RESEARCH PAPER

Nanotechnology-Based Drug Delivery Systems for Antihyperlipidemic Drugs: Advances, Challenges, and Future Perspectives

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Abstract

Hyperlipidemia is a major global health issue and a key risk factor for cardiovascular diseases, requiring effective and sustained treatment strategies. Although conventional antihyperlipidemic drugs, including statins, fibrates, and cholesterol absorption inhibitors, are clinically effective, their performance is often limited by poor aqueous solubility, low oral bioavailability, extensive first-pass metabolism, and associated side effects. In this context, nanotechnology-based drug delivery systems have emerged as a promising approach to overcome these limitations and improve therapeutic outcomes.

This review presents a comprehensive overview of nano drug delivery systems in antihyperlipidemic therapy. It discusses the pathophysiology of hyperlipidemia and highlights the shortcomings of conventional treatments. Various nanocarrier systems, including lipid- based nanoparticles, polymeric nanoparticles, nanocrystals, dendrimers, and hybrid systems, are critically examined. Particular emphasis is placed on formulation strategies, characterization methods, and mechanisms that enhance drug bioavailability, such as improved solubility, lymphatic uptake, reduced first-pass metabolism, and controlled drug release.

The application of nanotechnology in specific drugs, including statins (simvastatin, atorvastatin, and rosuvastatin), fibrates, and herbal compounds like curcumin and berberine, is also explored. Additionally, combination approaches, including co-delivery systems and bioenhancers such as piperine, are discussed. The review further covers in vitro and in vivo evaluation, safety concerns, regulatory aspects, and commercialization challenges.

Recent advances, including targeted delivery, gene-based therapy, personalized nanomedicine, and AI-driven design, highlight the future potential of this field. Overall, nanotechnology offersa transformative strategy for improving the efficacy, safety, and patient compliance of antihyperlipidemic therapy.

Keywords: Hyperlipidemia; Nano drug delivery systems; Statins; Bioavailability enhancement; Lipid-based nanoparticles; Polymeric nanoparticles; Targeted drug delivery

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1. Introduction

Hyperlipidemia has gradually transitioned from being a relatively under-recognized metabolic disorder to one of the most significant contributors to global cardiovascular morbidity and mortality. In contemporary clinical practice, it is rarely viewed in isolation; rather, it is closely associated with a broader spectrum of metabolic abnormalities, including obesity, insulin resistance, and metabolic syndrome. The modern lifestyle—characterized by reduced physical activity, increased consumption of processed foods, and chronic stress—has accelerated the prevalence of lipid abnormalities across all age groups. Despite the availability of multiple pharmacotherapeutic agents, optimal management remains elusive due to limitations in drug delivery, safety concerns, and interindividual variability in response. Consequently, there is a growing need to rethink conventional therapeutic approaches and adopt advanced strategies that enhance efficacy while minimizing adverse effects.

1.1 Overview of Hyperlipidemia

Hyperlipidemia is defined as an abnormal elevation of lipids or lipoproteins in the blood, primarily involving cholesterol and triglycerides. Clinically, it encompasses elevated levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and/or decreased levels of high-density lipoprotein cholesterol (HDL-C) [1]. These lipid abnormalities disrupt normal physiological processes and predispose individuals to atherosclerotic cardiovascular diseases.

The condition can be broadly categorized into primary and secondary forms. Primary hyperlipidemia arises from genetic defects affecting lipid metabolism, such as familial hypercholesterolemia. In contrast, secondary hyperlipidemia is associated with modifiable factors, including poor dietary habits, sedentary lifestyle, diabetes mellitus, hypothyroidism, and certain medications [2].

From a physiological perspective, lipids are indispensable for maintaining cellular integrity, energy storage, and hormone synthesis. However, when

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present in excess, particularly in the form of LDL-C, they contribute to pathological lipid deposition within arterial walls. Conversely, HDL-C plays a protective role by facilitating reverse cholesterol transport, thereby maintaining lipid homeostasis [3]. The imbalance between these lipoproteins is central to disease progression.

1.2 Pathophysiology of Dyslipidemia

The pathophysiology of dyslipidemia involves a complex interplay between lipid metabolism, oxidative stress, and inflammatory processes. The liver serves as the primary organ regulating lipid synthesis, transport, and clearance. Dysregulation at any stage of this tightly controlled system can lead to abnormal lipid profiles.

Elevated LDL particles penetrate the endothelial lining of blood vessels and undergo oxidative modification, forming oxidized LDL (oxLDL). This modified form is highly atherogenic and triggers endothelial dysfunction, characterized by reduced nitric oxide bioavailability and increased expression of adhesion molecules [4]. These changes facilitate the recruitment of circulating monocytes, which differentiate into macrophages and internalize oxLDL, forming lipid-laden foam cells.

The accumulation of foam cells results in fatty streak formation, representing the earliest visible stage of atherosclerosis. Over time, continued lipid deposition, smooth muscle cell proliferation, and extracellular matrix remodeling lead to plaque formation. These plaques may become unstable and rupture, initiating thrombus formation and acute cardiovascular events such as myocardial infarction or stroke [5].

Additionally, reduced HDL levels impair reverse cholesterol transport, further aggravating lipid accumulation. Genetic factors, including mutations in apolipoproteins, receptors, or enzymes such as lipoprotein lipase, can exacerbate these pathological processes and accelerate disease progression [6].

1.3 Clinical Significance and Global Burden

Hyperlipidemia is a major modifiable risk factor for cardiovascular diseases, which remain the leading cause of death worldwide. According to global health estimates, cardiovascular diseases account for nearly one-third of all deaths, with dyslipidemia being a primary contributing factor [7].

One of the most challenging aspects of hyperlipidemia is its asymptomatic nature during early stages. Many individuals remain undiagnosed until they present with complications such as coronary artery disease, stroke, or peripheral vascular disease. This silent progression significantly increases the clinical and economic burden on healthcare systems.

Epidemiological data consistently demonstrate a direct relationship between elevated LDL-C levels and cardiovascular risk. Even a modest reduction in LDL-C can lead to a substantialdecrease in the incidence of major cardiovascular events [8]. However, disparities in healthcare access, lack of awareness, and poor adherence to long-term therapy limit effective disease control, particularly in developing regions.

The global burden is further amplified by the increasing prevalence of lifestyle-related disorders, emphasizing the urgent need for improved therapeutic strategies that are both effective and accessible.

1.4 Limitations of Conventional Antihyperlipidemic Therapy

Conventional antihyperlipidemic therapies, including statins, fibrates, niacin, bile acid sequestrants, and cholesterol absorption inhibitors, have significantly improved the management of lipid disorders. Among these, statins are considered the cornerstone of therapy due to their potent LDL-C-lowering effects through inhibition of HMG-CoA reductase [9].

Despite their clinical efficacy, these agents are associated with several limitations. Many antihyperlipidemic drugs exhibit poor aqueous solubility, leading to low and variable oral bioavailability. Extensive first-pass metabolism further reduces systemic drug availability, necessitating higher doses to achieve therapeutic effects [10].

Higher dosing is often accompanied by adverse effects such as hepatotoxicity, myopathy, gastrointestinal disturbances, and, in rare cases, rhabdomyolysis. Additionally, interindividual variability in drug response and the occurrence of statin intolerance pose significant challenges in clinical practice.

Another critical limitation is the lack of targeted delivery. Conventional formulations distribute the drug systemically, which may lead to off-target effects and reduced therapeutic efficiency. Furthermore, the requirement for long-term therapy affects patient compliance, ultimately compromising treatment outcomes [11].

1.5 Need for Advanced Drug Delivery Systems

The limitations associated with conventional therapies underscore the need for advanced drug delivery systems that can enhance therapeutic efficacy while minimizing adverse effects. An ideal delivery system should improve drug solubility, protect the active pharmaceutical ingredient from degradation, and ensure controlled or sustained release.

For antihyperlipidemic drugs, targeted delivery to the liver is particularly desirable, as it is the central organ involved in lipid metabolism. Advanced delivery systems can facilitate site- specific drug accumulation, thereby enhancing efficacy and reducing systemic exposure [12]. Moreover, improving pharmacokinetic parameters such as absorption, distribution, metabolism, and elimination can significantly influence therapeutic outcomes. Controlled release formulations can maintain steady plasma drug concentrations, reducing dosing frequency and improving patient adherence.

The integration of innovative delivery approaches also enables the co-delivery of multiple agents, including bioenhancers and natural compounds, which can synergistically improve therapeutic performance. These advancements highlight the importance of adopting novel technologies in the management of

chronic conditions like hyperlipidemia.

1.6 Emergence of Nanotechnology in Drug Delivery

Nanotechnology has emerged as a transformative approach in pharmaceutical sciences, offering innovative solutions to the challenges associated with conventional drug delivery. Nanocarriers, typically ranging from 1 to 1000 nm in size, possess unique physicochemical properties that enable efficient drug encapsulation, protection, and targeted delivery [13].

One of the key advantages of nanotechnology is its ability to enhance the solubility and bioavailability of poorly water-soluble drugs, such as many statins. Nanocarriers can facilitate lymphatic uptake, thereby bypassing hepatic first-pass metabolism and increasing systemic availability [14].

Surface modification of nanoparticles allows for active targeting, enabling selective delivery to specific tissues or cells. This targeted approach not only improves therapeutic efficacy but also reduces off-target toxicity. Additionally, nanocarriers can provide controlled and sustained drug release, maintaining optimal drug levels over extended periods.

Various nanotechnology-based systems, including liposomes, solid lipid nanoparticles, polymeric nanoparticles, and nanoemulsions, have shown promising results in enhancing the delivery of antihyperlipidemic drugs. The incorporation of bioenhancers such as piperine and natural compounds like curcumin further expands the therapeutic potential of these systems. As research in this field continues to evolve, nanotechnology is expected to play a pivotal role in bridging the gap between drug efficacy and clinical performance, ultimately leading to more effective and patient-friendly treatment strategies.

