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Review Article

Nanostructure Lipid Carriers: A Promising Approach for Hyperlipidemia Treatment

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ABSTRACT

Hyperlipidemia, characterized by elevated levels of blood lipids such as triglycerides and cholesterol, remains a major contributor to cardiovascular diseases including atherosclerosis and coronary artery disease. Although statins are the first-line therapy for managing hyperlipidemia due to their ability to inhibit HMG-CoA reductase, they are associated with limitations such as low systemic bioavailability, extensive first-pass metabolism, and dose-dependent side effects. To address these challenges, nanostructured lipid carriers (NLCs) have emerged as a promising drug delivery system. NLCs, composed of a blend of solid and liquid lipids, improve drug encapsulation efficiency, enhance stability, and enable controlled drug release. They also facilitate lymphatic absorption, thereby bypassing hepatic metabolism and increasing the therapeutic potential of statins. Recent studies have demonstrated that statin-loaded NLCs significantly improve pharmacokinetic profiles and reduce dosing frequency. Additionally, NLCs are biocompatible, biodegradable, and capable of delivering both hydrophilic and lipophilic drugs. This review highlights the pathophysiology of hyperlipidemia, the limitations of current statin therapy, and the advantages of NLCs in enhancing statin delivery. It also discusses various preparation techniques, safety evaluations, and current research trends. Overall, NLCs offer a novel and effective strategy for the treatment of hyperlipidemia and hold great promise for future clinical applications.

INTRODUCTION

Triglycerides, phospholipids, cholesterol esters, or high cholesterol levels in the blood are referred to as hyperlipidaemia. Variations in these blood lipids may raise the risk of peripheral vascular illnesses, coronary artery disease, and cerebrovascular disease. **(1,2)** This disorder is characterized by raised plasma triglyceride (TG) levels (>200 mg/dL), decreased high-density

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lipoprotein, or HDL, levels (<40 mg/dL), and increased LDL (low-density levels (>190 mg/dL), all of which pilot to the growth of atherosclerosis. **(3,4).** Hyperlipidemia is typically characterized as a situation in which the quantity of cholesterol or lipoproteins carrying triglycerides in the circulation above a designated threshold is deemed normal. **(5,6)**. The liver is primarily responsible for regulating blood cholesterol levels. The liver produces around 80% of the total cholesterol, with the remaining 20% coming from diet, mostly from foods like meat, fish, and eggs. **(7,8).** The body uses lipoproteins to carry cholesterol and free fatty acids for four primary biological processes: the creation of bile acid, lipid deposition, steroid hormone synthesis, and energy utilization. The primary lipoproteins comprise very little-density lipoprotein (VLDL) cholesterol, HDL, LDL, chloroplasts, chylomicron remnants, and intermediate-density lipoprotein (IDL) **(9).** Medication of hypercholesteremia involves the use of statins. By blocking the hydroxymethylglutaryl-CoA reductase enzyme, statins reduce the levels of triglycerides, LDL, and total cholesterol. Atorvastatin, Rosuvastatin, Simvastatin, Pravastatin, Fluvastatin, Lovastatin, and Pitavastatin are a few statins that have FDA approval. Higher-intensity statin therapy is one of the most aggressive prevention measures needed for those at high risk for atherosclerotic cardiovascular disease. In order to help healthcare providers manage hypercholesteremia, participating experts analyze pharmacokinetics, clinical toxicology, dosage regimens, mechanisms of action, and monitoring techniques. (10) Statins specifically and competitively block the chemical responsible for hydroxymethylglutaryl-CoA (HMG-CoA) reductase, and this enzyme is in charge of converting HMG-CoA into mevalonate in the pathway that results in the creation of cholesterol. Reduced hepatic cholesterol synthesis leads to increased hepatic utilization of LDL-cholesterol into the bloodstream and activated LDL receptors. (11)

Role of Statin in treatment of hyperlipidaemia:

Statins are regarded as the first-line medication for controlling high cholesterol levels and are essential in the treatment of hyperlipidaemia. Low-density lipoprotein cholesterol (LDL-C), a primary cause of cardiovascular disease, can be effectively reduced by these drugs. Adults between the ages of 40 and 75 who have one or more cardiovascular risk factors, such as diabetes or hypertension, are advised by clinical recommendations to take statin medication because they stand to gain a great deal by lowering their cholesterol. (12,13) Studies have shown that statins help increase high-density lipoprotein cholesterol (HDL-C), which improves the lipid profile overall, in addition to lowering LDL-C and triglyceride levels (14). Because statin medication lowers the risk of all-cause mortality and future cardiovascular events, it is especially advantageous for people with established coronary heart disease (CHD) [15]. Additionally, statins have been shown to improve survival rates in individuals with a history of heart attacks or strokes when used in secondary prevention. (16)
events, it is especially advantageous for people with established coronary heart disease (CHD) [15]. Additionally, statins have been shown to improve survival rates in individuals with a history of heart attacks or strokes when used in secondary prevention. (16) Even though statins are usually well accepted, it's crucial to keep an eye out for any negative effects. Muscle soreness and elevated liver enzymes are common side effects that call for routine liver function testing to guarantee patient safety (17,18). Combination treatment with non-statin cholesterol-lowering medications is frequently advised when statins by themselves are unable to achieve lipid objectives. Overall, a large body of research supports the safety and efficacy

of statins in the treatment of hyperlipidemia, highlighting their critical role in preventing cardiovascular disease. (19)

Marketed Formulation of statins:

Statins are commonly prescribed medications used to lower high cholesterol levels and reduce the risk of heart-related conditions. Some of the well-known statin brands include Lipitor (atorvastatin), Crestor (rosuvastatin), Zocor (simvastatin), Pravachol (pravastatin), and Livalo (Pitavastatin) which shown in table no. 1. These medicines work by blocking an enzyme in the liver that's responsible for making cholesterol. By doing so, they help lower the levels of LDL, or 'bad' cholesterol, while supporting a rise in HDL, the 'good' cholesterol. The choice of statin and dosage depends on individual health needs and cholesterol levels.

Table 1: Marketed formulations of statins

Sr. no.	Drug	Dosage Form	Mode of Action	References
1.	Atorvastatin	Tablet	Lowers cholesterol by blocking an enzyme (HMG-CoA reductase) in the liver. This helps remove LDL from the blood more effectively.	**21**
2.	Rosuvastatin	Tablet	Stops cholesterol production in the liver and increases the number of LDL receptors to clear bad cholesterol from the bloodstream.	**26**
3.	Simvastatin	Tablet	Given as an inactive form that activates in the body to reduce liver cholesterol production and lower LDL levels.	**27**
4.	Pravastatin	Tablet	Specifically works in the liver to reduce cholesterol creation, helping the body use more LDL from the blood.	**25**
5.	Pitavastatin	Tablet	Slows down cholesterol formation and increases how much LDL cholesterol is absorbed and removed by liver cells.	**24**

Need For the Advancement in Drug Delivery System:

While statins are effective in lowering cholesterol, some patients still experience side effects or inadequate response. Issues like muscle pain, liver concerns, and limited effect in certain genetic conditions highlight the need for improved options. Advancements aim to create safer, more targeted therapies with fewer side effects. New formulations may also improve absorption and allow for personalized treatment. Nanostructured Lipid Carriers (NLCs) offer a promising delivery system to enhance the bioavailability of statins. They can help reduce dosing frequency and improve patient compliance by providing sustained release.

