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REVIEW ARTICLE

A Review on Mechanisms, Design, and Therapeutic Applications of Targeted Nanocarriers in Cardiovascular Conditions

Sindhuja Gandham, Sai Krishna N, Anusha Kusuma, SS Prasanna Kumar Ponnaganti, Appala Anjali*

Department of Pharmacology, A.K.R.G College of Pharmacy, Nallajerla, Andhra Pradesh, India

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Abstract: Cardiovascular diseases are of the leading causes of global morbidity and mortality despite significant advancements in conventional pharmacotherapy. Traditional small-molecule drugs are frequently hampered by unfavorable pharmacokinetic profiles, rapid systemic clearance, poor aqueous solubility, narrow therapeutic indices, and substantial off-target toxicities. Nanocarrier-based drug delivery systems offer targeted, controlled, and site-specific therapeutic interventions that fundamentally transform cardiovascular treatment paradigms. Through tailored physicochemical architectures, nanocarriers including liposomes, polymeric nanoparticles, dendrimers, inorganic nanomaterials, and cell-derived extracellular vesicles bypass physical and physiological barriers to concentrate therapeutic payloads within compromised cardiovascular tissues. Passive accumulation through compromised endothelial permeability, combined with active ligand-mediated targeting against inflammatory cell-surface markers, enhances drug localization at sites of atherosclerosis, myocardial infarction, and vascular restenosis. Stimuli-responsive constructs featuring pH-sensitive polymers, such as poly-L-histidine, and reactive oxygen species-cleavable linkages enable site-specific release triggered by pathological microenvironments. Biomimetic delivery systems such as reconstituted high-density lipoproteins facilitate reverse cholesterol transport and macrophage reprogramming, mitigating atherogenesis. Preclinical and clinical evaluations confirm that nanocarrier encapsulation restores bioactivity, reduces systemic dosage requirements, and attenuates cardiotoxicity associated with potent cardiovascular agents. Addressing manufacturing scalability, long-term biocompatibility, and regulatory standardization will catalyze the translation of nanotherapeutics into routine clinical cardiological practice.

Keywords: Cardiovascular drugs; Nanocarriers; Targeted drug delivery; Atherosclerosis; Myocardial infarction.

1. Introduction

Cardiovascular diseases (CVDs) like coronary artery disease, cerebrovascular disease, peripheral arterial disease, hypertension, and heart failure are the primary cause of global mortality, accounting for approximately 17.9 million deaths annually [1, 2]. The underlying pathology in the majority of CVDs involves progressive atherogenesis, vascular inflammation, endothelial dysfunction, and ischemic tissue injury [3]. Although contemporary pharmacological agents such as statins, antiplatelet therapies, angiotensin-converting enzyme inhibitors, and beta-blockers have substantially reduced cardiovascular mortality, conventional drug administration strategies encounter severe therapeutic bottlenecks [3, 4].

The clinical efficacy of orally or intravenously administered cardiovascular therapeutics is routinely constrained by suboptimal physicochemical properties [5]. A vast proportion of candidate molecules possess low aqueous solubility, poor bioavailability, short plasma half-lives, and high metabolic clearance rates, necessitating frequent, high-dose administration regimens [5, 6]. Systemic drug exposure engenders profound off-target toxicities, including statin-induced myopathy, systemic hemorrhages secondary to potent thrombolytics, and severe hypotension associated with unlocalized vasodilators [6, 7]. Non-targeted administration fails to deliver therapeutic concentrations to localized vascular lesions or ischemic myocardium, bounded by dense extracellular matrix networks and altered capillary hemodynamics [8]. Nanotechnology-based drug delivery platforms provide structural solutions to these pharmacokinetic and pharmacodynamic limitations [8, 9]. By encapsulating active pharmaceutical ingredients within sub-micron carrier structures (typically 1 to 200 nm), nanocarriers insulate labile drugs from premature enzymatic degradation, prolong systemic circulation time, improve aqueous solubilization, and alter biodistribution patterns [9, 10]. Most crucially, nanocarriers can be engineered to achieve passive accumulation at diseased sites via vascular hyperpermeability or active targeting through surface functionalization with specific ligands targeting inflamed vascular endothelium and ischemic cardiomyocytes [10, 11]. A broad range of nanocarriers spanning lipidic, polymeric, dendrimeric, inorganic, and biological vesicles has shown superior capability in restoring

* Corresponding author: Appala Anjali

damaged cardiovascular tissue and arresting disease progression [10, 11]. Table 1 provides an overview of major nanoparticle systems investigated for targeted cardiovascular therapeutics.

