RECENT FORMULATION AND CLINICAL ADVANCES IN APPLICATION OF NANOSTRUCTURED LIPID CARRIERS AS AN EMERGING DRUG DELIVERY MODEL.

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Abstract

Since the excellent physicochemical and biocompatible properties, NLCs have created an urgent need for the development of safe and valuable drug delivery methods. NLC-based formulations have been published and patented in recent years. They are a binary system that incorporates both solid and liquid lipids with the goal of producing a lipidic core that is less organised. Their ingredients have a significant impact on the finished product's physicochemical qualities and effectiveness. Accomplished applications of NLCs is emphasized in this review article. More NLCs must be used in order to overcome the constraints posed by the technological process of lipid-based nanocarrier creation and to gain a better understanding of the key mechanisms of their transport via diverse routes of administration. They can be administered by a variety of methods, including oral, cutaneous, ophthalmic, and pulmonary. This review paper aims to provide an overview of the current state of the art in the field of NLCs for future clinics by demonstrating how they can be used effectively. The data clearly shows that NLCs have the potential to be used in novel therapeutic applications in the future.

Keywords:- NLCs, lipid nanocarriers, formulations, drug delivery systems, applications, clinal trials.

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1. Introduction

A System containing nanoparticles has a significant promise as a potential platform for the therapy of drug which improves its executions and overcome its confines. Lipid Nanoparticles keep enormous aptitude in the field of medication delivery among the various nano systems studied. A liposome is a spherical vesicle with an aqueous interior cavity and a lipid bilayer membrane surrounding it. Liposome is made up of two Greek words: lipid, which means fat, and soma, which means body[1]. Historically, it was first developed and designated as solid lipid nanoparticles (SLN) by Müller and Gasco around 1990s for circumventing organic solvents involved in synthesis of polymeric nanoparticles[2]. At the time, SLN was a key system because it had superior stability than liposomes (which had previously been invented), it enabled regulated drug release, and it solidified at body temperature, eliminating hazardous effects associated with the use of organic solvent in the production[3]. Due to internal crystal lattice rearrangement and drug exclusion, only solid lipids are displayed as lipid content, which may result in poor drug payload. With the goal of increasing encapsulation of drug, the second generation of lipid nanoparticles, known as nanostructured lipid carriers, was produced.

NLCs are a two-part system that contains both type of lipids (solid and liquid), resulting in a lipidic core that is less organised[4].

These intrinsic design defects allow for greater drug room. NLCs therefore outweigh SLN because they can encapsulate larger amounts of medication, have less water in them, and provide better drug entrapment with less leakage during storage[5]. Following that, researchers and formulation developers concentrated on producing NLCs, which were then used in a variety of applications.

We have attempted to give a full illumination of the following features in this review paper: a) a brief data of NLC components and their incorporation into technological aspects of formulations; b) important uses and existing difficulties for the development of NLCs as delivery systems through various administrative channels.

2. Components and Formulation Aspects of NLC

M. Elmowafy and M.M. Al-Sanea 2021 described those methods can be categorized into three types based on their requirement of energy. (Table:1) NLCs are made up of a lipid phase, an aqueous phase, and a surfactant, similar to emulsions (s)[6]. However, the components chosen and their ratios might have a significant impact on the ultimate behaviour of the created formulation. The lipid phase is made up of an incomplete solid lipid matrix that is made by combining solid and liquid lipids mixed. Triglycerides, partial glycerides, fatty acids, steroids, and waxes are some of the lipids that have been employed in NLC formulations. Oils (liquid lipids) and fats are made up of a variety of mono-, di-, and triglycerides of fatty acids with varying chain lengths and degrees of unsaturation [7]. Physiological tolerance, physiochemical structure, medication solubility, and solid lipid/liquid lipid miscibility are all factors to consider when choosing a lipid. To begin, the lipids should be classified as GRAS (Generally recognized as Safe), meaning they are unlikely to cause substantial harmful effects at the concentrations utilised. Second, the state of lipid at normal temperature is determined by its physicochemical structure. Finally, the solubility of the active medication in lipid should be evaluated before to NLC production. Drug entrapment and loading will be extremely poor if the drug is not solubilized preferentially in the lipid core; instead, it will attach to particle surfaces or form micelles in the aqueous phase. Fourth, stability of the NLCs is another major concern, it can be stabilised by a single surfactant or a mixture of surfactants with concentration ranging from 1.5 percent to 5% (w/v). Surfactant type and concentration, on the other hand, play a crucial influence in NLC design. Different types of surfactants stabilise NLCs by efficiently adsorbing onto particle surfaces and lowering interfacial tension. Instead of using a single surfactant, a mixture of (hydrophilic and lipophilic) surfactants are commonly utilised in the manufacture since the blend improved the physical stability and functional qualities of the created system. A mixture of surfactants and biopolymers had been used in some circumstances. The particle size of NLCs is influenced by the surfactant content in particular. The smaller the particle sizes, the higher the surfactant concentration. Poloxamer 188, Tween 80, and lecithin are the most commonly utilised surfactants in the literature[8].