2. Antihyperlipidemic Drugs: Classification and Challenges

The pharmacological management of hyperlipidemia has evolved substantially over the past few decades, with multiple drug classes targeting different aspects of lipid metabolism. These agents have significantly reduced cardiovascular morbidity and mortality; however, their clinical effectiveness is often limited by inherent biopharmaceutical and pharmacokinetic challenges. A clear understanding of drug classification, mechanisms of action, and associatedlimitations is essential for optimizing therapy and guiding the development of advanced delivery systems.

2.1 Classification of Antihyperlipidemic Agents

Antihyperlipidemic drugs are broadly classified based on their mechanism of action and target pathways in lipid metabolism.

Statins

Statins are the first-line agents for the management of hyperlipidemia due to their potent ability to reduce low-density lipoprotein cholesterol (LDL-C). They act by competitively inhibiting 3- hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis [9]. This inhibition leads to upregulation of hepatic LDL receptors, thereby enhancing clearance of circulating LDL particles.

Common statins include simvastatin, atorvastatin, and rosuvastatin. Despite their efficacy, statins exhibit poor aqueous solubility and are subject to extensive hepatic metabolism, which can limit their bioavailability [10].

Fibrates

Fibrates, such as fenofibrate and gemfibrozil, primarily reduce triglyceride levels and modestly increase high-density lipoprotein cholesterol (HDL-C). Their mechanism involves activation of peroxisome proliferator-activated receptor-alpha (PPAR-α), which enhances fatty acid oxidation and reduces hepatic triglyceride synthesis [15].

Although effective in hypertriglyceridemia, fibrates may cause gastrointestinal disturbances and increase the risk of myopathy when used in combination with statins [16].

Bile Acid Sequestrants

Bile acid sequestrants, including cholestyramine and colesevelam, function by binding bile acids in the intestine, preventing their reabsorption. This interruption stimulates hepatic conversion of cholesterol into bile acids, thereby reducing LDL-C levels [17].

However, these agents are often associated with poor patient compliance due to gastrointestinal side effects such as constipation and bloating, as well as interference with the absorption of fat- soluble vitamins and other drugs.

Cholesterol Absorption Inhibitors

Ezetimibe is the primary agent in this class and works by selectively inhibiting the Niemann– Pick C1-like 1 (NPC1L1) transporter in the intestinal epithelium, thereby reducing dietary cholesterol absorption [18]. It is frequently used in combination with statins to achieve additional LDL-C reduction.

Ezetimibe is generally well tolerated but exhibits variable absorption and limited efficacy as monotherapy in severe hyperlipidemia.

PCSK9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, such as alirocumab and evolocumab, are monoclonal antibodies that enhance LDL receptor recycling by inhibiting PCSK9-mediated receptor degradation [19]. This results in significant reductions in circulating LDL-C levels.

Although highly effective, these agents are expensive and require parenteral administration, which may limit widespread use.

Niacin and Others

Niacin (nicotinic acid) reduces hepatic synthesis of very-low-density lipoprotein (VLDL) and LDL while increasing HDL levels. However, its clinical use has declined due to adverse effects such as flushing, hepatotoxicity, and insulin resistance [20].

Other agents include omega-3 fatty acids and emerging therapies targeting novel pathways in lipid metabolism. While these drugs offer additional therapeutic options, their efficacy and safety profiles vary.

2.2 Biopharmaceutical Challenges

Despite the availability of diverse drug classes, several biopharmaceutical limitations hinder optimal therapeutic outcomes.

Poor Solubility

Many antihyperlipidemic drugs, particularly lipophilic statins such as simvastatin, exhibit poor aqueous solubility. This limits their dissolution in gastrointestinal fluids and reduces absorption, ultimately affecting bioavailability [10].

Low Bioavailability

Oral bioavailability of several lipid-lowering drugs is significantly compromised due to poor solubility, limited permeability, and presystemic metabolism. For instance, simvastatin undergoes extensive hepatic metabolism, resulting in low systemic availability of the active form [21].

First-Pass Metabolism

A major fraction of orally administered antihyperlipidemic drugs is metabolized in the liver before reaching systemic circulation. While hepatic targeting is beneficial for statins, excessive first-pass metabolism reduces the effective drug concentration and necessitates higher dosing [22].

Short Half-Life

Certain drugs exhibit short biological half-lives, requiring frequent dosing to maintain therapeutic plasma levels. This can negatively impact patient adherence, particularly in chronic conditions requiring lifelong treatment [23].

Adverse Effects

Adverse drug reactions remain a significant concern. Statins are associated with muscle-related symptoms and hepatotoxicity, while niacin causes flushing and metabolic disturbances. Fibrates may increase the risk of gallstone formation and drug interactions [24].

These side effects often lead to dose reduction or discontinuation, compromising treatment efficacy.

2.3 Pharmacokinetic and Pharmacodynamic Limitations

The pharmacokinetic (PK) and pharmacodynamic (PD) profiles of antihyperlipidemic drugs play a crucial role in determining their therapeutic effectiveness. However, several limitations are associated with conventional formulations.

From a pharmacokinetic perspective, variability in absorption, distribution, metabolism, and elimination contributes to inconsistent drug responses among patients. Factors such as food intake, genetic polymorphisms in metabolic enzymes (e.g., CYP450), and drug–drug interactions further influence drug levels [25].

In terms of distribution, many drugs lack specificity and are widely distributed throughout the body, increasing the likelihood of off-target effects. Ideally, antihyperlipidemic drugs should preferentially accumulate in the liver, but conventional formulations do not provide such targeted delivery.

Pharmacodynamically, the relationship between drug concentration and therapeutic effect is often nonlinear. In some cases, increasing the dose does not proportionally enhance efficacy but instead elevates the risk of adverse effects. Additionally, delayed onset of action and incomplete lipid control in certain patient populations highlight the limitations of existing therapies [26].

These challenges underscore the necessity for innovative drug delivery strategies that can improve pharmacokinetic stability, enhance target specificity, and optimize therapeutic outcomes.

3. Fundamentals of Nanotechnology in Drug Delivery

Nanotechnology has emerged as a transformative discipline in pharmaceutical sciences, fundamentally altering the way therapeutic agents are designed, delivered, and evaluated. Unlike conventional dosage forms, which primarily focus on delivering drugs in bulk form, nanotechnology enables precise manipulation of materials at the molecular and atomic levels. This shift has introduced new possibilities for improving drug solubility, stability, targeting efficiency, and overall therapeutic performance [27,28].

In the context of antihyperlipidemic therapy, nanotechnology addresses several longstanding challenges, including poor aqueous solubility, low bioavailability, and lack of site-specific delivery. By engineering nanoscale carriers, drugs can be delivered more efficiently to their intended site of action, thereby enhancing efficacy while minimizing systemic toxicity [27].

3.1 Definition and Concepts of Nanotechnology

Nanotechnology refers to the science and engineering of materials at the nanoscale, typically ranging from 1 to 1000 nanometers. At this scale, materials exhibit unique physicochemical properties, including increased surface area, enhanced reactivity, and altered optical and mechanical characteristics [29].

In drug delivery, nanotechnology involves the design of nanosystems capable of encapsulating, protecting, and transporting therapeutic agents to specific biological targets. These nanosystems include liposomes, polymeric nanoparticles, solid lipid nanoparticles, dendrimers, and nanoemulsions [30-33]. Each system is engineered to optimize drug loading, release kinetics, and targeting capabilities.

A fundamental concept in nanotechnology-based delivery is the ability to modify surface properties. Surface functionalization with polymers such as polyethylene glycol (PEG) can improve circulation time by reducing recognition and clearance by the

reticuloendothelial system (RES) [34]. Additionally, ligand conjugation allows nanoparticles to selectively bind to specific receptors, enabling targeted therapy [28].

Another key concept is controlled and sustained drug release. Nanocarriers can be designed to release drugs over an extended period, maintaining therapeutic concentrations and reducing dosing frequency. This is particularly beneficial in chronic diseases such as hyperlipidemia, where long-term treatment is required.

3.2 Advantages of Nanocarriers

Nanocarriers offer several advantages over conventional drug delivery systems, making them highly attractive for improving the therapeutic performance of antihyperlipidemic drugs.

One of the most significant benefits is the enhancement of drug solubility. Many lipid-lowering agents, particularly statins, are poorly water-soluble. Encapsulation within nanocarriers improves their dispersion in biological fluids, thereby enhancing absorption and bioavailability [27,29].

Nanocarriers also provide protection against chemical and enzymatic degradation. Drugs that are unstable in the gastrointestinal environment can be shielded within nanoparticle matrices, ensuring their integrity until they reach the target site.

Another major advantage is the ability to achieve controlled and sustained drug release. By modulating the composition and structure of nanocarriers, drug release profiles can be tailored to maintain consistent plasma concentrations, reducing fluctuations and minimizing side effects [35].

Targeted delivery is a defining feature of nanocarriers. Through passive and active targeting mechanisms, nanoparticles can accumulate preferentially in specific tissues, such as the liver in the case of antihyperlipidemic drugs [37]. This targeted approach enhances therapeutic efficacy while reducing off-target toxicity.

Furthermore, nanocarriers can facilitate lymphatic uptake, bypassing hepatic first-pass metabolism and improving systemic availability. They also enable co-delivery of multiple agents, including drugs and bioenhancers, thereby supporting combination therapy strategies [38].

3.3 Mechanisms of Drug Targeting

Targeted drug delivery is one of the most significant advantages of nanotechnology. It ensures that therapeutic agents are delivered selectively to the site of action, improving efficacy and minimizing systemic exposure.

Passive Targeting

Passive targeting relies on the inherent physicochemical properties of nanoparticles, such as size, shape, and surface charge, to achieve preferential accumulation in specific tissues. One of the most well-known mechanisms is the enhanced permeability and retention (EPR) effect, observed in tissues with leaky vasculature and impaired lymphatic drainage [39].

Although the EPR effect is more commonly associated with tumor targeting, it can also be exploited in inflammatory conditions and certain metabolic disorders. Nanoparticles circulating in the bloodstream can passively accumulate in these regions due to increased vascular permeability [39].