Table 1. Classification, Target Indications, Payloads, and Biological Functions of Nanocarrier Systems in Cardiovascular Pharmacology

Nanocarrier Category	Specific System	Target Disease	Encapsulated Payload	Animal / Cell Model	Primary Biological Mechanism	Reference
Lipid-Based	Conventional Liposomes	Atherosclerosis	Glucocorticoids	Rabbit Model	Depletion of plaque macrophages and suppression of intra-plaque angiogenesis	[4]
	PEGylated Liposomes	Myocardial Infarction	Growth Factors & Cytokines	Rat & Mouse Cardiac Models	Prolonged circulation and localized delivery of cardioprotective cytokines to infarcted tissue	[5, 6]
Micelle-Based	Polymeric Micelles	Atherosclerosis	Antithrombin Agents	Mouse Model	Selective binding to clotted fibrin and exposed extracellular matrix in vascular plaque	[7, 8]
Polymeric	PLGA Nanoparticles	Atherosclerosis	Pitavastatin	ApoE-/- Mouse Model	Suppression of monocyte chemoattractant protein-1 (MCP-1) and stabilization of vulnerable plaque	[9]
	PLGA Nanoparticles	Pulmonary Arterial Hypertension	Beraprost Sodium	Rat PAH Model	Sustained pulmonary vasodilation and reduction of pulmonary vascular resistance	[9]
Dendrimeric	Poly-L-Histidine Conjugates	Myocardial Infarction	MicroRNAs (miRNA-126/21)	H9c2 Cardiomyocyte Cells	pH-dependent endosomal escape preventing hypoxia-induced cardiomyocyte apoptosis	[10, 11]
Inorganic	Gold Nanoparticles	Atherosclerosis	Statins / Cytokine Inhibitors	Mouse and Rabbit Models	Controlled payload release and suppression of arterial wall inflammatory cascades	[12, 13]
	Carbon Nanotubes	Anti-Atherosclerosis	siRNA / miRNA Complexes	Mouse Model	Targeted uptake by arterial macrophages and restoration of endothelial function	[14]
	Quantum Dots	Myocardial Infarction	Atorvastatin	Pig and Rodent Models	Simultaneous fluorescence bioimaging and mitochondrial protection in ischemic myocardium	[15, 16]

Nanocarrier Category	Specific System	Target Disease	Encapsulated Payload	Animal / Cell Model	Primary Biological Mechanism	Reference
Biological	Engineered Exosomes	Cardioprotection	Therapeutic miRNAs & mRNAs	Rodent and Rabbit Models	Anti-apoptotic signaling, inhibition of myocardial fibrosis, and stimulation of angiogenesis	[17, 19]
	Extracellular Vesicles	Myocardial Infarction	Statins and miRNA-126	Mouse Model	Neo-vascularization, attenuation of scar formation, and salvage of borderline myocardium	[20, 21]
	Reconstituted HDL	Atherosclerosis	Statins / Corticosteroids	ApoE-/- Mouse Model	Scavenger receptor class B member 1 (SR-B1) mediated reverse cholesterol transport and plaque regression	[22]

2. Pathophysiological Barriers and Targeting Strategies in Cardiovascular Nanomedicine

2.1. Vascular and Myocardial Microenvironmental Barriers

Effective delivery of cardiovascular therapeutics requires overcoming formidable physiological barriers present in both healthy and diseased cardiovascular systems [23]. In healthy vasculature, the continuous endothelial lining acts as a tightly regulated semi-permeable barrier, linked by tight junctions and adherens junctions that restrict the passage of molecules larger than 3 to 5 nm [23, 24]. In pathological conditions such as atherosclerosis and myocardial infarction, this barrier undergoes profound structural and functional alterations [24].

In atherogenesis, lipid accumulation and chronic shear stress induce endothelial activated states, leading to disrupted intercellular junctions, impaired nitric oxide bioactivity, and leukocyte extravasation [24, 25]. Simultaneously, high blood flow velocities, arterial wall shear stress, and dense extracellular matrix networks within mature atheromatous plaques create mechanical forces that limit the deep penetration of systemic therapeutic agents [25]. In ischemic myocardium, coronary occlusion causes rapid oxygen depletion, metabolic dysfunction, tissue acidosis, and microvascular microthrombosis, which impedes the convective and diffusive transport of systemic drugs into the ischemic core [26].

