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Application of Drug Delivery Systems in the Treatment of Atherosclerosis

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Abstract

Atherosclerosis (AS) is a progressive chronic inflammatory disease and the primary cause of global cardiovascular mortality, characterized by lipid deposition, endothelial dysfunction, foam cell formation, and plaque development. Conventional pharmacological interventions suffer from non-specific distribution, low bioavailability, and severe side effects, limiting their clinical efficacy. Rationally designed drug delivery systems (DDSs), including conventional liposomes, polymeric nanoparticles, micelles, dendrimers, hydrogels, and novel biomimetic, nanomotor, and mitochondria-targeted platforms, have emerged as promising strategies. These DDSs enable precise targeting to atherosclerotic plaques, controlled drug release, prolonged circulation time, and enhanced therapeutic efficacy while reducing adverse effects. This review systematically summarizes the classification, design principles, and applications of DDSs in AS treatment, highlighting their potential for optimizing AS diagnosis and therapy.

Keywords

Atherosclerosis, Drug Delivery Systems, Liposomes, Biomimetic Delivery, Targeted Therapy, Inflammation, Oxidative Stress

1. Introduction

Cardiovascular diseases pose a severe threat to human health and rank as the leading

cause of death worldwide, accounting for 45% of global mortality. Atherosclerosis (AS) is one of the most critical cardiovascular disorders with extremely high morbidity and mortality rates, far exceeding those of ischemic heart disease and stroke [1].

Atherosclerosis is mainly triggered by lipid metabolic disorders and vascular dysfunction [2]. Lipid deposition on the arterial wall facilitates the recruitment of monocyte-macrophages, and excessive plasma lipid levels contribute to the formation of lipid cores, namely atheromatous lesions [3]. Endothelial dysfunction serves as the initial pathological event of atherosclerosis pathogenesis, which promotes the accumulation of low-density lipoprotein (LDL) in the arterial wall and its subsequent transformation into oxidized low-density lipoprotein (Ox-LDL). Ox-LDL induces the activation and dysfunction of endothelial cells (ECs), migration and proliferation of vascular smooth muscle cells (VSMCs), as well as platelet activation. Furthermore, Ox-LDL stimulates ECs to generate adhesion molecules, mediating the adhesion of monocytes to the arterial wall and their differentiation into macrophages. Macrophages internalize large quantities of Ox-LDL, and the accumulated lipids cannot be metabolized in a timely manner, ultimately leading to the formation of foam cells. The gradual deposition of foam cells, cholesterol, fibroblasts, VSMCs, and other components contributes to the development of atherosclerotic plaques [4]. Lipids within foam cells accumulate in arterial wall lesions. Proteases secreted by foam cells degrade the fibrous cap of atherosclerotic plaques, resulting in plaque rupture and subsequent thrombosis. The formed thrombus blocks blood circulation, which is the primary cause of acute cardiac ischemia and stroke [5]. Atherosclerosis is a multistage, progressive chronic inflammatory disease involving pathological processes such as lipid accumulation, activation of pro-inflammatory signaling pathways, release of cytokines/chemokines, and elevated oxidative stress [6].

Clinically, besides surgical and interventional therapy, pharmacological intervention is a conventional strategy for cardiovascular disease management. Therapeutic drugs for atherosclerosis are classified into five categories: vasodilators, calcium channel blockers, lipid-regulating agents, antiplatelet drugs, and thrombolytics and anticoagulants. Nevertheless, conventional oral drugs are limited to the treatment of early-stage atherosclerosis due to their non-specific distribution, adverse reactions, low bioavailability, slow onset of action, and severe side effects [7].

With the advancement of pharmaceutical research, novel dosage forms and technologies have been continuously developed and play an increasingly important role in disease treatment. Novel drug delivery systems (DDSs) are rationally designed to target intimal macrophages, foam cells, and endothelial cells, intervening in the whole progression of atherosclerosis. These systems enable precise targeted drug release, prolong the *in vivo* action time of drugs, improve bioavailability, exert pharmacological effects while reducing adverse reactions, and exhibit great potential in optimizing the detection and treatment of atherosclerosis. Accordingly, the clinical application of DDSs is gradually expanding [8]. A variety

of biomedical materials, including natural polymers, synthetic polymers, metals, and ceramics, have been utilized to fabricate diverse DDSs, such as liposomes, polymeric nanoparticles, metal nanoparticles, micelles, dendrimers, and hydrogels. This chapter elaborates on their applications in the treatment of atherosclerosis. The pathological progression of atherosclerosis and the major intervention targets accessible to drug delivery systems are summarized in **Figure 1**.