Nanostructured Lipid Carriers:

An alternative form of nanoparticulate carrier system to oil-in-water nanoemulsion is called nanostructured lipid carriers, or NLCs. Water, fat, and emulsifying agents are its main constituents. In the room temperature lipid phase, there are both liquid (oil) and solid (fat) lipids. Because the medication dissolves in oil and concurrently encapsulates in solid lipid, NLC-based formulations produce particles with the oil integrated into a solid lipid core, improving loading capacity and achieving controlled drug

release. The advantages of NLCs include improved containment efficiency, drug loading, low crystalline index, reduced polymorphic transition, improved physical and psychological stability, bioavailability, and regulated release of encapsulated components. (28-33). To be effective in treatments, it is important to address the limited bioavailability of many medications and functional foods. As such, a drug carrier system that eliminates these problems has to be created. Many nanocarriers have recently been progressively investigated to improve therapeutic efficacy and long-term drug release properties while addressing problems such as limited solubility and poor bioavailability. Over the past several years, researchers have been increasingly interested in NLCs as a possible substitute for SLNs, liposomes, emulsions, microparticles, polymeric nanoparticles, and other materials. (34). Nanocarriers work well for delivering both lipophilic and hydrophilic medications. When it comes to drug delivery by oral, parenteral, ophthalmic, pneumonia, topical, and transdermal administration, non-lipid carriers (NLCs) have shown a great deal of promise. The distribution of nutraceuticals, cosmeceuticals, gene therapy, chemotherapeutics, brain targeting, and the food industry are just a few of the recent uses for NLCs. (35)

Advantages of Nanostructure Lipid Carriers (36-38)

- Higher drug stability
- Compact dimensions guarantee intimate touch with the stratum corneum.
- Enhanced skin moisture and suppleness.
- Greater ability to load certain medications.
- Being able to load medications that are hydrophilic and lipophilic.
- Enhance the drug bioavailability.
- Ease to scale up.
- Most affordable

Method of preparation of Lipid carriers in nanostructure:

Method of high-pressure homogenization:

High-pressure homogenization is a widely used and dependable technique for producing nanostructured lipid carriers (NLCs) on a commercial scale. This method is environmentally friendly since it avoids the use of harmful organic solvents. The drug is mixed with molten lipids and passed through a high-pressure homogenizer, forming fine and stable particles. Depending on the temperature, this process can be done through hot or cold homogenization. Cold homogenization is better for heat-sensitive drugs, while hot homogenization uses higher temperatures for emulsification. The process involves two main approaches: hot and cold homogenization.