2.2. Passive Accumulation and Enhanced Vascular Permeability

Passive targeting in cardiovascular nanomedicine exploits the structural compromise of vascular endothelial integrity that occurs during inflammatory and ischemic conditions [25]. Unlike the classic Enhanced Permeability and Retention (EPR) effect described in oncology, passive accumulation in cardiovascular pathology relies on acute microvascular hyperpermeability and transient endothelial fenestrations [25, 27].

During acute myocardial infarction and subsequent ischemia-reperfusion injury, endothelial cells contract, basement membranes degrade via matrix metalloproteinase activity, and intercellular gaps widening up to 100–500 nm emerge within the ischemic capillary bed [25]. Nanocarriers within a specific hydrodynamic diameter range (typically 30–150 nm) readily extravasate through these pathological gaps into the interstitial space of the injured myocardium [27]. Prolonged systemic circulation achieved by surface modification with hydrophilic polymers such as polyethylene glycol (PEG) is required for passive targeting, as it prevents rapid opsonization and clearance by the reticuloendothelial system (RES), maximizing the area-under-the-curve (AUC) available for extravasation [20, 27].

2.3. Active Targeting via Cell-Surface Receptors and Endothelial Biomarkers

Active targeting superimposes molecular recognition ligands onto the nanocarrier surface, directing nanocarriers to specific cell types or extracellular matrix components overexpressed in diseased cardiovascular tissues [24, 26].

2.3.1. Endothelial and Inflammatory Adhesion Molecules

Vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin are strongly upregulated on activated endothelial cells lining inflamed arterial walls and ischemic myocardium [26, 28]. Nanocarriers conjugated with peptide sequences (such as VCAM-1-binding peptide VHPKQHR) or monoclonal antibodies against ICAM-1 exhibit rapid binding and endocytosis into target endothelial cells, avoiding systemic washout under hemodynamic flow [28, 29].

2.3.2. Scavenger Receptors on Macrophages

Foam cell formation driven by uninhibited uptake of oxidized low-density lipoproteins (oxLDL) by arterial macrophages is a hallmark of atherosclerosis progression [26, 30]. Nanocarriers functionalized with ligands that bind Scavenger Receptor A (SR-A), CD36, or Scavenger Receptor Class B Member 1 (SR-B1) selectively target inflammatory macrophages within vulnerable plaques, delivering anti-inflammatory agents or gene-silencing therapeutics directly to the plaque core [26, 30].

2.3.3. Fibrin and Platelet-Targeted Modalities

In acute thrombotic events and myocardial infarction, extracellular matrix components such as activated platelets and fibrin lattices are exposed [7, 28]. Functionalizing nanocarriers with cyclic RGD (Arg-Gly-Asp) peptides targeting activated glycoprotein IIb/IIIa receptors on platelets or single-chain variable fragments (scFv) targeting cross-linked fibrin enables high-affinity binding to acute thrombi, facilitating localized thrombolytic release [7, 28].

2.4. Stimuli-Responsive Mechanisms: Microenvironmental Triggers

Smart nanocarrier architectures utilize the distinct chemical, physical, and enzymatic changes characteristic of pathological cardiovascular microenvironments to trigger targeted payload release [8, 10].

2.4.1. Acidic pH Sensitivity

Ischemia and intense arterial inflammation shift local cellular metabolism toward anaerobic glycolysis, accumulating lactic acid and lowering the local extracellular pH to 6.0–6.8 (and dropping below pH 5.5 within endolysosomal compartments) [10, 11]. Nanocarriers fabricated with pH-sensitive moieties, such as poly-L-histidine or acetal-functionalized polymers, undergo ionizable charge conversion or hydrophobic-to-hydrophilic transitions upon encountering acidic microenvironments, inducing core destabilization and rapid payload liberation [10, 11].

2.4.2. Reactive Oxygen Species (ROS) Responsiveness

Ischemia-reperfusion injury and hyperlipidemia generate localized bursts of reactive oxygen species, including hydrogen peroxide, superoxide anions, and peroxynitrite [8, 13]. Nanocarriers incorporating ROS-cleavable linkers, such as ferrocene, boronic ester esters, or thioether bonds, undergo chemical oxidation and structural disassembly exclusively at sites of elevated oxidative stress, limiting non-specific release in healthy systemic circulation [8, 13].