3. NLCs and Their Applications

3.1. Oral applications

Starting with the oral route because it's the most popular because of its painlessness, precision dosing, convenience of administration, and patient compliance.

3.1.1. Enhancement of oral bioavailability

As one of the barriers to low bioavailability is low drug solubility, boosting drug solubility is one technique for promoting bioavailability, particularly for class II such as resveratrol[9], raloxifene [10], lovastatin [11], spironolactone [12], and vinpocetine and class IV such as etoposide [13] and saquinavir [14] medications. Due to their fatty nature, NLCs are broken down by lipase and co-lipase into micelles (containing of drug and lipid monoglycerides) that form mixed micelles. In order to avoid the first pass effect and increase carrier transport through the unstirred layer that exists between the bulk fluid and the brush border membrane of enterocytes, mixed micelles are absorbed into lymphatic capillaries by chylomicron production. This results in better medication absorption[15]. The medicine will be absorbed alongside the fat absorption process since it is incorporated into the chylomicron[16]. Nanoparticulate systems, with NLCs, have been shown to increase oral medication bioavailability by intracellular uptake by Peyer's patches M cells[17].The action of various surfactants in the preparation, such as Tween 80, inhibits the efflux transporter (P-gp).Particles degrade slowly due to the steric hindrance effect of Pluronics, which was utilised as a hydrophilic surfactant during manufacture. Drug diffusion through the gastrointestinal barrier will be increased because drug release from nanoparticles is effective (high surface area), and as long as the concentration gradient is kept, passive diffusion will continue. Highly lipophilic surfactants temporarily open tight junctions (gaps between two adjacent intestinal epithelial cells), which enhance paracellular absorption[18]. Nanoparticle adhesion to the intestinal underlying epithelium, resulting in enhanced retention and absorption[19]. According to its lipidic structure, increases the duration spent in the stomach and upper small intestine, resulting in increased absorption.

3.1.2. GIT local disease therapies

Local GIT diseases, such as Crohn's disease and ulcerative colitis, are distinguished by highly secreted mucous, crypt distortions, ulcers, and immune cell infiltration. Inflammatory bowel illnesses are also thought of potential targets of orally delivered NLCs because to their improved adherence to and retention in gut wall epithelia[20]. Furthermore, and in relation to such disease, the physiological characteristics of the intestinal barrier are altered, particularly for intestinal lipids that are deficient in such cases[21].

<table>
<tr><th colspan="4">Methods for preparing NLCs</th></tr>
<tr><th colspan="2">High energy required methods</th><th>Low energy required methods</th><th>Very low or no energy required methods</th></tr>
<tr><td rowspan="2">I. High pressure homogenization</td><td rowspan="4">I. High shear homogenization/sonication</td><td>I. Microemulsion</td><td rowspan="2">I. Emulsification solvent evaporation</td></tr>
<tr><td>II. Double emulsion</td></tr>
<tr><td rowspan="2">i) Hot homogenization</td><td>III. Phase inversion</td><td rowspan="2">II. Emulsification solvent diffusion</td></tr>
<tr><td rowspan="2">ii) Cold homogenization</td><td rowspan="2">IV. Membrane contractor</td></tr>
<tr><td>III. Solvent injection</td></tr>
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Table 1: Different methods of preparing NLCs.