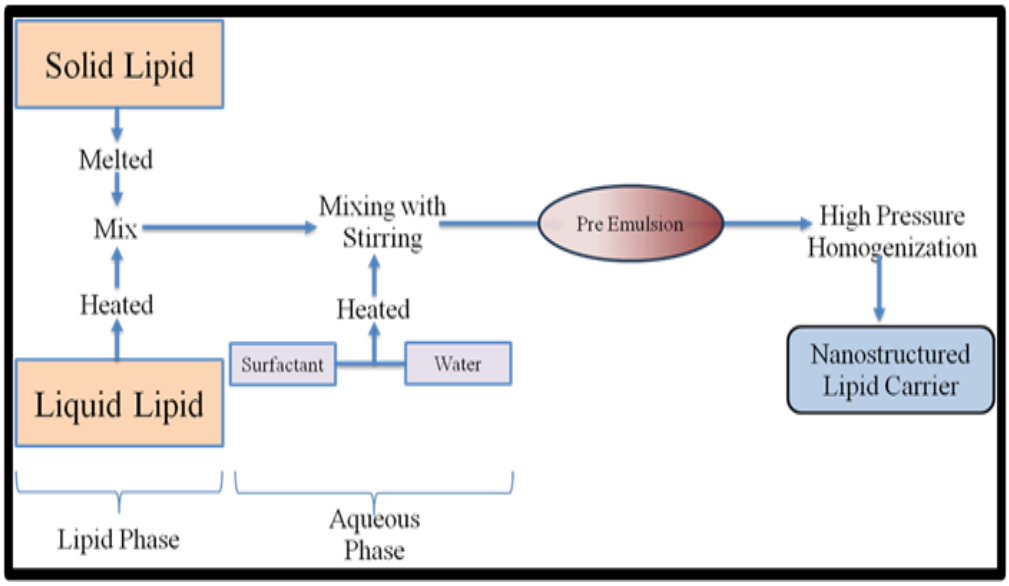

Fig. no. 1: High pressure homogenization

Cold homogenization: This technique involves melting solid lipids at temperatures 5–10°C above their melting point. The molten lipid is mixed with the drug, and the mixture is then dispersed into a pre-warmed surfactant solution using high-shear mixing to form a pre-emulsion. The pre-emulsion is processed in a high-pressure homogenizer (3–5 cycles at 500–1500 bar) while maintaining controlled temperatures. As the nanoemulsion cools, the lipids recrystallize to form nanoparticles. However, the high temperatures used in this method can degrade heat-sensitive compounds. Additionally, surfactants may lose emulsifying efficiency at temperatures above 85°C, potentially leading to instability in the nanocarriers. (40-43)

Hot Melt Extrusion Method: In this process, raw materials are fed into an extruder barrel using a volumetric feeder. A peristaltic pump introduces both fatty and aqueous solutions at the extrusion temperature. The mixture is extruded at the component melt temperature to form a pre-emulsion, which is then sonicated to reduce the particle size of the NLCs. (44-50)

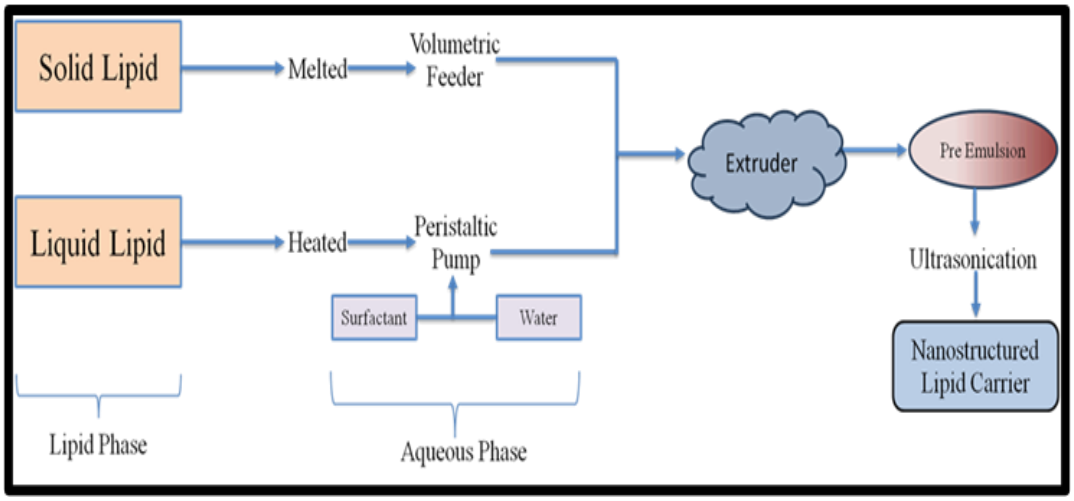

Fig. no. 2: Hot melt extrusion

Solvent emulsification evaporation method: This technique involves dissolving the drug in a water-immiscible solvent (e.g., cyclohexane or chloroform) along with solid and liquid lipids. The solution is dispersed into an aqueous emulsifier solution to form an oil-in-water (o/w) emulsion. The solvent is then evaporated under low pressure, causing the lipids to precipitate and form nanoparticles in the aqueous phase. While this method avoids thermal stress, the use of organic solvents is a drawback. The particle size, typically ranging from 30 to 100 nm, depends on the choice of solid lipid and surfactant. (51-52)