Particle size plays a crucial role in passive targeting. Nanoparticles within an optimal size range can evade rapid renal clearance while avoiding uptake by the RES, thereby prolonging circulation time and enhancing accumulation at the target site [40].

Active Targeting

Active targeting involves the functionalization of nanoparticle surfaces with specific ligands that can bind to receptors expressed on target cells. These ligands may include antibodies, peptides, sugars, or small molecules [28].

In the context of antihyperlipidemic therapy, active targeting strategies can be designed to direct nanoparticles to hepatocytes, the primary site of lipid metabolism. For example, ligands targeting low-density lipoprotein receptors (LDLR) or scavenger receptors can enhance hepatic uptake [37].

Upon binding to the target receptor, the nanoparticle is internalized via receptor-mediated endocytosis, allowing efficient intracellular delivery of the drug. This approach not only improves therapeutic efficacy but also reduces systemic side effects by limiting drug exposure to non-target tissues [28].

3.4 Nanoparticle–Biological Interactions

The interaction between nanoparticles and biological systems is a critical determinant of their safety and efficacy. Once administered, nanoparticles encounter a complex biological environment, including proteins, cells, and physiological barriers.

One of the first events following administration is the formation of a “protein corona,” where plasma proteins adsorb onto the nanoparticle surface. This corona influences the biological identity of the nanoparticle, affecting its distribution, cellular uptake, and clearance [41].

The reticuloendothelial system (RES), particularly macrophages in the liver and spleen, plays a significant role in nanoparticle clearance. Surface modification techniques, such as PEGylation, can reduce opsonization and prolong circulation time [36].

Cellular uptake of nanoparticles occurs through various mechanisms, including endocytosis, phagocytosis, and pinocytosis. The efficiency of uptake depends on factors such as particle size, surface charge, and hydrophobicity.

Biocompatibility and toxicity are also important considerations. While many nanocarriers are designed to be biodegradable and non-toxic, some materials may induce oxidative stress, inflammation, or immune responses. Therefore, careful selection of materials and thorough evaluation of safety profiles are essential for clinical translation[37].

Overall, understanding nanoparticle–biological

interactions is crucial for designing effective and safe drug delivery systems. By optimizing these interactions, it is possible to enhance targeting efficiency, improve therapeutic outcomes, and minimize adverse effects.

4. Types of Nano Drug Delivery Systems for Antihyperlipidemic Drugs

The therapeutic success of antihyperlipidemic drugs is often compromised by poor solubility, low bioavailability, and non-specific distribution. Nanotechnology-driven delivery systems have been developed to overcome these limitations by improving drug solubilization, protecting drugs from degradation, enabling controlled release, and facilitating targeted delivery to the liver—the central organ in lipid metabolism [42,43]. Different nanocarrier systems offer distinct structural and functional advantages, allowing customization based on drug properties and therapeutic needs.

4.1 Lipid-Based Nanocarriers

Lipid-based nanocarriers are highly suitable for antihyperlipidemic drugs due to their compatibility with lipophilic molecules and physiological membranes. These systems enhance oral absorption, promote lymphatic transport, and reduce first-pass metabolism [44].

4.1.1 Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles are composed of solid lipids stabilized by surfactants, forming a rigid matrix that encapsulates drug molecules. The solid state of lipids at physiological temperature provides structural integrity and sustained drug release.

SLNs improve the stability of labile drugs and enhance the bioavailability of poorly soluble statins by increasing surface area and facilitating intestinal uptake [45]. Additionally, they protect drugs from enzymatic degradation in the gastrointestinal tract.

However, their crystalline structure can lead to limited drug loading and potential drug expulsion during storage due to polymorphic transitions of lipids [46]. Despite these drawbacks, SLNs remain a widely investigated system for simvastatin and atorvastatin delivery.

4.1.2 Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers are an advancement over SLNs, incorporating both solid and liquid lipids to create a less ordered matrix. This structural imperfection increases drug accommodation and minimizes expulsion during storage.

NLCs exhibit superior drug loading capacity, improved stability, and enhanced release control compared to SLNs [45]. Importantly, they facilitate lymphatic uptake, which bypasses hepatic first-pass metabolism and significantly improves systemic availability of lipophilic drugs [44]. Their versatility makes them highly effective for delivering antihyperlipidemic agents requiring sustained plasma levels.

4.1.3 Liposomes

Liposomes are vesicular systems composed of phospholipid bilayers enclosing an aqueous core. Their amphiphilic nature allows encapsulation of both hydrophilic and lipophilic drugs.

In antihyperlipidemic therapy, liposomes improve drug pharmacokinetics, reduce toxicity, and enable targeted delivery through surface modification. PEGylated liposomes, for example, exhibit prolonged circulation time by evading the reticuloendothelial system (RES) [34,47]. Despite their advantages, liposomes face challenges such as physical instability, drug leakage, and high manufacturing costs, which may limit large-scale application.

4.1.4 Nanoemulsions

Nanoemulsions are colloidal dispersions consisting of oil and water phases stabilized by surfactants, with droplet sizes typically below 200 nm.

They significantly enhance the solubility and dissolution rate of lipophilic drugs, thereby improving oral bioavailability. Nanoemulsions also promote lymphatic transport, reducing hepatic metabolism and increasing drug exposure [48].

For antihyperlipidemic drugs such as fenofibrate and simvastatin, nanoemulsions have demonstrated improved absorption and faster onset of action. However, their stability is influenced by environmental factors such as temperature and pH.

4.2 Polymeric Nanoparticles

Polymeric nanoparticles are versatile carriers that offer controlled and sustained drug release. They can be engineered to modify drug release kinetics, improve stability, and enable targeted delivery [49].

4.2.1 Natural Polymers (Chitosan, Alginate)

Natural polymers are widely used due to their safety, biodegradability, and biocompatibility. Chitosan, a positively charged polymer, enhances mucoadhesion and opens tight junctions between epithelial cells, facilitating improved drug absorption across the intestinal barrier [50]. This property is particularly beneficial for drugs with poor permeability.

Alginate forms gel-like structures in the presence of calcium ions, providing controlled release and protection of drugs from gastric degradation [51]. It is especially useful in oral formulations requiring sustained release.

Both polymers have shown effectiveness in delivering statins and herbal antihyperlipidemic agents with improved bioavailability and reduced dosing frequency.

4.2.2 Synthetic Polymers (PLGA, PEG)

Synthetic polymers provide greater control over nanoparticle properties.

PLGA is a biodegradable polymer that undergoes hydrolysis into lactic and glycolic acid, making it safe for pharmaceutical applications. It allows precise control of drug release and protects drugs from degradation [52].

PEG is commonly used for surface modification to enhance circulation time by reducing protein adsorption and RES uptake, a process known as PEGylation [34].
PLGA-based nanoparticles have demonstrated improved pharmacokinetics and sustained release of antihyperlipidemic drugs, contributing to better therapeutic outcomes.

4.3 Nanocrystals
Nanocrystals are carrier-free systems composed entirely of drug particles reduced to nanoscale size. They are stabilized using surfactants or polymers.

4.3.1 Concept and Preparation
Nanocrystals enhance drug dissolution by increasing surface area and saturation solubility. Their preparation involves techniques such as high-pressure homogenization, wet milling, and antisolvent precipitation [43].
These methods produce stable nanosuspensions with uniform particle size distribution.

4.3.2 Applications in Poorly Soluble Drugs
Nanocrystals are particularly useful for Biopharmaceutics Classification System (BCS) Class II drugs, which exhibit low solubility and high permeability.
For antihyperlipidemic drugs like statins and fibrates, nanocrystals significantly improve dissolution rate and oral absorption, leading to enhanced bioavailability and therapeutic efficacy [54].
Their high drug loading capacity and simplicity of formulation make them attractive for commercial applications.

4.4 Dendrimers
Dendrimers are highly branched, nanoscale macromolecules with a well-defined architecture consisting of a core, branching units, and terminal functional groups.

4.4.1 Structure and Properties
Dendrimers exhibit monodispersity, high surface functionality, and internal cavities capable of hosting drug molecules. Their size, shape, and surface chemistry can be precisely controlled during synthesis [55].
These properties enable efficient drug encapsulation and targeted delivery.

4.4.2 Drug Loading Mechanisms
Drugs can be incorporated into dendrimers through multiple mechanisms:
- Physical encapsulation within internal cavities
- Electrostatic interactions between drug and surface groups
- Covalent conjugation to terminal functional groups

These versatile loading strategies allow customization of drug release profiles and targeting efficiency. However, potential toxicity and high synthesis cost remain challenges [55].

4.5 Metallic Nanoparticles
Metallic nanoparticles possess unique optical, electronic, and catalytic properties, making them useful in biomedical applications.

4.5.1 Gold Nanoparticles
Gold nanoparticles are highly stable and biocompatible. Their surface can be easily functionalized with ligands for targeted drug delivery.
They have shown potential in delivering antihyperlipidemic drugs and reducing oxidative stress associated with atherosclerosis [56].

4.5.2 Silver Nanoparticles
Silver nanoparticles exhibit strong antimicrobial and anti-inflammatory properties. They may contribute to reducing inflammation in atherosclerotic conditions.
However, their application is limited due to concerns regarding cytotoxicity and long-term safety [57].

4.6 Hybrid Nanocarriers
Hybrid systems integrate multiple materials to combine the advantages of different nanocarriers while minimizing their limitations.

4.6.1 Lipid–Polymer Hybrid Systems
These systems consist of a polymeric core surrounded by a lipid shell, combining the structural stability of polymers with the biocompatibility of lipids.
They provide high drug loading, controlled release, and improved targeting efficiency, making them ideal for antihyperlipidemic therapy [58].

4.6.2 Stimuli-Responsive Nanocarriers
Stimuli-responsive nanocarriers are designed to release drugs in response to specific triggers such as pH, temperature, enzymes, or external stimuli.
These systems enable site-specific drug release, improving therapeutic precision and minimizing systemic side effects. For example, pH-sensitive nanoparticles can release drugs in targeted regions of the gastrointestinal tract or diseased tissues [59].