2.4.3. Enzyme-Triggered Release

Atherosclerotic plaques and infarcted tissue express high local concentrations of matrix metalloproteinases (MMP-2 and MMP-9) and phospholipases [9, 26]. Peptide crosslinkers sensitive to MMP digestion can be integrated into polymeric matrix carriers, allowing payload liberation in proportion to local proteolytic activity [9, 26].

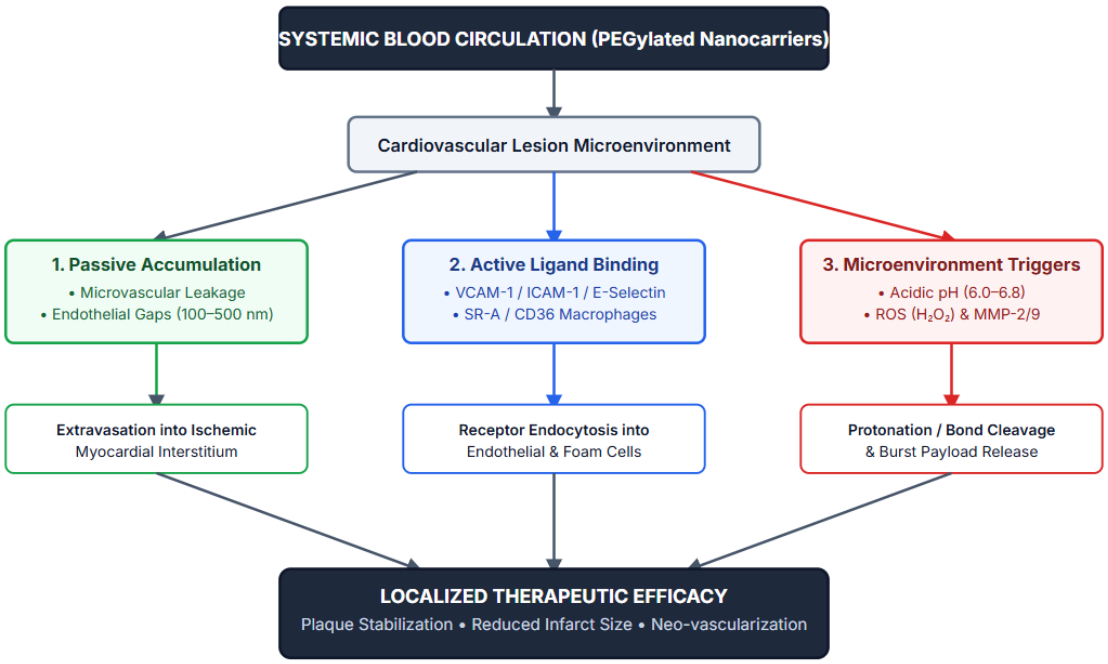

Figure 1. Pathophysiological Barriers and Targeted Nanocarrier Delivery in Cardiovascular Lesions.

3. Lipid-Based and Micellar Nanocarrier Platforms

3.1. Liposomes and PEGylated Formulations

Liposomes represent self-assembling spherical lipid bilayers consisting of amphiphilic phospholipids surrounding an aqueous core [4, 6]. This structural configuration permits the simultaneous encapsulation of hydrophilic drugs within the interior core and hydrophobic molecules within the lipophilic bilayer [4].

3.1.1. Structural Characteristics and Modifications

Conventional liposomes composed solely of phosphatidylcholine and cholesterol are rapidly recognized as foreign particulates by the reticuloendothelial system, leading to rapid hepatic and splenic clearance [5, 6]. Surface modification with polyethylene glycol (PEGylation) creates a sterically protective hydration layer around the liposome [5]. This steric barrier suppresses plasma protein opsonization, extends systemic half-life from minutes to several hours, and enables enhanced passive accumulation within compromised cardiovascular tissue [5, 6].

3.1.2. Mechanism of Action in Cardiovascular Lesions

PEGylated liposomes accumulate passively within ischemic myocardium through microvascular fenestrations [5]. Following accumulation, liposomes fuse with local cell membranes, undergo endocytosis by tissue macrophages, or slowly release their payload into the interstitial space [4, 6]. Ligand-targeted liposomes modified with antibodies against E-selectin or VCAM-1 bind directly to inflamed vascular beds, internalizing via receptor-mediated endocytosis to deliver therapeutic payloads intracellularly [4, 28].