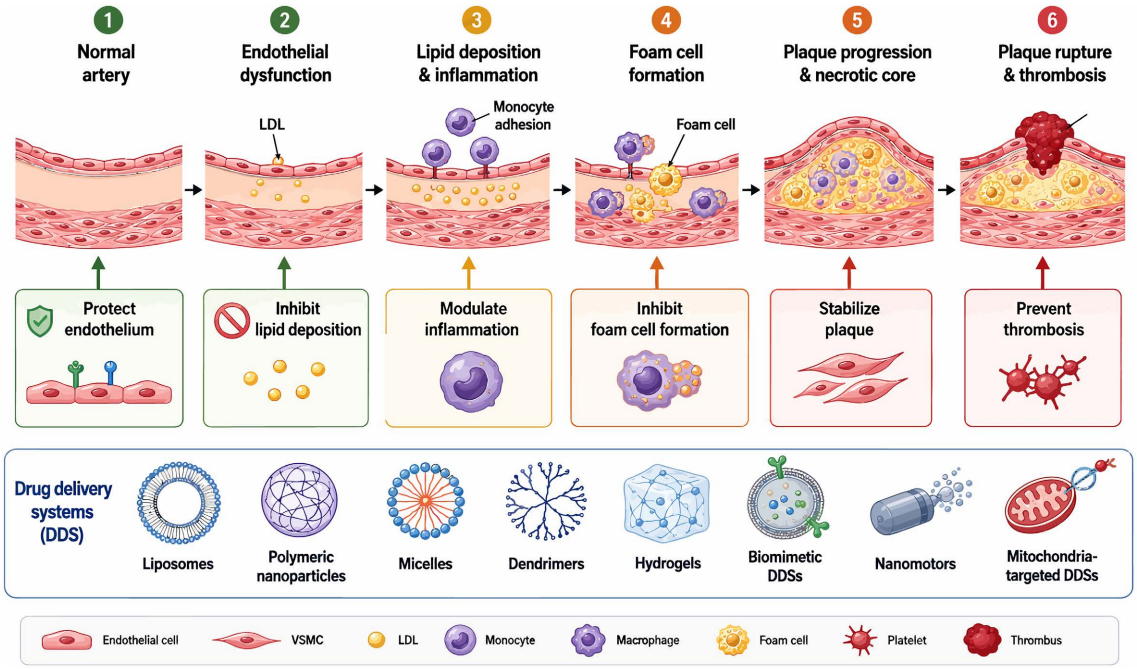

Figure 1. Pathological progression of atherosclerosis and intervention targets of drug delivery systems.

2. Conventional Drug Delivery Systems

2.1. Liposomes

Liposomes are nanovesicles composed of phospholipid bilayers. Owing to their excellent biocompatibility, high encapsulation capacity for both hydrophilic and hydrophobic drugs, improved therapeutic index, and facile functional modification, liposomes have become widely used drug delivery carriers [9]. They have been proven to deliver multiple bioactive substances, including low-molecular-weight drugs, imaging agents, peptides, proteins, and nucleic acids, and achieve sustained drug release to maintain prolonged drug exposure at lesion sites and enhance therapeutic efficacy. In particular, liposomes possess unique advantages in atherosclerosis treatment by facilitating cholesterol efflux from circulating lipoproteins or atherosclerotic vascular walls [10].

Targeted therapy based on liposomal drug delivery systems has attracted extensive research attention. Li *et al.* [11] developed a ROS-responsive biomimetic nanoliposome co-loaded with Geniposide and Emodin, which was hybridized with a macrophage membrane to evade immune clearance and actively target atherosclerotic plaques. They demonstrated that the thioketal-based system enabled

controlled drug release specifically in ROS-rich plaque microenvironments, thereby inhibiting endothelial cell apoptosis, reducing macrophage lipid accumulation, and promoting cholesterol efflux. The study concludes that this dual-cell-targeting nanocomplex exerts synergistic therapeutic effects, significantly reducing plaque area and ROS levels while restoring endothelial function, offering a promising strategy for atherosclerosis regression.