Additionally, The capacity of NLCs to control immunological response (Landesman-Milo and Peer 2012)[22].In 2018 Sinhmar and co-workers developed a NLCs of budesonide which are coated with Eudragit S100 for colonic targeting[23]. Despite only the pellets which are enteric-coated were evaluated only in vitro by the authors. They came to the conclusion that NLCs which were coated with Eudragit S100 could be a hopeful option in treating inflammatory bowel disease. In order to deliver curcumin to the intestinal mucosa, Chanburee and co-workers investigated the outcome of mucoadhesive properties of different polymers (polyvinyl alcohol, polyethylene glycol, and chitosan) in NLCs which are coated with polymers [24]. Polyethylene glycol and polyvinyl alcohol coated NLCs were adhered more efficiently in the intestinal mucosa of porcine when compared with the formulations which are coated with chitosan. This was attributed by the authors to reduced particle size and un-protonated chitosan at neutral pH, which shows mucin have less interaction. Sinhmar and co-workers worked on NLCs based on mannosylated for budesonide to target tissues of inflamed bowel [25]. Because the surface of macrophages at the site of inflammation overexpresses C-type lectin receptors that recognise mannose, adding a mannose group to the NLC surfaces could actively deliver the encapsulated drug to inflamed tissues. The system was then coated with Eudragit S100 to maximise drug release at the desired location while also protecting it from harsh gastric conditions. The results of cytotoxicity demonstrated that the developed NLCs were non-toxic, while in vivo evaluation revealed a significant decrease in clinical activity scoring, macroscopic and microscopic indexing, colonic myeloperoxidase activity, and inflammatory cytokines. Beloqui and colleagues successfully develop and deliver curcumin[26] and budesonide[27] loaded NLCs to inflammatory bowel diseases. The authors proposed that encapsulating anti-inflammatory drugs in lipid-based nanocarriers could be a powerful strategy for treating inflammatory bowel

disease. The authors compared NLCs to self-nanoemulsifying drug delivery systems (SNEDDS) and lipid core–shell protamine nanocapsules in their curcumin study (NC). In vitro, NC had the greatest permeability across Caco-2 cell monolayers, whereas only NLCs and SNEDDS significantly reduced TNF-a secretion by lipopolysachharide-activated macrophages.

Surprisingly, In vivo, only NLCs could reduce submucosal edoema and altered mucosa structures, as well as neutrophil infiltration and the expression of the pro-inflammatory cytokine TNF-a. In the case of budesonide, blank and drug-loaded NLCs significantly reduced in vitro TNF-a secretion and in vivo IL-1b and TNF-a in the colon, with significant histological improvement of altered tissue characteristics.

3.1.3. Easing of drug associated toxic effects

Overproduction of highly reactive metabolites is the key toxicity predisposing factor in the case of highly metabolised medicines in the liver. As a result, bypassing the liver and absorption via the lymphatic system could reduce the formation of such metabolites, hence reducing their harmful effects. To improve drug solubility, decrease plasmatic fluctuation, and reduce carbamazepine-induced toxicity, Elmowafy and colleagues synthesised carbamazepine in bees wax containing NLCs[28]. After two months of treatment, the scientists looked at hepatic and testicular toxicity. In terms of biochemical, histological, and immunohistochemical alterations, NLCs were the safest formulation when compared to carbamazepine suspension and the market product (Tegretol TM).

Since carbamazepine toxicity is linked to the reactive metabolite carbamazepine-10,11-epoxide [29], the authors hypothesised that bypassing the liver with NLCs would reduce toxicity, albeit they did not measure serumcarbamazepine-10,11-epoxide concentrations.

3.2. Cutaneous Application

If a systemic effect (transdermal) is desired, the active must be subjected to acid degradation or a first pass effect before being administered orally. If a local cutaneous effect (dermal) is desired, the skin must be the target site of action (in the case of local diseases such as acne, dematitis, and dermal fungal infection).The major barrier to absorption for both effects is assumed to be the stratum corneum (SC), which is the topmost layer. Ceramides (45 to 50 percent), cholesterol (25 percent), long-chain free fatty acids (22 and 24 carbon atoms chain length; 15 percent), and other lipids produced by corneocytes as a result of keratinocyte apoptosis make up the horny layer of the SC (5 percent).

Multilamellar bilayers organise these lipids. SC primarily serves as a barrier to water loss and invading harmful chemicals and bacteria. Transepidermal (across intact epidermis, which is the most common route) and/or transappendageal (through skin appendages such as hair follicles) routes are used for cutaneous medication diffusion[30]. The latter is frequently used to treat disorders connected with the sebaceous glands, such as seborrheic dermatitis, alopecia, and acne.