5. Formulation Strategies for Antihyperlipidemic Nanoformulations
The successful development of nanoformulations for antihyperlipidemic drugs requires a rational and systematic formulation approach that integrates drug physicochemical properties, carrier selection, preparation techniques, and surface engineering. Unlike conventional dosage forms, nanoformulations demand precise control over particle size, surface characteristics, and drug release behavior to achieve optimal therapeutic performance. Given that many antihyperlipidemic agents suffer from poor solubility, extensive first-pass metabolism, and variable bioavailability, formulation strategies must be carefully designed to overcome these barriers and enhance clinical outcomes.

5.1 Drug Selection Criteria

The selection of a suitable drug candidate is the first and most critical step in nanoformulation design. Not all drugs benefit equally from nanotechnology; therefore, careful evaluation of physicochemical and biopharmaceutical properties is essential.

Drugs belonging to the Biopharmaceutics Classification System (BCS) Class II (low solubility, high permeability), such as many statins and fibrates, are ideal candidates for nanoformulation approaches [10]. Poor aqueous solubility limits their dissolution rate, which directly affects absorption and bioavailability.

Key criteria for drug selection include:

- **Solubility profile:** Poorly water-soluble drugs benefit most from nanoformulation [60].
- **Partition coefficient (log P):** Lipophilic drugs are suitable for lipid-based systems [61].
- **Molecular weight and stability:** Drugs prone to degradation require protective carriers [62].
- **Dose and therapeutic index:** Drugs with narrow therapeutic windows require controlled release systems [63]..

Additionally, the site of action must be considered. Since the liver is the primary organ involved in lipid metabolism, drugs that can benefit from hepatic targeting are particularly suitable for nano-delivery systems [37].

5.2 Methods of Preparation

The preparation method significantly influences the physicochemical characteristics, stability, and performance of nanoformulations. Selection of an appropriate technique depends on the type of nanocarrier, drug properties, and desired release profile.

Solvent Evaporation Method

The solvent evaporation technique is widely used for preparing polymeric nanoparticles. In this method, the drug and polymer are dissolved in an organic solvent, which is then emulsified into an aqueous phase containing surfactants. The organic solvent is subsequently evaporated, leading to nanoparticle formation [64].

This method offers advantages such as:

- Good control over particle size
- High encapsulation efficiency
- Suitability for hydrophobic drugs

However, limitations include the use of organic solvents and the potential for residual solvent toxicity.

High-Pressure Homogenization

High-pressure homogenization is a top-down approach commonly used for preparing nanocrystals and lipid nanoparticles. The drug is subjected to high shear forces and cavitation under elevated pressure, resulting in particle size reduction to the nanoscale [65].

This method is advantageous due to:

- Scalability for industrial production
- Absence of organic solvents
- Production of uniform particle size distribution

It is particularly effective for improving the dissolution rate of poorly soluble antihyperlipidemic drugs.

Nanoprecipitation Method

Nanoprecipitation, also known as the solvent displacement method, involves the rapid mixing of a drug-polymer solution in a water-miscible organic solvent with an aqueous phase. This leads to instantaneous precipitation of nanoparticles due to solvent diffusion [66].

Key advantages include:

- Simplicity and rapid processing
- Low energy requirement
- Narrow particle size distribution

However, this method is primarily suitable for hydrophobic drugs and may exhibit lower encapsulation efficiency for hydrophilic compounds.

Microemulsion Technique

The microemulsion technique utilizes thermodynamically stable mixtures of oil, water, surfactant, and co-surfactant to form nanoscale droplets. These droplets act as templates for nanoparticle formation upon dilution or solvent removal [67].

This method offers:

- Excellent control over particle size
- High reproducibility
- Mild processing conditions

Microemulsions are particularly useful for preparing lipid-based nanocarriers such as SLNs and NLCs for antihyperlipidemic drugs.

5.3 Surface Modification and Functionalization

Surface engineering plays a pivotal role in determining the biological fate of nanoparticles. Once administered, nanoparticles interact with biological components, and their surface characteristics influence circulation time, biodistribution, and cellular uptake.

One of the most widely used strategies is PEGylation, where polyethylene glycol (PEG) is attached to the nanoparticle surface. PEGylation reduces protein adsorption (opsonization) and prevents rapid clearance by the reticuloendothelial system (RES), thereby prolonging systemic circulation [34].

Active targeting can be achieved by conjugating ligands such as antibodies, peptides, or small molecules to the nanoparticle surface. These ligands bind to specific receptors on target cells, such as hepatocytes, enabling receptor-mediated endocytosis and improved drug delivery efficiency [28].

Other functionalization approaches include:

- Charge modification to enhance cellular uptake [68]
- Stimuli-responsive coatings for controlled release [59]
- Mucoadhesive coatings (e.g., chitosan) to improve intestinal absorption [50]

These strategies collectively enhance the therapeutic potential of nanoformulations by improving specificity and reducing off-target effects.

5.4 Drug Loading and Encapsulation Efficiency

Drug loading and encapsulation efficiency are critical parameters that determine the effectiveness and feasibility of nanoformulations.

- Drug loading (%) refers to the amount of drug present relative to the total weight of the nanoparticle.
- Encapsulation efficiency (%) indicates the proportion of drug successfully entrapped within the carrier system.

High drug loading is desirable to minimize the quantity of carrier material required, while high encapsulation efficiency ensures minimal drug loss during formulation [68].

Several factors influence these parameters:

- Drug solubility in the carrier matrix
- Polymer or lipid composition
- Preparation method
- Drug–carrier interactions

For lipophilic antihyperlipidemic drugs, lipid-based carriers typically exhibit higher encapsulation efficiency due to better solubility within the lipid matrix. In contrast, polymeric nanoparticles provide better control over drug release but may exhibit moderate loading capacity [69].

Optimization of formulation variables is essential to achieve a balance between drug loading, release kinetics, and stability. Advanced techniques such as factorial design and response surface methodology are often employed to optimize these parameters systematically [70].

6. Characterization of Nanoparticles

Comprehensive characterization of nanoparticles is a critical step in the development of nano drug delivery systems. It ensures consistency, reproducibility, stability, and optimal therapeutic performance. For antihyperlipidemic nanoformulations, characterization not only confirms the successful incorporation of the drug but also predicts in vivo behavior such as absorption, biodistribution, and drug release. Each parameter provides essential insights into the physicochemical and functional properties of the formulation, guiding optimization and quality control.

6.1 Particle Size and Size Distribution

Particle size is one of the most fundamental characteristics influencing the biological performance of nanoparticles. It directly affects drug release rate, cellular uptake, biodistribution, and stability.

Nanoparticles typically range from 10 to 1000 nm; however, for oral delivery of antihyperlipidemic drugs, a size range of 50–300 nm is often considered optimal for enhanced absorption and lymphatic uptake [71]. Smaller particles provide a larger surface area, leading to improved dissolution rate and bioavailability, especially for poorly soluble drugs.

Size distribution is equally important and is commonly expressed as the polydispersity index (PDI). A low PDI (≤ 0.3) indicates a uniform particle population, which is desirable for consistent drug release and predictable pharmacokinetics [72].

Dynamic light scattering (DLS) is the most widely used technique for determining particle size and PDI, offering rapid and reliable measurements.

6.2 Zeta Potential

Zeta potential is a measure of the surface charge of nanoparticles and plays a crucial role in determining their physical stability. It reflects the degree of electrostatic repulsion between particles in a dispersion.

Nanoparticles with high zeta potential values (typically $> \pm 30$ mV) exhibit strong repulsive forces, preventing aggregation and ensuring colloidal stability [10]. Conversely, low zeta potential may lead to particle aggregation and instability.

In addition to stability, zeta potential influences biological interactions. Positively charged nanoparticles tend to exhibit enhanced cellular uptake due to electrostatic attraction with negatively charged cell membranes, while negatively charged or neutral particles may demonstrate prolonged circulation times [12].

Measurement is commonly performed using electrophoretic light scattering techniques.

6.3 Morphology (SEM, TEM)

Morphological characterization provides detailed information about the shape, surface structure, and physical appearance of nanoparticles.

- Scanning Electron Microscopy (SEM) is used to analyze surface morphology and particle shape. It provides high-resolution images that reveal surface texture and aggregation patterns.
- Transmission Electron Microscopy (TEM) offers deeper insights into internal structure and particle size at the nanoscale level, often with higher resolution than SEM [73].

For antihyperlipidemic nanoformulations, spherical and smooth-surfaced nanoparticles are generally preferred, as they facilitate uniform drug release and improved cellular uptake.

Morphology also helps confirm successful formulation and detect structural anomalies such as aggregation or irregular shapes.

6.4 Drug Content and Entrapment Efficiency

Drug content and entrapment efficiency are critical parameters that determine the therapeutic potential of a nanoformulation.

- Drug content refers to the total amount of drug present in the formulation.
- Entrapment efficiency (EE%) indicates the percentageof drug successfully ncapsulated within the nanoparticle system.

High entrapment efficiency is particularly important for antihyperlipidemic drugs to ensure sufficient drug delivery at lower doses. Lipid-based nanoparticles often exhibit higher EE% for lipophilic drugs due to better solubility in lipid matrices [10].

These parameters are typically determined using analytical techniques such as UV–visible spectroscopy, high-performance liquid chromatography (HPLC), or

LC-MS [74].
Factors influencing entrapment efficiency include:
- Drug–carrier compatibility
- Preparation method
- Polymer/lipid composition
- Drug solubility

- USP dissolution apparatus The release profile may exhibit
- :
- Immediate release (burst effect)
- Sustained release
- Controlled release

For antihyperlipidemic therapy, sustained and controlled release is desirable to maintain therapeutic plasma concentrations and reduce dosing frequency.
Drug release kinetics are often analyzed using mathematical models such as:
- Zero-order kinetics
- First-order kinetics
- Higuchi model
- Korsmeyer–Peppas model [75]

These models help elucidate the mechanism of drug release, whether diffusion-controlled, erosion-controlled, or a combination of both.