Conventional high-resolution magnetic resonance imaging (MRI) is capable of detecting atherosclerotic plaques. A neointimal injury model was established by placing a constrictive collar around the right carotid artery of APOE-/- mice, and conventional multispectral MRI failed to distinguish thickened vascular walls from surrounding tissues. Song *et al.* [12] developed a hierarchical theranostic nanoagent that integrates near-infrared II fluorescence, photoacoustic, and magnetic resonance imaging modalities to provide complementary information on plaque location, depth, and morphology in atherosclerotic lesions. The nanoagent co-encapsulates atorvastatin within responsive nanocarriers camouflaged with macrophage membranes and equipped with a foam cell-targeting peptide, enabling precise targeting to inflamed plaques and controlled drug release that promotes lipid efflux and reduces inflammatory signaling. The study demonstrates that this imaging-guided therapeutic platform effectively enhances plaque stabilization in female atherosclerotic mouse models, offering a promising strategy for the precise diagnosis and treatment of cardiovascular disease. In another study, liposome delivery to inflamed vascular walls was monitored via MRI in a rabbit atherosclerosis model [13]. Liposomes can prolong the *in vivo* circulation half-life and action duration of drugs without systemic toxicity. After a single administration, MRI observation revealed gradual plaque regression at atherosclerotic lesions along with sustained drug release.

However, liposomes for atherosclerosis therapy suffer from poor *in vivo* stability, easy drug leakage, and insufficient plaque targeting ability. They also face slow blood clearance, potential immune responses, difficult large-scale production, and strict safety verification barriers, greatly hindering their further clinical transformation and popularization.

2.2. Polymeric Nanoparticles

Polymeric nanoparticles represent an emerging strategy for the prevention, diagnosis, and treatment of cardiovascular diseases. Systemic drug exposure and drug-drug interactions remain major concerns for nearly all cardiovascular therapeutics, including statins, antithrombotic, and thrombolytic agents. In addition, poor targeting efficiency and low bioavailability limit their application in vascular disease treatment. Rational design of polymeric nanoparticles enables nanocarriers to deliver drugs precisely to therapeutic targets or even lesion sites, overcome biological barriers, and enhance therapeutic outcomes. Moreover, advances in molecular imaging have promoted the development of theranostic nanoparticles, which serve as dual carriers for therapeutic drugs and imaging probes. Nanoplatforms have wide applications in targeted drug delivery and non-invasive imaging for atherosclerotic

intervention [14].

Current studies have demonstrated that vascular permeability is significantly increased at cardiovascular lesion sites. Nanodelivery systems with appropriate particle sizes can easily penetrate vascular walls into the systemic circulation and accumulate at lesions via passive targeting. Furthermore, functional groups specifically binding to surface receptors of lesion cells can be modified on nanocarriers to enhance active targeting capability.

Innate immune cells are massively recruited in atherosclerosis, myocardial infarction, and restenosis, triggering intense inflammatory responses. Strategies targeting circulating monocytes and monocyte subsets via polymeric nanoparticles have been developed for targeted therapy and diagnosis of cardiovascular diseases [15]. Monocytes and macrophages play indispensable roles throughout lesion progression, ranging from foam cell formation to regulation of plaque size and apoptotic cell clearance [16]. In advanced atherosclerotic lesions, functional defects of lesional macrophages lead to intracellular accumulation of toxic substances and subsequent plaque necrosis. Nanotherapies targeting macrophages have been developed to inhibit monocyte recruitment and infiltration into plaques [17], suppress macrophage proliferation [18], promote cholesterol metabolism [19], and polarize macrophages toward the anti-inflammatory M2 phenotype [20].

Polymer nanoparticles still have obvious limitations and clinical transformation obstacles in atherosclerosis treatment. They exhibit unsatisfactory biocompatibility, slow *in vivo* degradation, and inadequate lesion accumulation. Besides, complicated preparation processes, unclear long-term biosafety, and high production costs severely restrict their further clinical application.