Traditional skin preparations, such as ointments, creams, gels, and hydrogels, have a wide range of skin delivery patterns. Hydrophobic drug release is prolonged by fatty-based ointments, whereas hydrogels and O/W creams provide rapid release. Furthermore, the viscosity of the system remains at the site of application for a longer period of time, which prolongs drug delivery. NLCs function better than traditional formulations in both the dermal and transdermal routes without a doubt. NLCs have the ability to do things those conventional formulations cannot, like preserve integrated pharmaceuticals from chemical deterioration, enable drug release adaptability, and boost drug absorption[31].NLCs, on the other hand, have a variety of pathways via which they can pass the SC barrier and enter the skin for medicinal and aesthetic purposes:

* Film formation on the skin's surface. As a result, this film may improve skin hydration by reducing water loss and increasing drug penetration throughout the SC[32].
* Because of the small particle size, a controlled occlusive effect is created. By hydrating the SC, this blockage promotes the dispersion of active ingredients into the deeper skin layers[33].
* Rearrangement of SC lipids, which aids active penetration.
* Penetration is further aided by the miscibility or mixing of NLC lipid components with stratum corneum lipids.
* Inclusion of surfactants alters skin structure and enhances absorption.
* Development of distinct intercellular packing changes, decreased corneocyte packing, and wider inter-corneocyte gaps[34].

3.2.1. Dermal effect

Because NLCs preferentially concentrate in the skin, they can be employed to treat local cutaneous problems in order to maximise therapeutic effectiveness. To combat skin damage brought on by reactive oxygen species, Chen-yu developed quercetin-loaded NLCs[35].After a 12-hour in vivo skin penetration examination, NLCs dramatically increased the amount of quercetin deposited into the epidermis and dermis compared to quercetin solution (1.52 and 3.03 times, respectively). Histological analysis of skin samples after the application of NLCs indicated weaker and enlarged SC. As a result, NLCs were more effective than normal saline suspension injected intraperitoneally in inhibiting xylene-induced ear edema. Elmowafy and colleagues focused on dapsone skin delivery via differently charged NLCs.

Elmowafy and colleagues investigated dapsone skin delivery via differently charged NLCs in order to achieve maximum anti-acne and anti-Rosaceae activity[36]. The authors relied on hydrophilic surfactants to generate surface charge, with polysorbate 80 producing negatively charged particles, positively charged particles are produced by Cetyltrimethylammonium Bromide, while neutral particles are produced by Transcutol P. In full thickness skin, positively charged particles deposited more dapsone than negatively charged or neutral particles. The electrostatic attraction between positively charged particles and negatively charged lipids in SC, according to the authors, is what caused the results. As a result, the skin layers in the Rosaceae model caused by croton oil fully recovered.

Even though atopic dermatitis is characterised by an unorganised skin barrier and an abundance of bacterial infection, adhesive NLC was a viable treatment option because it can build up and repair the distorted barrier through adhesion and film formation. In a coating concentration dependent way, coating with NLCs enhanced the surface charge and had a detrimental impact on skin deposition. The authors attributed the difference in surface charge between the polysaccharide from chitosan and the epithelium. Puglia and colleagues created ketoprofen and naproxen-loaded NLCs with controlled release behaviour to achieve maximum dermal effect[37].

When compared to corresponding free drugs, The researchers found that NSAIDs like ketoprofen and naproxen formulated in NLCs had lower skin penetration and increased accumulations in the horny layer. They also demonstrated prolonged anti-inflammatory activity with prolonged epidermal release.

3.2.2. Transdermal effect

Transdermal drug delivery (TDD) provides an additional route to systemic circulation for medicines with low bioavailability and/or plasma variations.

NLCs, are thought to be a potential TDD system for entrapping medicines. Mendes and colleagues created donepezil-loaded NLCs and integrated in a Carbopol 940 gel foundation to promote transdermal permeability while experimenting with other permeation enhancers[38]. The boosting effect of their components and the lipid nanocarriers themselves boosted donepezil penetration from NLC gel in vitro skin permeation results. Only 0.56 percent of the donepezil administered onto the skin is reserved, according to the research. To improve transdermal permeability and local anaesthetic efficacy, Chen and colleagues created ropivacaine loaded NLCs[39]. In a 24-hour in vitro skin penetration examination, the steady-state flux (Js) of NLCs was roughly two times that of propylene glycol drug solution.

The pharmacodynamic activity demonstrated an inhibition rate of 89.1 percent for the writhing response. Blank and drug-loaded NLCs both had enlarged structures within the SC. The transdermal impact of NLCs also protected acid-sensitive lansoprazole[40]. The study found that NLC hydrogels containing 3.75 percent isopropyl myristate significantly improved medication penetration. In a pharmacokinetic investigation, injectable lansoprazole solution had a greater elimination rate constant than NLC hydrogel, indicating prolonged plasma residency and thus prolonged inhibition of stomach acid secretion. Recently, NLCs loaded with Ocimum sanctum L. leaf extract (which is high in ursolic acid) were produced and tested for anti-inflammatory effects after topical application[41]. When compared to commercially available diclofenac gel, NLCs demonstrated superior anti-arthritic efficacy. Amorndoljai and colleagues produced ginger extract loaded NLCs for the treatment of knee osteoarthritis in another investigation[42].