6.6 Stability Studies
Stability studies are crucial to ensure that nanoformulations maintain their physicochemical properties, efficacy, and safety over time.
Stability evaluation includes:
- Particle size and PDI changes
- Zeta potential variation
- Drug content retention
- Physical appearance (aggregation, precipitation) Studies are conducted under various conditions, including:
- Accelerated conditions (e.g., 40°C ± 2°C / 75% RH)
- Long-term storage conditions (e.g., 25°C ± 2°C / 60% RH)

These conditions are based on International Council for Harmonisation (ICH) guidelines [76].
Instability may arise due to:
- Particle aggregation
- Drug leakage
- Chemical degradation

Surface modification techniques such as PEGylation and the use of stabilizers can significantly improve nanoparticle stability [77].
For antihyperlipidemic nanoformulations, maintaining stability is particularly important to ensure consistent drug delivery during long-term therapy.

6.5 In vitro Drug Release Studies
In vitro drug release studies are essential for evaluating the release profile of drugs from nanoparticles and predicting in vivo performance.
These studies are typically conducted using:
- Dialysis bag method
- Franz diffusion cell

7. Mechanisms of Enhanced Bioavailability
One of the primary objectives of nano drug delivery systems in antihyperlipidemic therapy is to enhance the oral bioavailability of drugs that otherwise exhibit poor absorption and extensive metabolism. Bioavailability is influenced by multiple factors, including solubility, permeability, metabolic stability, and drug release kinetics. Nanotechnology addresses these barriers through a combination of physicochemical and biological mechanisms, ultimately improving therapeutic efficacy and reducing dose-related side effects.

7.1 Improved Solubility and Dissolution
Poor aqueous solubility is a major limitation for many antihyperlipidemic drugs, particularly statins and fibrates, which belong to Biopharmaceutics Classification System (BCS) Class II. These drugs exhibit dissolution-limited absorption, meaning that their rate of absorption is governed by their dissolution rate in gastrointestinal fluids [10].
Nanotechnology enhances solubility primarily by reducing particle size to the nanometer scale, which significantly increases surface area according to the Noyes–Whitney principle. This leads to a higher dissolution rate and increased saturation solubility, thereby improving drug absorption [78].
Additionally, nanocarriers such as lipid nanoparticles and nanoemulsions improve drug dispersion in the gastrointestinal environment, facilitating better interaction with the absorptive epithelium. Encapsulation within lipid matrices further enhances solubilization by maintaining the drug in a dissolved state, preventing precipitation in the intestinal lumen [79].
Another important aspect is the use of surfactants and stabilizers in nanoformulations, which reduce interfacial tension and enhance wettability, further promoting dissolution. Collectively, these mechanisms significantly improve the oral bioavailability of poorly soluble antihyperlipidemic agents.

7.2 Lymphatic Uptake
Lymphatic transport is a key mechanism by which nano drug delivery systems enhance bioavailability, particularly for lipophilic drugs. Unlike conventional absorption pathways, which involve transport through the portal vein to the liver, lymphatic uptake allows drugs to bypass hepatic metabolism.
Lipid-based nanocarriers, such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers

(NLCs), and nanoemulsions, promote the incorporation of drugs into chylomicrons within enterocytes. These chylomicrons are then transported via the lymphatic system, leading to systemic circulation without initial hepatic degradation [14].

This pathway is especially beneficial for antihyperlipidemic drugs that undergo extensive first-pass metabolism. By enhancing lymphatic uptake, nanoformulations increase the fraction of drug reaching systemic circulation, thereby improving therapeutic efficiency.

The efficiency of lymphatic transport depends on several factors, including:

- Lipophilicity of the drug (log P > 5 preferred)
- Particle size and composition
- Type of lipid used in the formulation

Optimizing these parameters can significantly enhance drug absorption through the intestinal lymphatic system.

7.3 Reduced First-Pass Metabolism

First-pass metabolism in the liver is a major barrier to the oral bioavailability of many antihyperlipidemic drugs. After absorption from the gastrointestinal tract, drugs are transported via the portal vein to the liver, where they undergo extensive metabolic degradation, reducing the amount of active drug reaching systemic circulation [22].

Nanocarriers reduce first-pass metabolism through multiple mechanisms. As discussed, lymphatic uptake enables drugs to bypass the hepatic portal system. Additionally, encapsulation within nanoparticles protects the drug from enzymatic degradation in the gastrointestinal tract and liver.

Surface modification strategies, such as PEGylation, further enhance circulation time and reduce recognition by metabolic enzymes and clearance systems [80]. Controlled release properties of nanoparticles also contribute by maintaining lower, sustained drug concentrations, thereby reducing the burden on metabolic pathways.

These combined effects lead to a significant increase in systemic drug availability and improved pharmacokinetic profiles.

7.4 Controlled and Sustained Release

Controlled and sustained drug release is another critical mechanism through which nanotechnology enhances bioavailability and therapeutic outcomes. Conventional dosage forms often produce rapid drug release, leading to fluctuations in plasma concentration, which may result in suboptimal efficacy or increased side effects.

Nanocarriers are designed to release drugs in a controlled manner over an extended period. This is achieved through diffusion, polymer degradation, or erosion mechanisms, depending on the carrier system [13].

Sustained release offers several advantages:

- Maintains therapeutic plasma concentrations for longer durations
- Reduces dosing frequency, improving patient compliance
- Minimizes peak-trough fluctuations, reducing adverse effects

In antihyperlipidemic therapy, sustained drug release is particularly beneficial due to the chronic nature of the condition. Polymeric nanoparticles (e.g., PLGA-based systems) and lipid carriers can be engineered to provide prolonged drug release, ensuring consistent lipid- lowering effects.

Mathematical modeling of release kinetics, such as Higuchi and Korsmeyer–Peppas models, helps in understanding and optimizing drug release behavior [75].

8. Applications in Specific Antihyperlipidemic Drugs

Nanotechnology-based drug delivery has transitioned from theoretical promise to practical application in several antihyperlipidemic agents. Many lipid-lowering drugs exhibit suboptimal pharmacokinetic profiles due to poor aqueous solubility, extensive metabolism, and limited permeability. Nanoformulations provide a platform to address these issues by enhancing solubility, facilitating targeted delivery, and enabling controlled release. This section presents an in-depth discussion of nano-enabled delivery systems for statins, fibrates, herbal compounds, and combination therapies.

8.1 Nanoformulations of Statins

Statins are the first-line pharmacological agents for the management of hyperlipidemia due to their potent inhibition of HMG-CoA reductase. However, their therapeutic efficiency is often limited by poor oral bioavailability and high hepatic first-pass metabolism [21,22].

Simvastatin

Simvastatin is a lipophilic prodrug with very low aqueous solubility and oral bioavailability (~5%). Its rapid metabolism in the liver significantly reduces systemic drug availability.

Nanoformulation strategies such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and polymeric nanoparticles have been extensively investigated. SLNs improve drug solubilization and provide sustained release, while NLCs offer enhanced drug loading due to their imperfect lipid matrix [81].

Studies have shown that simvastatin-loaded NLCs can increase oral bioavailability by enhancing lymphatic uptake and reducing first-pass metabolism [82]. Additionally, PLGA- based nanoparticles provide prolonged drug release, maintaining therapeutic plasma levels over extended periods.

These improvements translate into enhanced lipid-lowering efficacy and reduced dosing frequency.

Atorvastatin

Atorvastatin is one of the most widely prescribed

statins, but it suffers from poor solubility and variable bioavailability (~12%) [83].
Nanoemulsion-based systems significantly enhance dissolution and intestinal absorption by increasing drug dispersion in gastrointestinal fluids [84]. Polymeric nanoparticles provide controlled release and improved pharmacokinetics, while liposomal systems enable targeted delivery and reduced systemic toxicity [85].
Advanced formulations such as self-nanoemulsifying drug delivery systems (SNEDDS) and lipid-polymer hybrid nanoparticles have demonstrated superior bioavailability and improved lipid profile outcomes in preclinical studies.

Rosuvastatin
Rosuvastatin is relatively hydrophilic but exhibits limited permeability and moderate bioavailability (~20%). It is a substrate for hepatic uptake transporters, which can limit systemic exposure.
Nanocarriers such as polymeric nanoparticles and lipid-based systems have been developed to improve permeability and prolong circulation time. Surface-functionalized nanoparticles can enhance hepatic targeting, increasing drug concentration at the site of action [86].
These nanoformulations have shown improved pharmacodynamic responses, including enhanced reduction in LDL cholesterol levels.

8.2 Nanoformulations of Fibrates
Fibrates, particularly fenofibrate, are used to reduce triglyceride levels and increase high- density lipoprotein (HDL) cholesterol. However, fenofibrate is highly lipophilic and poorly water-soluble, resulting in inconsistent absorption.
Nanocrystal technology has been successfully applied to fenofibrate, significantly improving its dissolution rate and bioavailability. Reduction of particle size increases surface area, enhancing drug solubilization and absorption [87].
Lipid-based nanoformulations, such as nanoemulsions and NLCs, further improve lymphatic transport and reduce hepatic metabolism [88]. These systems provide more consistent pharmacokinetic profiles and improved therapeutic outcomes.
Polymeric nanoparticles have also been explored for sustained release, ensuring prolonged lipid-lowering effects and improved patient adherence.

8.3 Herbal Antihyperlipidemic Compounds
Herbal compounds are increasingly being explored as complementary or alternative therapies for hyperlipidemia. However, their clinical application is often hindered by poor solubility, low stability, and limited bioavailability.

Curcumin
Curcumin possesses potent antihyperlipidemic, antioxidant, and anti-inflammatory properties. It modulates lipid metabolism, reduces oxidative stress, and inhibits atherosclerotic progression.
Despite its therapeutic potential, curcumin exhibits extremely low bioavailability due to poor solubility, rapid metabolism, and systemic elimination [89].
Nanoformulations such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles significantly enhance curcumin solubility and stability. These systems protect curcumin from degradation and improve intestinal absorption [13].
Curcumin-loaded nanoparticles have demonstrated improved lipid profile modulation and reduced inflammatory markers in experimental studies.