2.3. Micelles

Micelles self-assembled from amphiphilic polymers possess the advantages of small particle size and rapid tissue penetration for encapsulated bioactive components. Researchers fabricated micelles composed of hydrophobic branched segments and hydrophilic polyethylene glycol (PEG), which exerted potent anti-atherosclerotic effects by directly inhibiting Ox-LDL uptake by macrophages [21]. Amphiphilic polymers with ether linkages between hydrophobic arms and sugar chains exhibited enhanced degradation stability, storage stability, and anti-atherosclerotic bioactivity. In another study, biodegradable polymeric micelles loaded with simvastatin were constructed based on hyaluronic acid-coated polyethylene glycol-poly (tyrosine ethyl oxalate) (PEG-Ptyr-EO) [22]. The hyaluronic acid coating endows micelles with targeting capability toward CD44-positive inflammatory macrophages. Benefiting from the reactive oxygen species (ROS)-responsive properties of PEG-Ptyr-EO, the micelles are not only enzymatically degradable but also consume excessive ROS at lesion sites, thereby effectively inhibiting pro-inflammatory macrophage accumulation and alleviating oxidative stress. Cellular uptake assays revealed that the micelles were efficiently internalized by LPS-induced macrophages with negligible cytotoxicity to normal LO2 cells. *In vivo* experiments

in atherosclerotic mice verified that intravenous administration of the micelles significantly reduced plaque cholesterol content with satisfactory therapeutic efficacy. In summary, polymeric micelles represent a promising innovative platform for anti-atherosclerotic therapy.

However, polymeric micelles face multiple limitations and clinical translation hurdles in atherosclerosis therapy. They possess low structural stability in the blood circulation and suffer from premature drug leakage. Moreover, insufficient plaque targeting efficiency, ambiguous long-term biosafety, and high preparation costs greatly impede their widespread clinical application.

2.4. Dendrimers

Dendrimers have attracted extensive attention in biomedical applications due to their unique dendritic architecture and tunable surface properties. Abundant terminal functional groups enable covalent conjugation of drug molecules onto dendrimer surfaces, while the internal cavity structure allows encapsulation of small-molecule drugs [23]. Dendrimers possess multiple superior properties, including precisely controllable physicochemical characteristics, large internal space for drug loading, and dense surface active groups for functional modification.

Researchers prepared and constructed ROS and shear stress dual-responsive red blood cell-based dendrimers, which achieve microenvironment-triggered drug release and superior safe anti-atherosclerotic efficacy over free drugs [24]. The engineered dendrimers exhibited negligible *in vitro* cytotoxicity, specifically bound to folate receptor-expressing macrophage cell lines, and selectively accumulated at inflammatory sites *in vivo*. With relatively low intrinsic cytotoxicity and minimal off-target immune activation, dendrimers are regarded as one of the most effective and promising drug delivery carriers [25].

But dendrimers have distinct drawbacks hindering their clinical translation for atherosclerosis treatment. They easily induce systemic cytotoxicity and show poor blood circulation stability. Additionally, complex synthesis procedures, high cost, and uncertain *in vivo* metabolic behaviors further limit their practical clinical application.

2.5. Hydrogels

Hydrogels are ideal delivery carriers owing to their biomimetic molecular structure similar to the extracellular matrix, facile fabrication and functional modification under mild conditions, and minimally invasive administration routes [26]. In addition, hydrogels can undergo timely degradation during vascular remodeling. These inherent advantages endow hydrogels with great potential as biomimetic matrices for vascular disease intervention.

Intravenous administration of anti-inflammatory nanocarriers confers atherosclerotic protection mediated by upregulated regulatory T cells in lymphoid organs and atherosclerotic lesions. An injectable filamentous hydrogel carrier (FM carrier) was designed for low-dose and sustained delivery of anti-inflammatory

nanotherapeutics [27]. Vitamin D suppresses the bioactivity of pro-inflammatory transcription factor NF-κB via activating the nuclear hormone receptor vitamin D receptor (VDR). Vitamin D was stably loaded into polyethylene glycol-block-poly(propyl sulfide) (PEG-b-PPS) filamentous hydrogels. The vitamin D-loaded filaments undergo morphological transformation and release monodisperse drug-loaded micelles upon oxidation. After in situ gelation via multi-arm PEG cross-linking, a single subcutaneous injection of the FM carrier into mice maintained high levels of regulatory T cells in lymphoid organs and atherosclerotic lesions for several weeks. Therefore, the FM carrier provides an immunomodulatory delivery platform for the development and evaluation of nanomedicine-based anti-inflammatory cardiovascular immunotherapies.

