoretic Light Scattering (ELS), and the data is interpreted using the Smoluchowski equation. This measurement ensures that the NLCs maintain their dispersion quality over time and do not settle or aggregate (Thatipamula et al., 2011)(Averina et al., 2011)

3.3 Morphology and Surface Characteristics

The morphological evaluation of NLCs provides insight into their shape, size uniformity, and surface smoothness. This is

typically carried out using advanced imaging techniques such as Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), and Atomic Force Microscopy (AFM). TEM allows for visualization of internal structures and confirmation of spherical shape, while SEM provides detailed images of the particle surface. AFM offers 3D topographical information and roughness measurements. These techniques confirm whether the NLCs are spherical, smooth-surfaced, and non-aggregated, all of which are essential for efficient skin adhesion and permeation (Tan et al., 2010)(Makoni et al., 2019)

3.4 Drug Loading and Entrapment Efficiency

Drug loading (DL%) and entrapment efficiency (EE%) are critical parameters to evaluate the effectiveness of drug encapsulation within NLCs. Entrapment efficiency is defined as the percentage of drug entrapped within the nanoparticles relative to the total amount of drug used in formulation, while drug loading refers to the ratio of the drug incorporated to the total weight of the lipid matrix. These parameters are usually determined by ultracentrifugation of the NLC dispersion, followed by analysis of the supernatant using UV–Visible spectroscopy or High-Performance Liquid Chromatography (HPLC). High EE and DL values indicate a stable formulation with efficient drug incorporation and minimal drug loss.(Wu et al., 2022).(Souto et al., 2004)

3.5 Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) is used to investigate the thermal behavior of NLCs and to assess the physical state of the drug within the lipid matrix. DSC helps determine whether the drug is present in a crystalline or amorphous form and whether any interaction has occurred between the drug and excipients. During DSC analysis, the NLC sample is heated at a controlled rate, and heat flow is recorded. A shift in melting peaks, reduction in enthalpy, or complete disappearance of the drug's melting point suggests its successful incorporation into the lipid matrix and possible reduction in crystallinity, which can improve drug solubility and bioavailability (Jaiswal et al., 2016)

3.6 X-ray Diffraction (XRD)

X-ray Diffraction (XRD) analysis is performed to study the crystalline or amorphous nature of the drug and lipids in NLC formulations. The technique involves passing X-rays through the powdered sample and detecting the diffraction pattern. Pure crystalline drugs exhibit sharp peaks at specific 2θ angles, while amorphous forms show broad humps. In the case of NLCs, the disappearance or reduction in intensity of these peaks suggests that the drug has been converted into an amorphous form or molecularly dispersed within the lipid matrix. This transformation is beneficial as it typially enhances solubility and therapeutic efficacy (Pardeike et al., 2009).

3.7 Fourier Transform Infrared Spectroscopy (FTIR)

Fourier Transform Infrared Spectroscopy (FTIR) is used to identify any potential chemical interactions between the drug and the lipid excipients in NLCs. FTIR analysis involves scanning the sample in the infrared region and observing the characteristic absorption bands of functional groups. Any changes in peak position, intensity, or the appearance/disappearance of bands may indicate interactions such as hydrogen bonding or complex formation. Such interactions can influence the stability and release behavior of the drug. FTIR thus confirms the chemical compatibility of the drug with excipients used in the formulation .(Tan et al., 2010)

3.8 In Vitro Drug Release Study

In vitro drug release studies provide valuable information on how the drug is released from the NLC matrix over time. The most commonly used method is the dialysis bag diffusion technique, in which the NLC formulation is placed inside a dialysis membrane that is immersed in a receptor medium such as phosphate-buffered saline (PBS). The system is maintained at physiological temperature (37°C), and samples are withdrawn at regular intervals for analysis. The release data is then fitted into mathematical models (e.g., zero-order, first-order, Higuchi, or Korsmeyer–Peppas) to understand the drug release kinetics. A controlled and sustained release profile is generally desirable for topical formulations (Tan et al., 2010)(Madane & Mahajan, 2016)

3.9 Stability Studies

Stability studies are conducted to evaluate the physical and chemical stability of NLC formulations over time. These studies involve storing the formulations at different temperature and humidity conditions, as prescribed by ICH guidelines (e.g., 25°C/60% RH, 40°C/75% RH), and periodically monitoring parameters such as particle size, zeta potential, PDI, drug content, and visual appearance. A stable formulation shows minimal changes in these parameters over the test duration, indicating good shelf life and robustness of the formulation. These studies are essential for product development and regulatory approval(Obeidat et al., 2010)(Teeranachaideekul et al., 2007)

4. APPLICATION OF NLC

Biocompatibility, capacity to encapsulate hydrophilic and lipophilic medicines, controlled release behavior, and better drug stability make Nano Lipid Carriers (NLCs) a versatile and effective drug delivery method. Their therapeutic uses and administration routes are varied.

4.1. Topical/Transdermal Drug Delivery: Dermatology uses NLCs to administer medications to the skin due to their small particle size and lipidic nature, which improves skin penetration and retention. They control medication release, stabilize, and minimize discomfort. Delivery of anti-inflammatory, antifungal, corticosteroids, and cosmetic actives are examples.

4.2. Oral Drug Delivery: NLCs increase solubility, preserve medicines from enzymatic degradation, and aid lymphatic transport to increase oral bioavailability of weakly water-soluble medications. Curcumin, ibuprofen, and paclitaxel had enhanced oral bioavailability with NLC formulations.(Üner et al., 2005)

4.3. Ocular Drug Delivery: NLCs are effective ocular medication carriers due to their mucoadhesive characteristics and prolonged release. They increase drug residence duration in the eye, reduce dose frequency, and improve glaucoma, conjunctivitis, and dry eye syndrome treatment.