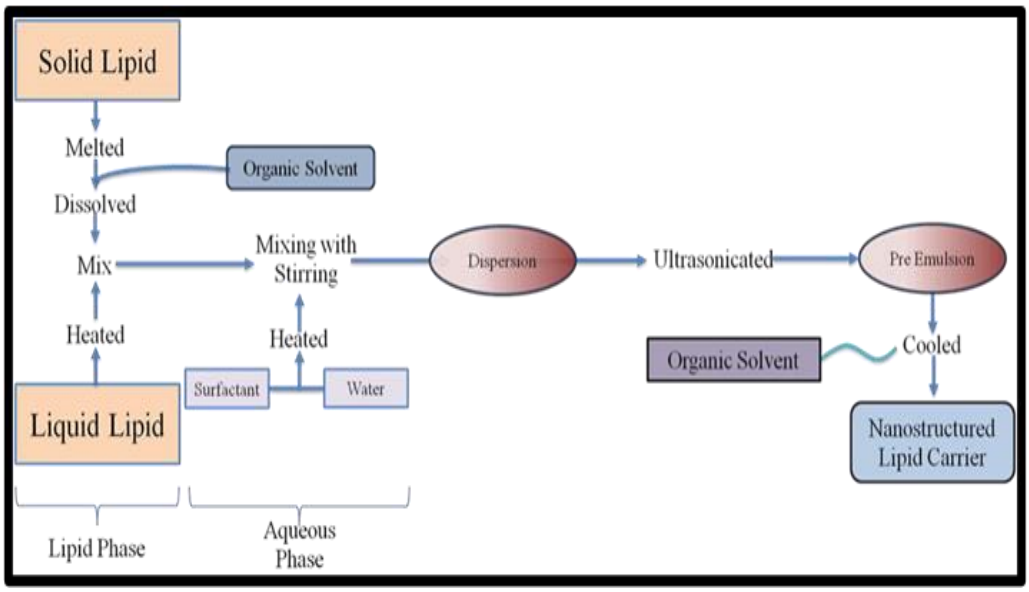

Fig. no. 3: Solvent emulsification evaporation

Double Emulsion Technique: This method is primarily used for encapsulating hydrophilic drugs in lipid nanoparticles. It addresses the challenge of water-soluble components migrating from the oil phase to the aqueous phase. The process involves dispersing the drug in an aqueous solution (inner phase), which is then mixed with a lipid phase containing surfactants and lipophilic components at the same temperature. The primary water-in-oil (w/o) emulsion is further emulsified into a larger aqueous solution to form a double emulsion (w/o/w). The nanoparticles are then refined using solvent evaporation or ultrafiltration. (54-55)

Here, the lipid phase is dissolved in a water-miscible solvent or a solvent mixture, and the solid lipid is melted using heat. The organic phase is rapidly injected into an aqueous surfactant or buffer solution under continuous stirring. As the solvent disperses, the lipids crystallize to form nanocarriers. The particle size is influenced by the solvent diffusion rate and the concentration of the emulsifier. These methods offer diverse approaches to NLC production, each with unique advantages and limitations, making them suitable for different applications in drug delivery and cosmetics. (56)

Solvent Injection Technique

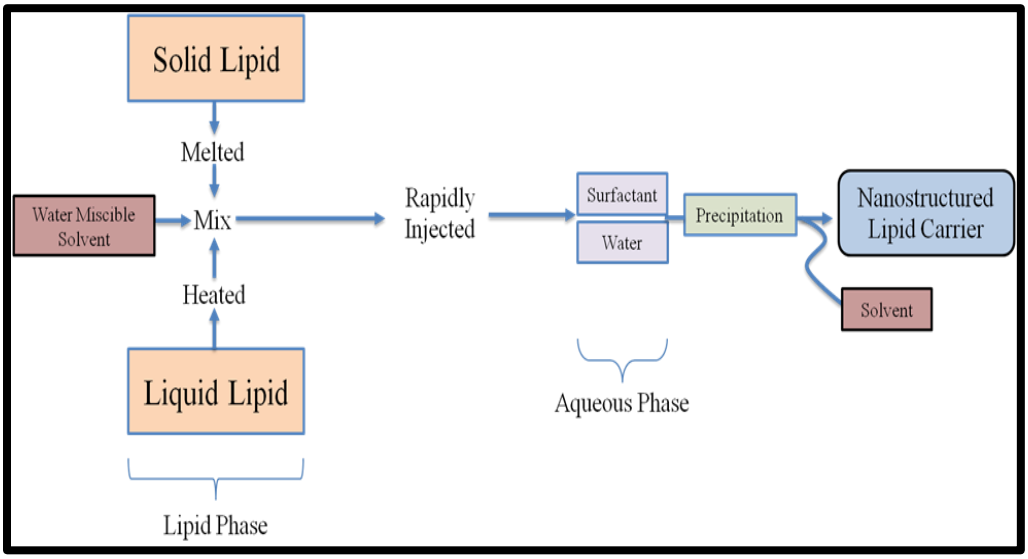

Fig. no. 4: Solvent injection technique

Mechanism of NLC in Hyperlipidemia Management:

Innovative drug delivery methods called Nanostructured Lipid Carriers (NLCs) are intended to boost the effectiveness of statins and other drugs used to treat hyperlipidaemia. By enabling the medicine to be absorbed through the lymphatic system, avoiding the liver's first-pass metabolism, they contribute to increased therapeutic efficacy. Patients will need to take the drug sooner as a result of improved bioavailability and a continuous, regulated release. Furthermore, NLCs have a good selectivity for cell membranes, which facilitates the drug's entry into target cells. They are a potential technique in contemporary therapy because of their inherent compatibility with the body, safe breakdown, and great drug carrying capacity. (70)

Enhanced Lymphatic Uptake to Bypass First-Pass Metabolism: Nanostructured Lipid Carriers (NLCs) enhance the oral bioavailability of poorly soluble or hydrophobic drugs by promoting absorption through the intestinal lymphatic system. This route helps bypass liver first-pass metabolism, a major barrier to drug effectiveness. (71) Factors like particle size, lipid composition, surface charge, and emulsifier concentration influence this uptake. Optimal particle sizes (10–100 nm) support better lymphatic absorption (72). For example, vinpocetine-loaded NLCs showed over a 300% increase in bioavailability compared to standard suspension, largely due to this mechanism. NLCs also aid lymphatic transport through chylomicron formation and interaction with bile salts, further improving drug delivery. (73)

Sustained Drug Release to Lower Dosing Frequency: NLCs offer sustained drug release, which is especially useful for chronic conditions like hyperlipidemia by reducing dosing frequency and extending therapeutic effects. For instance, simvastatin-loaded NLCs released about 87% of the drug over 48 hours, leading to better cholesterol control. Similarly, rosuvastatin and fluvastatin NLCs showed prolonged release and significantly improved bioavailability. (74) These extended-release effects are due to the drug being trapped within the lipid matrix, with release patterns often following the Higuchi model, suggesting a diffusion-controlled mechanism. (75)

Improved Interaction with Lipid Membranes to Enhance Cellular Uptake: NLCs improve drug absorption by interacting with lipid

membranes, helping drugs cross biological barriers. Their small size and lipid-based composition support absorption through mechanisms like transcellular transport and uptake by M-cells in the intestine. The lipid content can also trigger bile secretion, forming micelles that promote lymphatic absorption and bypass liver metabolism. Surface modifications, such as charge adjustments, further enhance cellular uptake. Instead of fusing directly with cell membranes, NLCs often enter cells via endocytosis. Excipients like lecithin may boost uptake through Peyer's patches, improving drug delivery efficiency. (76)

Current research and finding of NLC:

Nanostructured Lipid Carriers (NLCs) have gained significant attention in pharmaceutical and cosmetic research due to their ability to enhance drug solubility, stability, and bioavailability. Recent advancements focus on optimizing formulations, improving drug delivery efficiency, and exploring novel applications. Below table no.2 research findings and trends in NLC technology.

Table 2: Research finding and trends in NLC

SR. NO.	Drug	Study/Research	Finding	Advantages	References
1.	Atorvastatin	Exploring Atorvastatin NLC in Depth	concentrated on improving the particle size and bioavailability of NLC loaded with atorvastatin.	Augmentation of bioavailability	77
2.	Simvastatin	Progress in the Formulations of Simvastatin NLC	In experimental models, the results demonstrated enhanced pharmacological effectiveness in lowering hyperlipidemia.	Enhanced stability and encapsulation of the medication	78
3.	Rosuvastatin	Development of Rosuvastatin NLCs	demonstrated efficient lipid-lowering capabilities with improved distribution through the use of nanostructured carriers.	Effective in reducing lipids	79
4.	Lovastatin	Effectiveness of NLC	The solubility and bioavailability of lovastatin were enhanced by NLC	Enhance release	80