Although hydrogels show promising potential in atherosclerosis therapy, they still face severe clinical translation dilemmas. They have poor injectability and slow *in vivo* degradation. Meanwhile, insufficient lesion targeting, unstable drug release, and unsatisfactory long-term biocompatibility greatly restrict their clinical popularization.

A systematic comparison of the major DDS platforms discussed in this review is provided in **Figure 2**.

DDS platforms	Liposomes	Polymeric nanoparticles	Micelles	Dendrimers	Hydrogels	Biomimetic DDSs	Nanomotors	Mitochondria-targeted DDSs
Size (nm)	50–200	50–200	10–100	5–20	> 100	50–200	200–500	50–150
Drug loading capacity	High	High	Medium–Low	High	High	High	Medium–Low	High
Stability in blood	Medium–Low	Medium–Low	Low	Medium–Low	High	High	Medium–Low	Medium–Low
Targeting ability	Medium–Low	High	Medium–Low	High	Medium–Low	High	Medium–Low	High
Biocompatibility	High	Medium–Low	High	Medium–Low	High	High	Medium–Low	Medium–Low
Key advantages	High biocompatibility, versatile	Stable, tunable, controlled release	Small size, deep penetration	High loading, multifunctional	Injectable, sustained release	Immune evasion, natural targeting	Active penetration, controllable	Organelle targeting, high efficacy
Main limitations	Low stability, leakage	Slow degradation, low accumulation	Poor stability, drug leakage	Complex synthesis, potential toxicity	Slow degradation, low targeting	Complex preparation, low stability	High cost, biosafety concerns	Off-target effects, complex design

High Moderate Medium–Low Low

Figure 2. Comparative overview of major drug delivery systems for atherosclerosis therapy.

3. Novel Drug Delivery Systems

3.1. Biomimetic Drug Delivery Systems

With the advancement of drug delivery technology, cell membrane-camouflaged

biomimetic delivery systems have been extensively developed. Recent studies have confirmed that biomimetic DDSs achieve prolonged blood circulation time and enhanced immune evasion capability. Moreover, biomimetic nanocarriers are recognized as "self-components" by the immune system, exhibiting improved biocompatibility compared with conventional nanoparticles [28]. These cell-derived delivery systems enable the successful transfer of phospholipid bilayers with intact functional surface proteins from natural cells to synthetic carrier materials and possess superior targeting performance [29].

The application of biomimetic technology in cardiovascular disease therapy is expanding rapidly, mainly classified into three categories: whole cell-based, cell membrane-camouflaged, and extracellular vesicle-based delivery systems. As atherosclerosis is a systemic circulatory disorder, cell-mediated drug delivery holds important research significance. Multiple cell types, including red blood cells (RBCs), platelets, monocyte-macrophages, neutrophils and stem cells, have been exploited for therapeutic delivery, with distinct advantages: RBCs prolong the *in vivo* circulation time of loaded drugs; platelets secrete endogenous cytokines involved in hemostasis and tissue repair [30]; monocyte-macrophages exhibit high drug loading capacity and optimal targeting performance toward endothelial cells [31]; neutrophils are suitable for large-scale preparation and administration and selectively accumulate at inflammatory sites [32]; stem cells secrete multiple beneficial cytokines and possess multidirectional differentiation potential for vascular tissue remodeling [33].

Wang *et al.* [34] designed a macrophage membrane-camouflaged ROS-responsive biomimetic delivery system. The macrophage membrane coating not only protected nanoparticles from clearance by the reticuloendothelial system but also endowed targeting capability toward inflammatory lesions, while the ROS-responsive property enabled controlled drug release in the pathological microenvironment. In addition, the macrophage membrane sequestered pro-inflammatory cytokines to alleviate local inflammation. The synergistic effects of targeted drug delivery and inflammatory cytokine sequestration significantly improved the therapeutic efficacy of atherosclerosis.