4.4. Pulmonary Drug Delivery: NLCs can be inhaled to treat respiratory disorders. They aid deep lung deposition and regulated drug release for asthma, COPD, and pulmonary infections.

4.5. Cancer Treatment: NLCs are being employed to passively (EPR effect) or actively target anticancer medicines to tumor tissues. Improve cytotoxic drug solubility, reduce systemic toxicity, and increase tumor accumulation. Paclitaxel- or doxorubicin-loaded NLCs are examples.

4.6. Brain-targeting and neurodegenerative diseases: The lipidic structure of NLCs helps them pass the blood–brain barrier (BBB), making them suited for central nervous system medication delivery. NLCs have been explored for Alzheimer's, Parkinson's, and brain tumor medication delivery.

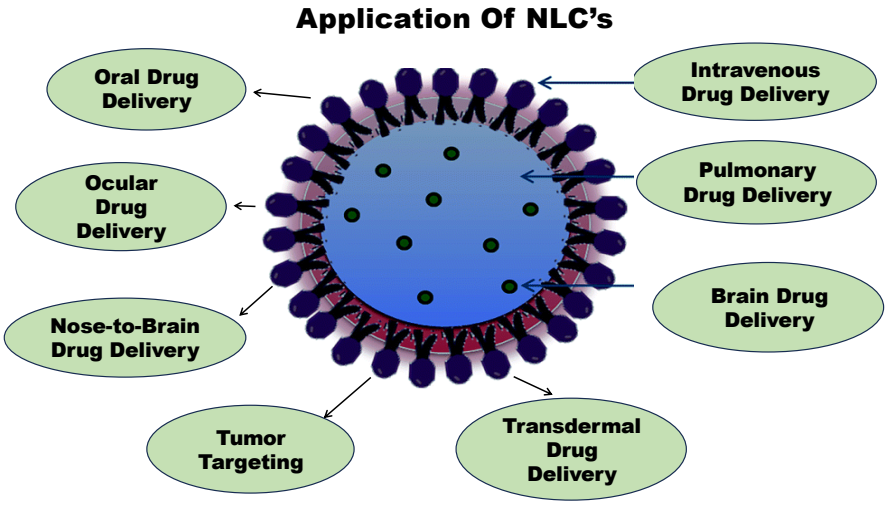
4.7. Gene and vaccine delivery: NLCs can carry DNA, RNA, or peptide vaccines. Their capacity to preserve nucleic acids and aid cellular absorption makes them intriguing therapeutic and genetic engineering tools.

4.8. Antimicrobial Treatment: NLCs promote antibiotic effectiveness by increasing cellular absorption and decreasing resistance. They target and reduce adverse effects for bacterial, viral, and fungal infections.

4.9. Cosmetics: Vitamins, antioxidants, and anti-aging chemicals are delivered using NLCs in cosmetics. They improve skin hydration, penetration, and controlled release, enhancing product performance.(Souto & Müller, 2008)

Nanotechnology has transformed pharmaceutical sciences by creating medication delivery technologies that circumvent formulation restrictions. Lipid-based nanoparticles are popular due to their biocompatibility, solubility improvement, and targeted delivery. Nano Lipid Carriers (NLCs) are the second generation of lipid nanoparticles that overcome the issues of Solid Lipid Nanoparticles (SLNs) such low drug loading and storage ejection. The various applications of NLCs are as mentioned below in **Fig-2.**

Fig-2- Various Applications of NLCs in Drug Delivery.



NLCs are surfactant-stabilized colloidal carriers of solid and liquid lipids (oils) 50–300 nm in size. This provides an irregular crystalline structure that holds more drug molecules and reduces leakage. By enhancing solubility, stability, bioavailability, and site-specific distribution, NLCs boost medication therapeutic index. They are ideal for encapsulating lipophilic chemicals, weakly water-soluble medicines, and sensitive biological components like proteins, peptides, and nucleic acids. NLCs solve drug transport issues such as enzymatic degradation, membrane permeability, pharmacokinetics, and systemic toxicity, which is why they were developed. NLCs provide regulated, prolonged medication release, minimize administration frequency, and increase patient compliance. Their lipid composition resembles biological membranes, improving cellular

absorption and reducing toxicity. NLCs show potential in oral, topical, ophthalmic, pulmonary, parenteral, and transdermal administration. They have been studied for treating cancer, neurological disorders, infectious diseases, inflammatory conditions, and cosmetics. Due to their adaptability, scalability, and safety, NLCs are one of the most successful nanocarriers for modern drug delivery and are still being studied in academia and industry.(Taghipour et al., 2018)

5. CONCLUSION

The NLCs are the carrier systems with the right viewpoints for effective marketing. NLCs are a new class of formulations that offer enhanced performance in creating final dosage forms, including injectables, creams, pills, capsules, and more. They also offer considerably more flexibility in drug loading and release modulation. NLC dispersion's can be employed in a variety of compositions due to their high uniformity. This particular type of NLC's nanostructure also aids in improving the drug's bioavailability, drug loading, and solubility in a variety of settings and conditions. These carriers can also improve the drug's distribution to the target organ, alter the pharmacokinetic properties of drug carriers to improve the therapeutic effect, and lessen unfavorable side effects.

List of short abbreviation-

NLCs - Nanostructured Lipid Carriers, **SLNs - Solid Lipid Nanoparticles**, **GRAS -Generally Recognized As Safe**, **O/F/W - Oil/Fat/Water, PEG - Polyethylene Glycol (PEG)**, **BBB - Blood-Brain Barrier**, **CNS - Central Nervous System**, **PK - Pharmacokinetics**, **FDA - Food and Drug Administration**, **IV - Intravenous.**

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