3.3. Pulmonary Application

As a delivery channel for non-invasive actives for localised and generalised acting medications, the lung has numerous advantages. It has a huge surface area (about 100 m^2), a high perfusion rate

(around 5 l/min), and a delayed drug absorption. Biological barriers to pulmonary delivery exist in respiratory airway systems, including mucus, ciliated cells, and alveolar macrophages[43].

When particle sizes are less than 0.5 um, lipid nanocarrires are one of the most ideal methods for pulmonary drug administration because they can reach the lower respiratory tract, resulting in high drug accumulation and diffusion[44]. Smaller particle sizes (less than 260 nm) have also been shown to prevent macrophage clearance[45]. Lipophilic components, in particular, contribute to improved bioadhesive properties and long-term release behaviour of NLCs[46].

Patlolla and colleagues investigated celecoxib-loaded NLCs for lung targeting by looking at drug release, aerodynamic characteristics, and cytotoxicity. It was possible to achieve controlled release behaviour and an appropriate aerodynamic diameter. The majority of nebulized NLCs were found in mice's alveolar areas.

A pharmacokinetics investigation indicated that plasma levels remained steady for 6 hours[46]. To treat pulmonary aspergillosis in falcons, Pardeike and colleagues produced isotonic, sterile, and non-toxic itraconazole-loaded NLCs[47]. The particle size of nebulized NLCs was in the range of 100–200 nm, indicating deep respiratory tract penetration and accumulation. Gamma scintigraphic pictures indicating that nebulized NLCs made contact with two of the primary infection foci served as evidence of the system's effectiveness in treating aspergillosis. For the purpose of treating tuberculosis, mannosylated rifampicin-loaded NLCs have also been created to target alveolar macrophages by mannose receptor uptake[48]. To treat pulmonary hypertension, Nafee and colleagues produced sildenafil-loaded NLCs[49].NLCs outperformed free solution in terms of decreased intra-alveolar haemorrhage frequency and regularity of lung tissue parenchyma.

3.4. Ocular application

Lipid nanoparticles, for example, have been shown to increase the corneal permeability of actives, resulting in effective ocular administration[50]. NLCs can generally bypass ocular obstacles through a variety of mechanisms:
Increased drug release and, as a result, the encapsulated drug's residence period.

- Enhancement of the encapsulated drug's ocular bioavailability via both transcellular and paracellular processes.
- Breaking through blood-ocular boundaries.
- Protection of encapsulated medicines against lacrimal enzyme deactivation.
- Lowering the dose frequency to improve patient compliance.

Additionally, NLCs are quite safe for the administration of ocular medications because of their biocompatible lipids and surfactants and lack of chemical solvents. They are also simple to sterilise on a wide scale. Lakhani and colleagues used the Box-Behnken design to optimise amphotericin B loaded PEGylated NLCs and investigated ocular biodistribution of the optimised formulation after topical treatment[51]. The results indicated superior antifungal effectiveness over commercial medicines against wild type Candida albicans and amphotericin B resistant Candida albicans (Fungizone™ and AmBisome™).

Amphotericin B was detected in all ocular tissues at 7 hours after administration of PEGylated NLCs in an in vitro transcorneal investigation, and levels were equivalent to AmBisome™.Shen and colleagues investigated muco adhesion characteristics and corneal deposition using cysteine-polyethylene glycol stearate and cysteine surface modified cyclosporine A loaded NLCs[52].

The mucoadhesion of cysteine-polyethylene glycol stearate and cysteine surface modified NLCs was significantly enhanced as compared to polyethylene glycol stearate and non-modified NLCs. Cysteine surface modified NLCs had a longer surface residence in the cul-de-sac as compared to unmodified NLCs (up to 6 hours).

4. Patents on NLCs formulation

Recently nano-lipid compositions have been the subject of numerous patents. Table 2 displays a brief summary of patents on the subject of original invention in nanostructure lipid carriers.