Engineered extracellular vesicles loaded with small-molecule therapeutic agents are ideal candidates for disease intervention. Gan *et al.* [35] identify a novel protein, circBTBD7-420aa, which inhibits vascular smooth muscle cell proliferation via the ubiquitin-proteasome pathway. Researchers constructed engineered exosomes loaded with circBTBD7-420aa and modified with targeting peptides for osteopontin. These biomimetic carriers achieved targeted delivery to vascular lesions, effectively suppressing atherosclerosis progression in coronary artery disease models. This approach highlights the potential of engineered exosomal platforms for precise vascular intervention.

However, biomimetic drug delivery systems still confront limitations and clinical translation difficulties for atherosclerosis treatment. Their complex fabrication raises production costs, while low storage stability restricts practical use.

Furthermore, unclear long-term biosafety and insufficient large-scale application data greatly hinder clinical promotion.

3.2. Nanomotor Delivery Systems

The emergence of nanomotor technology has driven the innovation of novel drug delivery systems. Previous studies have shown that nanomotors possess favorable cytocompatible surface chemistry and autonomous locomotion capability, enabling deep penetration into target cells. The integration of nanomotors into drug-coated balloons represents a promising strategy to overcome the low local drug retention limitation of conventional balloons. Wan's team at Nanjing University developed a novel drug-coated balloon based on Janus aminated mesoporous silica (JAMS) porous nanomotors with autonomous motion capability [36]. Platelet membrane modification of nanomotors reduced premature drug leakage before plaque accumulation. The study systematically investigated the photothermal performance, sustained drug release behavior, and therapeutic application of nanomotors under NIR irradiation, and characterized the biomimetic immune evasion and encapsulation effects of platelet membranes as well as the clearance of inflammatory macrophages. The results confirm that porous nanomotors coated on drug-coated balloons can penetrate atherosclerotic plaques, improve local drug retention efficiency, and achieve short-term photothermal anti-inflammatory effects, providing a novel strategy for high-efficiency balloon-based therapy of atherosclerosis.

But nanomotor delivery systems still have notable flaws blocking their clinical translation against atherosclerosis. They suffer from weak biological stability and poor controllable movement in the blood. High preparation difficulty, potential biosafety risks, and immature *in vivo* application evidence further limit their clinical progression.

3.3. Mitochondria-Targeted Drug Delivery Systems

Mitochondria play a critical role in the pathogenesis of atherosclerosis by driving oxidative stress, chronic inflammation, and lipid metabolism dysfunction in lesional macrophages. Emerging evidence suggests that targeted delivery systems designed to restore mitochondrial homeostasis hold great therapeutic promise. Advanced nanocarriers, including triphenylphosphonium (TPP)-modified liposomes and biomimetic macrophage membrane-coated nanoparticles, enable precise subcellular delivery of therapeutic agents to dysfunctional mitochondria. These strategies effectively scavenge mitochondrial reactive oxygen species, enhance mitochondrial respiration, and promote macrophage repolarization from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype, thereby attenuating plaque progression and improving stability. Such mitochondria-targeted approaches represent a paradigm shift in the treatment of atherosclerotic cardiovascular disease.

However, mitochondria-targeted drug delivery systems still face obstacles in

atherosclerosis treatment and clinical translation. They show unsatisfactory tissue penetration and off-target side effects. Complex modification techniques, unclear long-term toxicity, and insufficient *in vivo* therapeutic data severely restrict their further clinical application.

The major construction strategies and targeting mechanisms of biomimetic DDSs are illustrated in **Figure 3**.