Comparison of bioavailability and pharmacokinetic profiles of statin-loaded NLCs versus conventional Statin formulations

Table3: comparison between NLC vs conventional statin formulations

Aspect	Statin loaded NLC	Conventional statin formulation	References
Bioavailability	Atorvastatin-loaded NLCs have shown a 3.6-fold increase in bioavailability compared to traditional formulations.	generally low bioavailability (around 12% for atorvastatin) as a result of significant first-pass metabolism and poor solubility.	81
Peak Plasma concentration (Cmax)	With NLC formulations, higher Cmax is quickly attained, resulting in quicker therapeutic benefit	Because absorption rates are slower, Cmax is attained more slowly.	82,83

Time to reach Cmax (Tmax)	decreased Tmax in comparison to traditional forms, enabling a quicker start to action	Increased Tmax, which causes a delayed therapeutic response	84
Area under the cuve	Greater total drug exposure is indicated by higher AUC values, such as the notable increases observed in pharmacokinetic studies.	Reduced systemic availability due to lower AUC	85
Release profile	Enhances total dose frequented adherence by demonstrating a regulated and prolonged release.	Rapid medication elimination from immediate release necessities more more frequent dose	86
Dose adjustment	decreased likelihood of side effects as a result of smaller dosages and less systemic exposure	Higher incidence of side effect like myopathy and liver complication due to increased dose required	87

Toxicological and safety assessment of Nanostructured Lipid Carriers:

Nanostructured Lipid Carriers (NLCs) are recognized as a biocompatible, non-toxic, and safe nano-drug delivery system, distinguishing them from polymeric or metallic nanoparticles. Their safety, stability, and high drug loading capacity make them attractive for formulating effective drug carriers. NLCs offer several advantages, including biocompatibility, biodegradability, non-immunogenicity, and controlled drug release. They have gained attention for their potential in managing various diseases, including hyperlipidemia. Below table 4 shows the safety and toxicological assessment of NLC.

Table 4: Toxicological and safety assessment of Nanostructured Lipid Carriers

NLC Formulation	Toxicological/Safety parameters Assessed	Key finding	References
Zerumbone loaded NLC	LD50, Clinical/behavioural abnormalities, toxicological symptoms, feed consumption, gross appearance, historical assessment of tissues (liver,kidney,spleen,lung, heart, brain) total haemogram,bone marrow stem cells, serum biochemical parameters	All assessed parameters were normal	88
Lipid-core nanocapsule (LNC) containing simvastatin (sv-LNC)	Biochemical markers (hepatic, pancreatic renal, mineral, bony, alkaline phosphate, glucose, uric acid) haematological parameters (red and white blood cell counts)	LNC and SV-LNC were not more toxic than simvastatin crystals. No toxicity for haematological parameters	89
Lipid-core nano capsules (LNCs) with poly(ε-caprolactone) and polysorbate 80	Mortality, body weight changes, histological examination (liver, spleen), hepatotoxicity markers, nephrotoxicity markers, hematologic parameters	Most hepatotoxicity and nephrotoxicity markers were normal, with slight alterations in hematologic parameters.	90

CONCLUSION:

Nanostructured Lipid Carriers (NLCs) represent a significant advancement in the field of drug delivery for hyperlipidemia management. By enhancing the bioavailability and therapeutic efficacy of statins, NLCs offer a promising alternative to conventional formulations. These carriers not only overcome limitations such as poor solubility and extensive first-pass metabolism but also allow sustained drug release, reducing dosing frequency and improving patient compliance. The safety profile, versatility in encapsulating both hydrophilic and lipophilic drugs, and adaptability across various administration routes highlight their broad potential. Future research focusing on clinical translation and large-scale production will be crucial in establishing NLCs as a standard therapeutic approach in cardiovascular disease management.

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