Berberine
Berberine is an alkaloid with significant lipid-lowering effects mediated through upregulation of LDL receptors and modulation of lipid metabolism pathways.Its clinical use is limited by poor intestinal absorption and extensive first-pass metabolism. Nanoformulations improve its permeability and reduce efflux, enhancing systemic exposure [90].
Polymeric nanoparticles and lipid-based carriers have shown improved pharmacokinetic profiles and enhanced antihyperlipidemic efficacy of berberine compared to conventional formulations.

8.4 Combination Nanoformulations
Combination therapy is often required for effective management of hyperlipidemia, particularly in patients with mixed dyslipidemia. Nanotechnology enables the co-delivery of multiple therapeutic agents within a single carrier, offering synergistic benefits.

Statin + Bioenhancer (e.g., Piperine)
Bioenhancers such as piperine can significantly improve drug bioavailability by inhibiting metabolic enzymes and enhancing intestinal absorption.
Piperine inhibits cytochrome P450 enzymes, thereby reducing first-pass metabolism and increasing systemic availability of statins [91]. When co-encapsulated in nanoparticles, piperine enhances the pharmacokinetic profile of statins while reducing the required dose.
This strategy not only improves efficacy but also minimizes dose-related adverse effects.

Dual Drug-Loaded Nanoparticles
Dual drug-loaded nanoparticles allow simultaneous delivery of two drugs with complementary mechanisms of action, such as statins and fibrates or statins and natural compounds.
These systems offer:
- Synergistic lipid-lowering effects
- Controlled and sustained drug release
- Reduced dosing frequency
- Improved patient compliance

Lipid–polymer hybrid nanoparticles are particularly effective for dual drug delivery due to their high loading capacity and tunable release characteristics [92].
Such systems represent a promising advancement in personalized and combination therapy for

hyperlipidemia.

9. In vitro and In vivo Evaluation

The successful translation of nano drug delivery systems from laboratory research to clinical application requires comprehensive evaluation through both in vitro and in vivo studies. These evaluations provide critical insights into the safety, efficacy, pharmacokinetics, and pharmacodynamics of antihyperlipidemic nanoformulations. While in vitro studies offer mechanistic understanding at the cellular level, in vivo studies validate therapeutic performance in biological systems, ensuring reliability and reproducibility.

9.1 Cell Line Studies

In vitro cell culture models are essential for preliminary screening of nanoformulations. These studies evaluate cellular uptake, cytotoxicity, permeability, and intracellular drug release [92]. Commonly used cell lines in antihyperlipidemic research include:

- Caco-2 cells (intestinal epithelial model) for studying drug absorption and permeability
- HepG2 cells (human hepatocellular carcinoma) for evaluating hepatic uptake and lipid metabolism
- RAW 264.7 macrophages for assessing anti-inflammatory and anti-atherosclerotic effects

Nanoparticles enhance cellular uptake primarily through endocytosis mechanisms such as clathrin-mediated, caveolae-mediated, and macropinocytosis pathways [92]. Surface properties such as charge and hydrophobicity significantly influence uptake efficiency.

Cytotoxicity studies are commonly performed using assays such as:

- MTT assay
- LDH release assay
- Trypan blue exclusion test

These assays ensure that the nanoformulation is biocompatible and does not induce significant cellular toxicity [93].

Permeability studies using Caco-2 monolayers help predict intestinal absorption. Nanoformulations often demonstrate enhanced permeability due to improved solubility and interaction with epithelial membranes.

9.2 Animal Models for Hyperlipidemia

In vivo evaluation in animal models is crucial for assessing the therapeutic efficacy and safety of antihyperlipidemic nanoformulations under physiological conditions.

Common animal models include:

Diet-Induced Hyperlipidemia Models

Rodents (rats or mice) are fed a high-fat or high-cholesterol diet to induce hyperlipidemia. This model closely mimics human metabolic conditions and is widely used for evaluating lipid- lowering efficacy [94].

Genetic Models

Genetically modified animals, such as:

- LDL receptor-deficient mice
- ApoE knockout mice

These models exhibit elevated lipid levels and are used to study atherosclerosis and long-term cardiovascular effects [95].

Chemically Induced Models

Agents such as Triton WR-1339 are used to induce acute hyperlipidemia by inhibiting lipoprotein lipase, allowing rapid screening of lipid-lowering activity [96].

In these models, nanoformulations are evaluated for:

- Reduction in total cholesterol (TC)
- Decrease in low-density lipoprotein (LDL)
- Increase in high-density lipoprotein (HDL)
- Reduction in triglyceride levels

Histopathological analysis of liver and aortic tissues is also performed to assess lipid accumulation and tissue integrity.

9.3 Pharmacokinetic Studies

Pharmacokinetic (PK) studies evaluate the absorption, distribution, metabolism, and excretion (ADME) of drugs. These studies are essential for understanding how nanoformulations alter drug behavior in the body.

Key pharmacokinetic parameters include:

- Cmax (maximum plasma concentration)
- Tmax (time to reach Cmax)
- AUC (Area Under Curve)
- Half-life (t½)
- Bioavailability (%)

Nanoformulations often demonstrate:

- Increased Cmax due to improved absorption
- Prolonged half-life due to sustained release
- Higher AUC indicating enhanced systemic exposure

For example, lipid-based nanoparticles enhance lymphatic uptake, bypassing hepatic first-pass metabolism and increasing bioavailability [14]. Polymeric nanoparticles provide controlled release, maintaining therapeutic drug levels over extended periods.

Pharmacokinetic studies are typically conducted using analytical techniques such as:

- High-performance liquid chromatography (HPLC)
- LC-MS/MS

These techniques enable precise quantification of drug concentration in plasma and tissues.

9.4 Pharmacodynamic Studies

Pharmacodynamic (PD) studies assess the biological and therapeutic effects of nanoformulations. In antihyperlipidemic therapy, PD evaluation focuses on lipid profile modulation and related physiological outcomes.

Key pharmacodynamic endpoints include:

- Reduction in total cholesterol (TC)
- Decrease in LDL cholesterol
- Increase in HDL cholesterol

- Reduction in triglycerides

Nanoformulations often exhibit enhanced pharmacodynamic effects due to improved bioavailability and targeted delivery. For instance, statin-loaded nanoparticles demonstrate greater inhibition of cholesterol synthesis compared to conventional formulations [21].

In addition to lipid profile analysis, PD studies may include:

- Measurement of inflammatory markers (e.g., CRP, TNF-α)
- Oxidative stress markers (e.g., malondialdehyde)
- Histological examination of atherosclerotic plaques

These evaluations provide a comprehensive understanding of therapeutic efficacy beyond lipid lowering.

Correlation between pharmacokinetics and pharmacodynamics (PK–PD relationship) is crucial for optimizing dosing regimens and predicting clinical outcomes.

10. Toxicity and Safety Considerations

While nanotechnology offers significant advantages in enhancing the bioavailability and therapeutic efficacy of antihyperlipidemic drugs, safety remains a critical concern. The unique physicochemical properties of nanoparticles—such as small size, high surface area, and surface reactivity—can lead to unintended biological interactions. Therefore, a thorough evaluation of toxicity and safety is essential to ensure successful clinical translation.

Nanoparticle-induced toxicity may arise from the material composition, size, shape, surface charge, and dose. In the context of chronic conditions such as hyperlipidemia, where long-term administration is required, understanding both acute and chronic toxicity profiles becomes particularly important.

10.1 Cytotoxicity

Cytotoxicity refers to the potential of nanoparticles to induce cellular damage or death. It is one of the primary safety parameters evaluated during early-stage development using in vitro models.

Nanoparticles can induce cytotoxic effects through several mechanisms:

- Generation of reactive oxygen species (ROS) leading to oxidative stress
- Disruption of cellular membranes
- Mitochondrial dysfunction
- DNA damage and apoptosis

The extent of cytotoxicity depends on nanoparticle characteristics such as size, surface charge, and composition. Smaller nanoparticles tend to exhibit higher reactivity due to increased surface area, which may enhance cellular uptake but also increase toxicity risk [97].

Cytotoxicity is commonly assessed using assays such as MTT, XTT, and LDH release. Studies have shown that biocompatible materials such as lipids and biodegradable polymers (e.g., PLGA) generally exhibit low cytotoxicity, making them suitable for drug delivery applications [98].

However, metallic nanoparticles and certain synthetic materials may induce significant cytotoxic effects, necessitating careful optimization and dose control.

10.2 Immunogenicity

Immunogenicity refers to the ability of nanoparticles to trigger immune responses. Upon administration, nanoparticles interact with the immune system, particularly macrophages and other components of the reticuloendothelial system (RES).One of the key processes is opsonization, where plasma proteins bind to the nanoparticle surface, marking them for recognition and clearance by immune cells [99]. This can lead to rapid elimination from circulation, reducing therapeutic efficacy.

In some cases, nanoparticles may activate the complement system, resulting in hypersensitivity reactions or inflammation. This phenomenon, known as complement activation-related pseudoallergy (CARPA), is particularly relevant for certain liposomal and polymeric formulations [100].

Surface modification strategies such as PEGylation help reduce immunogenicity by minimizing protein adsorption and immune recognition, thereby prolonging circulation time. Understanding and controlling immunogenic responses are essential for ensuring the safety and effectiveness of nanoformulations, especially for repeated or long-term administration.

10.3 Long-term Toxicity

Long-term toxicity is a major concern for nanoformulations used in chronic diseases like hyperlipidemia, where prolonged exposure is inevitable.

Potential long-term risks include:

- Accumulation of nanoparticles in organs such as liver, spleen, and kidneys
- Chronic inflammation
- Oxidative stress and tissue damage
- Interference with normal cellular functions

Non-biodegradable nanoparticles are particularly associated with accumulation and persistence in biological systems. In contrast, biodegradable materials such as PLGA and lipid-based carriers degrade into non-toxic metabolites, reducing long-term toxicity risks [101].

Repeated dosing may also lead to changes in pharmacokinetics and immune responses. Therefore, long-term animal studies are essential to evaluate:

- Organ toxicity (histopathological analysis)
- Biochemical markers (liver enzymes, renal function)
- Immunological responses

Careful material selection and optimization of dosing regimens are critical to minimizing long- term adverse effects.