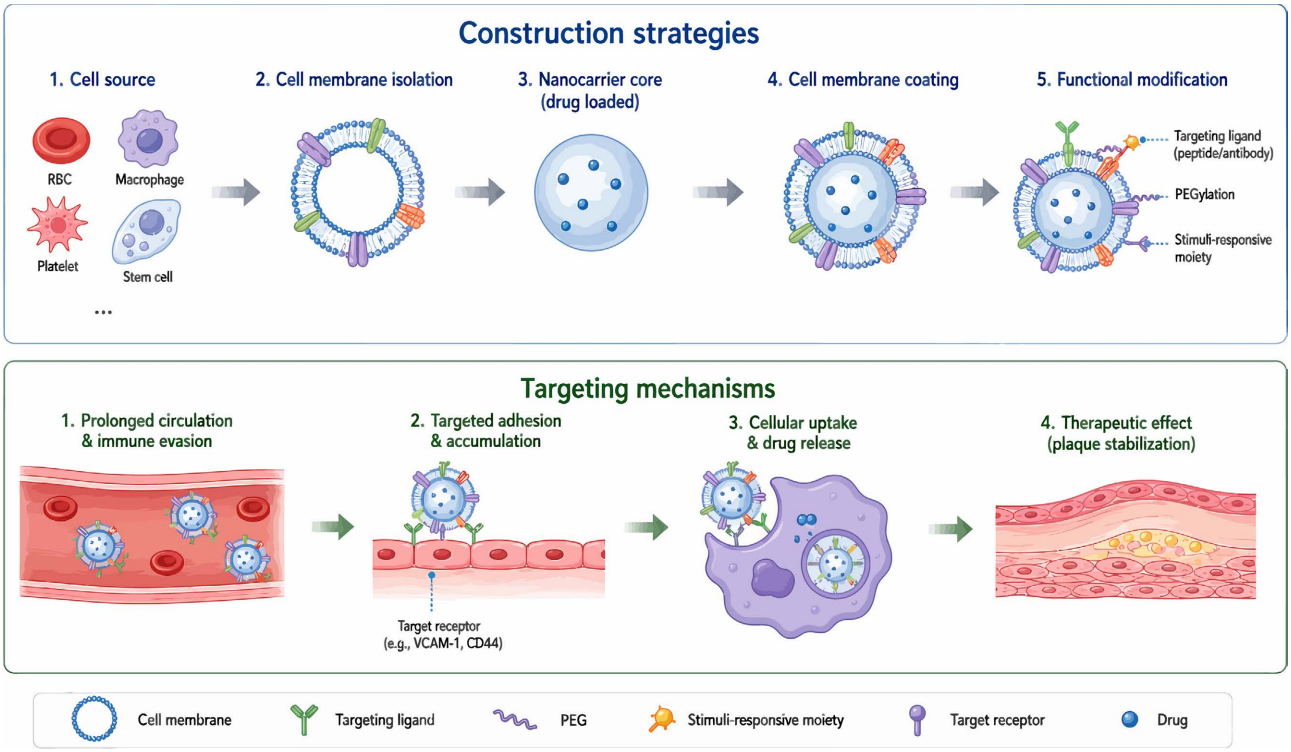

Figure 3. Construction strategies and targeting mechanisms of biomimetic drug delivery systems.

4. Current Challenges in Clinical Translation

Despite remarkable preclinical achievements of various drug delivery systems for atherosclerosis treatment, multiple tough challenges still hinder their smooth clinical translation. Firstly, most nanocarriers suffer from unsatisfactory *in vivo* stability, unexpected premature drug release, and insufficient specific accumulation at atherosclerotic plaques, which greatly weaken actual therapeutic efficacy. Secondly, complicated synthesis and modification processes lead to high production costs and difficulty in large-scale standardized preparation.

In addition, the long-term biosafety, *in vivo* metabolic pathways, and potential immune rejection responses remain insufficiently verified. Differences between animal models and human pathological conditions also make preclinical experimental results hard to replicate in clinical trials. Moreover, unified evaluation standards and mature clinical administration schemes are still lacking, further restricting the practical clinical promotion of these advanced delivery strategies.

5. Conclusion

Drug delivery systems have revolutionized the therapeutic landscape of atherosclerosis by addressing the limitations of conventional therapies. Conventional DDSs (liposomes, polymeric nanoparticles, etc.) exhibit excellent biocompatibility and drug-loading capacity, while novel biomimetic, nanomotor, and mitochondria-targeted platforms further enhance immune evasion, plaque penetration, and subcellular precision. These advanced DDSs effectively intervene in key pathological processes of AS, including lipid accumulation, inflammation, and oxidative stress, thereby stabilizing plaques and improving therapeutic outcomes. Despite current challenges such as scale-up production and clinical translation, DDSs hold great promise for developing safe, efficient, and personalized therapeutic strategies for atherosclerosis in the future.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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