Patent Name	Patent number	Inventors
Nanostructured carriers for guided and targeted on-demand substance delivery	US Patent Application 20170119891	Lal et al., 2017
Nano-structured lipid carrier comprising α-tocopherol and preparing method thereof	KR101777616B1	Geun et al., 2017
Preparation of nanostructured lipid carriers (NLC) method and products made	CN102283809B	Ismail et al., 2016
Lipid nanoparticles for wound healing	EP2821077A1	Lafuente et al., 2015
A method for producing nanolipid formulation for skin care and/or repair and a nanolipid formulation of the same	WO2015105407A1	Ujang et al., 2015
A composition for treating leukemia	WO2014123406A1	Abdullah et al., 2014
Nanoparticle formulations for skin delivery	US8715736B2	Sachdeva et al., 2014
Coenzyme Q nanostructured lipid carrier and preparation method thereof	CN101658468A	Summer et al., 2013
Bionic lovastatin nano-structured lipid carrier and preparation method thereof	CN102935077A	Jianping et al., 2013

Table 2: Recent Patent status of NLC formulation.

5. safety and toxic aspects

Safety & toxicity of NLCs is deemed as one of the major concerns. For oral application, NLCs are seen as reasonably safe nanocarriers since they include lipids that degrade and are necessary for life. which both in vivo tests and in vitro cytotocity show to be well tolerated. On the other hand, When compared to emulsions, NLCs have a lower concentration of surfactants and cosurfactants, which enhances their safety profile. after oral delivery, the toxicity of zerum bone-loaded NLCs in a BALB/c mouse model. Based on histopathological abnormalities, they observed that NLCs did not exhibit any signs of toxicity on the lungs, liver, or kidney, and that a higher lethal dose (LD_{50}) of NLCs was reported. Studies on the cytotoxicity of Caco-2 cells in vitro revealed that the NLCs system did not exhibit substantial cytotoxicity and that cell viability was greater than 90%[53].According to research on the cytotoxic effects of five commonly used solid lipids on human dermal fibroblast when applied topically or transdermally, Compritol 888 ATO was shown to be the safest lipid because of its neutral cytotoxic effect[54].The likelihood of an enhancer irritating your skin is largely unrelated to how well it penetrates. Additionally, they stated that L-alpha-lecithin, Azone, and Dlimonene often had the most irritating qualities, followed by fatty acids. Due to their biocompatible lipids, non-ionic and biocompatible surfactants, and organic solvent-free formulations, NLCs are considered to be considerably safer for ocular distribution [55]. However, the place of administration largely determines the level of clearance and toxicity (topical, intravitreal, intravenous, transscleral, suprochoroidal or subretinal). For the purpose of treating cataracts, the irritancy potential and ocular tolerability of a formulation of mangiferin loaded NLCs were examined. They displayed a strong safety record [56].

6. Approaches to clinical trials

Although NLCs have a lot of potential as drug delivery vehicles, there are still not enough preclinical and clinical research. As a result, it is essential to expand the scope of their applications in order to include clinical studies that adhere to appropriate ethical standards. Lack of critical evaluation of NLCs' safety profile as medication carriers may be to blame for this. However, the most common ones in that respect were cutaneous and oral applications. For instance, NLC formulations of the antihypercholesterolemic drug lovastatin, which is used to treat individuals with moderate hypercholesterolemia, have demonstrated improved stability and clinical efficacy[57].The positive traits of NLCs can be further explored by conducting additional research on their uptake, distribution, metabolism, and excretion. Clinical research should also be done on ways to scale up their production and how they will be used in clinical trials in the near future. The outcomes are anticipated to present a novel approach for a delivery system that is both safer and more capable.

7. perspective and conclusion

NLCs are lipid-based nanocarriers that include a mixture of solid and liquid lipids and allow lipophilic actives to be entrapped, protecting them from degradation and enhancing their stability. They are safe to use because they are made out of FDA-approved surfactants and biocompatible lipids. Since they combine crucial components of smart formulation like high drug payload, the ability to target particular sites through surface modification, and increased understanding of the fundamental principles of transport across various routes of administration, they have been widely

used in the pharmaceutical and biomedical sectors over the past ten years. As a result, they can be utilised to treat and control a variety of ailments in a variety of applications. NLCs are strong competitors for improving medication bioavail ability, treating inflammatory bowel illnesses, and reducing drug-induced toxicity due to decreased particle disintegration and longer GIT residence periods following oral administration. They can also get past the lung's natural defences and collect there. They provide extended residence time in the eye, enhancing ocular bioavailability of the actives with no/minimal adverse effects.

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