10.4 Regulatory Safety Concerns

The regulatory evaluation of nanomedicines presents unique challenges due to their complex structure and behavior. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require comprehensive safety assessment before approval.

Key regulatory considerations include:

- Detailed physicochemical characterization
- Toxicological evaluation (acute, sub-chronic, and chronic toxicity)
- Pharmacokinetic and biodistribution studies
- Immunogenicity assessment

The International Council for Harmonisation (ICH) provides general guidelines for drug safety evaluation, but specific guidelines for nanomedicines are still evolving [102].

Regulatory challenges arise from:

- Lack of standardized testing methods
- Complexity in predicting in vivo behavior
- Variability in nanoparticle properties

To address these issues, a risk-based approach is often adopted, where safety evaluation is tailored based on the type of nanocarrier, route of administration, and duration of exposure.

Additionally, regulatory agencies emphasize the importance of:

- Good Manufacturing Practices (GMP)
- Batch-to-batch consistency
- Scalability of production

These considerations are crucial for ensuring the safety, quality, and efficacy of nano-based antihyperlipidemic therapies.

11. Regulatory and Commercial Aspects

The advancement of nano drug delivery systems from laboratory research to clinical and commercial application requires rigorous regulatory evaluation and scalable manufacturing processes. While nanotechnology offers significant therapeutic advantages, its complexity introduces challenges in standardization, quality control, and regulatory approval. Understanding the regulatory framework and commercialization pathways is essential for the successful translation of antihyperlipidemic nanoformulations into clinical practice.

11.1 Regulatory Guidelines (FDA, EMA)

Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) play a crucial role in ensuring the safety, efficacy, and quality of nanomedicines. Although there are no universally harmonized guidelines exclusively dedicated to nanotechnology-based drug delivery systems, both agencies have issued recommendations addressing their unique characteristics.

The FDA emphasizes a case-by-case evaluation approach, considering factors such as particle size, surface properties, and material composition. Developers are required to provide detailed characterization data, including:

- Particle size distribution
- Surface charge (zeta potential)
- Morphology and structural properties
- Stability and aggregation behavior

Additionally, comprehensive toxicological and pharmacokinetic studies must be conducted to assess biodistribution, metabolism, and potential accumulation of nanoparticles [103].

The EMA similarly requires detailed documentation under its quality, safety, and efficacy framework, with particular emphasis on:

- Nanomaterial characterization
- Risk assessment strategies
- Immunogenicity and long-term toxicity evaluation

Both agencies rely on existing guidelines such as those from the International Council for Harmonisation (ICH), including stability (ICH Q1A), quality (ICH Q8), and safety (ICH M3) guidelines, while adapting them to accommodate nanomedicines [104].

A key regulatory challenge lies in the lack of standardized testing protocols, which can lead to variability in evaluation and approval processes across regions. Consequently, regulatory bodies encourage early dialogue with developers to ensure compliance and streamline approval pathways.

11.2 Challenges in Scale-Up

Scaling up nanoformulations from laboratory to industrial production presents significant technical and economic challenges. While small-scale preparation methods may produce highly controlled nanoparticles, replicating these conditions at large scale is often difficult.

One of the primary challenges is maintaining batch-to-batch consistency. Variations in particle size, drug loading, and surface characteristics during scale-up can significantly impact therapeutic performance and safety [105].

Other key challenges include:

- Process reproducibility: Techniques such as nanoprecipitation and solvent evaporation may be difficult to control at large scale.
- Equipment limitations: High-pressure homogenizers and microfluidizers require significant capital investment.
- Stability issues: Nanoparticles may aggregate or undergo physicochemical changes during storage and transportation.
- Cost of production: Complex manufacturing processes and expensive raw materials increase overall production costs.

To address these challenges, advanced manufacturing approaches such as continuous processing and Quality by Design (QbD) principles are increasingly adopted. QbD involves systematic optimization of formulation and process parameters to ensure consistent product quality [106].

Furthermore, compliance with Good Manufacturing Practices (GMP) is mandatory, requiring strict control

over raw materials, production processes, and quality assurance.

11.3 Marketed Nanoformulations

The successful commercialization of nanomedicines demonstrates the practical feasibility of nano drug delivery systems. Although most marketed nanoformulations are developed for oncology and infectious diseases, several lipid-based and nanocrystal formulations relevant to antihyperlipidemic therapy have reached the market.

Nanocrystal-based formulations of drugs such as fenofibrate represent one of the most successful applications. These formulations improve dissolution rate and bioavailability without requiring complex carrier systems [107].

Lipid-based formulations, including nanoemulsions and self-emulsifying drug delivery systems (SEDDS), are widely used for improving the oral absorption of lipophilic drugs. Several commercial products utilize these technologies to enhance bioavailability and therapeutic performance [108].

Examples of marketed nanotechnology-based systems include:

- Liposomal formulations (e.g., doxorubicin liposomes) demonstrating the success of vesicular carriers
- Polymeric nanoparticle-based systems under clinical evaluation
- Lipid-based oral formulations for poorly soluble drugs

Although specific nanoformulations of statins are still largely in developmental or clinical trial stages, the success of similar systems in other therapeutic areas supports their future commercialization potential.

The market for nanomedicine is expanding rapidly, driven by increasing demand for targeted therapies and improved drug delivery systems. Continued advancements in formulation technology, regulatory clarity, and manufacturing processes are expected to accelerate the commercialization of antihyperlipidemic nanoformulations.

12. Recent Advances and Innovations

The field of nano drug delivery has rapidly evolved beyond conventional carrier systems, incorporating advanced technologies such as targeted delivery, gene-based therapies, personalized medicine, and artificial intelligence (AI). These innovations are reshaping the landscape of antihyperlipidemic therapy by enabling precise, efficient, and individualized treatment strategies. The integration of multidisciplinary approaches has significantly enhanced the therapeutic potential of nanomedicine, paving the way for next-generation lipid- lowering interventions.

12.1 Targeted Drug Delivery Systems

Targeted drug delivery represents a major advancement in nanotechnology, aiming to deliver drugs specifically to the site of action while minimizing systemic exposure and adverse effects. Two primary targeting approaches are employed:

Passive Targeting

Passive targeting relies on the natural biodistribution of nanoparticles. Lipid-based nanocarriers can preferentially accumulate in specific tissues, such as the liver—the primary site of lipid metabolism. This is particularly advantageous for antihyperlipidemic drugs, as hepatic targeting enhances therapeutic efficacy [109].

Active Targeting

Active targeting involves functionalizing nanoparticles with ligands such as antibodies, peptides, or small molecules that bind to specific receptors on target cells. For example, hepatocyte-targeting ligands can enhance the delivery of statins directly to liver cells, improving lipid-lowering efficiency [109].

Recent innovations include:

- Receptor-mediated targeting (e.g., LDL receptor targeting)
- Aptamer-based targeting systems
- Stimuli-responsive nanoparticles that release drugs in response to pH, enzymes, or temperature changes

These strategies significantly improve drug localization, reduce off-target toxicity, and enhance therapeutic outcomes.

12.2 Gene-based Nanotherapy

Gene-based nanotherapy is an emerging approach that utilizes nanoparticles to deliver genetic material such as DNA, siRNA, or mRNA for therapeutic purposes. This strategy targets the underlying genetic and molecular mechanisms of hyperlipidemia.

Nanocarriers protect nucleic acids from enzymatic degradation and facilitate cellular uptake. For example:

- siRNA-based therapies can silence genes involved in lipid metabolism, such as PCSK9, leading to reduced LDL cholesterol levels
- mRNA-based approaches can enhance the expression of beneficial proteins involved in lipid regulation

Lipid nanoparticles (LNPs) have shown significant success in gene delivery due to their ability to encapsulate and protect nucleic acids while enabling efficient cellular uptake [110].

Gene-based nanotherapy offers:

- High specificity
- Potential for long-term therapeutic effects
- Ability to target previously “undruggable” pathways

Despite its promise, challenges such as stability, immunogenicity, and delivery efficiency remain areas of active research.

12.3 Personalized Nanomedicine

Personalized nanomedicine represents a paradigm shift from the traditional “one-size-fits-all” approach to individualized therapy. It involves tailoring

nanoformulations based on patient- specific factors such as genetic profile, disease severity, and metabolic status.

In antihyperlipidemic therapy, patient variability in drug metabolism and response is a significant concern. Personalized nanomedicine addresses this by:

- Optimizing drug dose and release profile
- Selecting appropriate nanocarriers based on patient characteristics
- Enhancing therapeutic efficacy while minimizing adverse effects

Pharmacogenomic data can guide the selection of statins and nanoformulations, improving treatment outcomes. For example, patients with genetic variations affecting statin metabolism may benefit from targeted or controlled-release nanoformulations [111].

Advances in diagnostic technologies and biomarker identification further support the development of personalized nanotherapeutics, enabling more precise and effective lipid management.

12.4 AI in Nanocarrier Design

Artificial intelligence (AI) and machine learning (ML) are revolutionizing the design and optimization of nanocarriers. These technologies enable rapid analysis of complex datasets, facilitating the prediction of nanoparticle behavior and performance.

AI applications in nanomedicine include:

- Formulation optimization: Predicting optimal composition and preparation conditions
- Drug–carrier interaction modeling: Understanding molecular interactions for improved drug loading
- Pharmacokinetic prediction: Simulating in vivo behavior of nanoformulations
- Toxicity prediction: Identifying potential safety issues early in development

Machine learning algorithms can analyze relationships between nanoparticle properties (size, charge, composition) and biological outcomes, significantly reducing trial-and-error experimentation [112].

Recent developments include:

- Deep learning models for nanoparticle design
- AI-driven high-throughput screening
- Integration of big data and computational modeling

These approaches accelerate the development process, reduce costs, and enhance the precision of nanoformulation design.

13. Challenges and Limitations

Despite the significant advancements in nano drug delivery systems for antihyperlipidemic therapy, several challenges and limitations hinder their widespread clinical translation and commercialization. These challenges arise from the inherent complexity of nanoscale systems, variability in biological interactions, and regulatory uncertainties. Addressing these limitations is essential to fully realize the potential of nanotechnology in lipid-lowering therapy.

13.1 Stability Issues

Stability remains one of the most critical challenges in the development of nanoformulations. Nanoparticles are thermodynamically unstable systems due to their high surface energy, which predisposes them to aggregation, coalescence, or phase separation over time.

Common stability issues include:

- Particle aggregation leading to increased particle size and reduced bioavailability
- Drug leakage from the carrier system
- Chemical degradation of both drug and excipients
- Polymorphic transitions in lipid-based systems

Environmental factors such as temperature, pH, and light exposure can further exacerbate instability. For example, lipid nanoparticles may undergo crystallization changes during storage, resulting in drug expulsion [113].

Stability can be improved through:

- Use of surfactants and stabilizers
- Surface modification (e.g., PEGylation)
- Lyophilization (freeze-drying) with cryoprotectants

However, these approaches add complexity to formulation design and may increase production costs.

13.2 High Production Cost

The development and manufacturing of nano drug delivery systems are often associated with high costs, which can limit their commercial viability.

Factors contributing to high production costs include:

- Expensive raw materials (e.g., high-purity lipids, polymers)
- Specialized equipment (e.g., high-pressure homogenizers, microfluidizers)
- Complex and multi-step manufacturing processes
- Stringent quality control and characterization requirements

In addition, the need for advanced analytical techniques such as electron microscopy, dynamic light scattering, and chromatography further increases overall costs [114].

Compared to conventional formulations, nanoformulations require greater investment in research and development, process optimization, and regulatory compliance. These factors can significantly impact pricing and accessibility, especially in resource-limited settings.

13.3 Scale-Up Difficulties

Scaling up nanoformulation processes from laboratory to industrial production presents substantial technical challenges. Techniques that work efficiently at a small scale often fail to maintain consistency and reproducibility at larger volumes.

Key scale-up challenges include:

- Batch-to-batch variability in particle size, drug loading, and surface properties
- Process reproducibility issues due to sensitivity of formulation parameters
- Equipment limitations and need for specialized large-scale machinery
- Maintaining product stability during manufacturing

and storage

For example, methods such as nanoprecipitation and solvent evaporation are difficult to control uniformly at industrial scale, leading to variability in product quality [115].

To address these challenges, modern approaches such as:

- Continuous manufacturing
- Microfluidic-based production
- Quality by Design (QbD)

are being increasingly adopted. These strategies aim to ensure consistent product quality and facilitate regulatory approval.

13.4 Regulatory Barriers

Regulatory approval of nanomedicines remains a complex and evolving process. Unlike conventional drugs, nanoformulations exhibit unique physicochemical and biological properties that are not fully addressed by existing regulatory frameworks.

Major regulatory challenges include:

- Lack of universally accepted definitions and classification of nanomaterials
- Absence of standardized testing protocols for safety and efficacy
- Difficulty in predicting in vivo behavior based on in vitro data
- Limited long-term safety data

Regulatory agencies such as the FDA and EMA require extensive characterization and safety evaluation, including:

- Physicochemical characterization
- Toxicological studies (acute, sub-chronic, chronic)
- Pharmacokinetic and biodistribution studies
- Immunogenicity assessment

The complexity of these requirements can prolong the approval process and increase development costs [116]

Furthermore, regulatory uncertainty may discourage investment and slow down innovation in the field of nanomedicine. Harmonization of guidelines and development of standardized evaluation methods are essential to overcome these barriers.

14. Future Perspectives

The future of nano drug delivery systems in antihyperlipidemic therapy is highly promising, driven by rapid advancements in material science, biotechnology, and computational tools. While current nanoformulations have demonstrated improved bioavailability and therapeutic efficacy, ongoing innovations aim to enhance precision, safety, and clinical applicability. The integration of multidisciplinary approaches is expected to transform lipid-lowering therapy into a more targeted, personalized, and efficient healthcare strategy.

14.1 Emerging Trends

Recent developments in nanotechnology are shaping the next generation of drug delivery systems with enhanced functionality and adaptability.

One of the most significant trends is the development of stimuli-responsive nanocarriers, which release drugs in response to specific physiological triggers such as pH, temperature, enzymes, or oxidative stress. These systems enable site-specific drug release, minimizing systemic exposure and adverse effects [117].

Another important advancement is the emergence of multifunctional nanocarriers, capable of combining therapeutic, diagnostic, and targeting functions within a single platform (theranostics). These systems allow real-time monitoring of drug delivery and therapeutic response.

Lipid nanoparticles (LNPs) have gained considerable attention, particularly in nucleic acid delivery, due to their high biocompatibility and efficiency. Their success in recent biomedical applications has accelerated interest in their use for lipid metabolism disorders [118].

Additionally, green nanotechnology is gaining momentum, focusing on the use of biodegradable, biocompatible, and environmentally friendly materials for nanoparticle synthesis. This approach addresses concerns related to toxicity and environmental impact.

The integration of nanotechnology with advanced biomaterials, such as dendrimers and hybrid systems, further enhances drug loading capacity, targeting efficiency, and controlled release properties.

14.2 Translational Opportunities

Despite significant progress in research, the translation of nanoformulations into clinical practice remains limited. Bridging this gap requires addressing challenges related to scalability, reproducibility, and regulatory approval.

One of the key translational opportunities lies in liver-targeted delivery systems, as the liver is the primary organ involved in lipid metabolism. Nanocarriers designed to selectively target hepatocytes can significantly improve the therapeutic efficiency of antihyperlipidemic drugs. Another promising area is the development of oral nanocarriers that enhance drug stability and absorption in the gastrointestinal tract. These systems can improve patient compliance by reducing dosing frequency and eliminating the need for invasive administration routes [119]. Combination nanotherapy also offers strong translational potential. Co-delivery of statins with bioenhancers or natural compounds within a single nanoparticle system can provide synergistic effects, improving therapeutic outcomes while minimizing side effects [120].

Collaboration between academia, industry, and regulatory agencies is essential to accelerate the translation process. Adoption of Quality by Design (QbD) principles and advanced manufacturing techniques can further facilitate the development of scalable and reproducible nanoformulations [121].

14.3 Clinical Research Scope

Clinical research plays a pivotal role in validating the safety and efficacy of nano drug delivery systems. Although several nanoformulations have shown promising results in preclinical studies, clinical data for antihyperlipidemic applications remain relatively limited.

Future clinical research should focus on:

- Long-term safety evaluation, particularly for chronic use in hyperlipidemia
- Pharmacokinetic and pharmacodynamic profiling in diverse patient populations
- Comparative studies between nanoformulations and conventional therapies
- Dose optimization and therapeutic window determination

The incorporation of pharmacogenomics into clinical research can further enhance treatment outcomes by enabling personalized therapy based on genetic variations [122].

Large-scale, randomized controlled trials are essential to establish the clinical benefits of nanoformulations and support regulatory approval. Additionally, post-marketing surveillance studies are required to monitor long-term safety and effectiveness.

Emerging technologies such as AI-driven clinical trial design and real-world data analytics can significantly improve the efficiency and accuracy of clinical research, accelerating the development of next-generation therapies [123].

15. Conclusion

The evolution of nano drug delivery systems has marked a transformative shift in the management of hyperlipidemia, addressing many of the long-standing limitations associated with conventional pharmacotherapy. Traditional antihyperlipidemic drugs, although clinically effective, are often constrained by poor aqueous solubility, low bioavailability, extensive first- pass metabolism, and dose-related adverse effects. The integration of nanotechnology into drug delivery has provided innovative solutions to these challenges, enabling more efficient, targeted, and controlled therapeutic interventions.

Through the development of diverse nanocarrier systems—including lipid-based carriers, polymeric nanoparticles, nanocrystals, dendrimers, and hybrid systems—significant improvements have been achieved in drug solubility, stability, and systemic availability. These systems not only enhance pharmacokinetic profiles but also allow for controlled and sustained drug release, thereby maintaining therapeutic plasma concentrations over extended periods and improving patient compliance. Furthermore, targeted delivery strategies have demonstrated the potential to localize drug action, particularly in the liver, which plays a central role in lipid metabolism.

The application of nanotechnology to specific antihyperlipidemic agents such as statins, fibrates, and herbal compounds has shown promising results in both preclinical and early clinical studies. Nanoformulations of compounds like simvastatin, atorvastatin, curcumin, and berberine have exhibited enhanced therapeutic efficacy, reduced variability in drug response, and improved safety profiles. Additionally, combination strategies, including the co-delivery of drugs with bioenhancers such as piperine, highlight the potential for synergistic effects and dose optimization.

Advances in formulation strategies, characterization techniques, and in vitro and in vivo evaluation methods have strengthened the scientific foundation of nano-based drug delivery. At the same time, emerging innovations—such as gene-based nanotherapy, personalized nanomedicine, and artificial intelligence-driven design—are expanding the scope of nanotechnology beyond conventional drug delivery, offering new avenues for precision medicine.

However, despite these advancements, several challenges remain. Issues related to nanoparticle stability, large-scale manufacturing, high production costs, and regulatory complexities continue to limit the widespread clinical translation of nanoformulations. Safety concerns, including cytotoxicity, immunogenicity, and long-term accumulation, necessitate thorough evaluation and standardized assessment protocols. Moreover, the lack of harmonized regulatory guidelines underscores the need for coordinated efforts among researchers, industry stakeholders, and regulatory authorities.

Looking ahead, the future of nano drug delivery systems in antihyperlipidemic therapy lies in overcoming these barriers through interdisciplinary collaboration, technological innovation, and robust clinical validation. Emphasis on scalable manufacturing processes, cost-effective formulation strategies, and comprehensive safety evaluation will be critical for successful commercialization. Furthermore, the integration of advanced tools such as artificial intelligence and pharmacogenomics is expected to facilitate the development of personalized and highly efficient therapeutic systems.

In conclusion, nanotechnology holds immense potential to redefine the landscape of antihyperlipidemic therapy by offering more effective, safer, and patient-centric treatment options. Continued research and clinical translation will be essential to fully harness this potential and address the growing global burden of cardiovascular diseases associated with dyslipidemia.

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