3.2. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Solid Lipid Nanoparticles (SLNs) were developed to overcome the physical instability, drug leakage, and batch-to-batch variability sometimes associated with fluidic liposomes [29, 30]. SLNs consist of a solid lipid matrix at room and body temperature, stabilized by biocompatible surfactants [30].

Nanostructured Lipid Carriers (NLCs) represent a second-generation evolution formed by mixing solid lipids with spatially incompatible liquid lipids (oils), producing a highly disordered lipid matrix [30]. This imperfect crystalline lattice provides significantly higher drug loading capacity and prevents drug expulsion during prolonged storage [30]. Solid lipid systems excel at

solubilization and sustained oral/systemic delivery of highly lipophilic cardiovascular drugs such as carvedilol, simvastatin, and felodipine [29, 30].

3.3. Polymeric Micelles

Polymeric micelles are core-shell nanostructures (10–100 nm) formed by the spontaneous self-assembly of amphiphilic block copolymers in aqueous solutions above the critical micelle concentration (CMC) [7, 8]. The inner core typically composed of hydrophobic blocks such as poly(L-lactic acid) (PLLA), poly(caprolactone) (PCL), or poly(propylene oxide) (PPO) serves as a high-capacity reservoir for hydrophobic drugs [7]. The outer hydrophilic shell, commonly formed by PEG, provides steric stabilization and prolongs circulation [7, 8].

Due to their small hydrodynamic diameter (<50 nm), polymeric micelles exhibit superior arterial wall penetration compared to larger liposomal carriers [7]. Micelles functionalized with targeting moieties can penetrate deep into atheromatous plaques, delivering antiproliferative or anti-inflammatory drugs directly to vascular smooth muscle cells and macrophages [7, 8].

3.4. Therapeutic Applications in Atherosclerosis and Ischemic Heart Disease

Lipid-based and micellar carriers have achieved notable successes in preclinical cardiovascular models [4, 6, 7].

3.4.1. Attenuation of Atherosclerotic Inflammation

Liposomal encapsulation of lipophilic glucocorticoids (e.g., prednisolone phosphate) selectively targets pro-inflammatory macrophages in atherosclerotic plaques [4]. In hyperlipidemic rabbit models, systemic administration of prednisolone-loaded liposomes produced marked reductions in plaque macrophage content and intra-plaque microvascular density without inducing systemic glucocorticoid side effects such as hyperglycemia and immunosuppression [4, 26].

3.4.2. Targeted Thrombolysis and Ischemic Salvage

Direct systemic administration of tissue plasminogen activator (tPA) carries a severe risk of lethal intracranial hemorrhage [7, 28]. Encapsulating tPA or antithrombin agents within clot-targeted liposomes or amphiphilic polymeric micelles restricts fibrinolytic activity strictly to the thrombus interface [7]. In animal models of acute arterial thrombosis, targeted thrombolytic nanocarriers achieved rapid clot lysis at a fraction of the standard systemic dose, eliminating systemic bleeding complications [7, 28]. Furthermore, PEGylated liposomal formulations delivering cardioprotective cytokines and growth factors to ischemic myocardium significantly reduced infarct area and preserved left ventricular ejection fraction following acute myocardial infarction [5, 6].

4. Polymeric Nanoparticles and Dendrimeric Delivery Systems

4.1. Biodegradable Polymeric Nanoparticles: PLGA, PLA, and Polycaprolactone Formulations

Solid polymeric nanoparticles (PNPs) encompassing nanospheres (matrix systems) and nanocapsules (vesicular core-shell systems) utilize synthetic or natural biodegradable polymers to encapsulate therapeutic payloads [12]. Poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), and polycaprolactone (PCL) represent the most extensively validated synthetic polymers due to their established human biocompatibility and hydrolytic degradation into non-toxic metabolic intermediates (lactic acid and glycolic acid) [12].

Polymeric nanoparticles protect encapsulated therapeutic molecules including small molecules, peptides, and fragile nucleic acids from systemic enzymatic degradation [12]. The release kinetics of PNPs can be programmed by altering polymer molecular weight, lactide-to-glycolide ratios, surface charges, and hydrophilic-lipophilic balances, enabling zero-order sustained payload release over periods ranging from days to weeks [12].

4.2. Smart Polymeric Nanocarriers and Microenvironment-Responsive Payload Release

Polymeric nanocarrier architectures can be engineered with chemical bonds that respond to physical or biochemical changes in pathological tissues [11, 12].

In vascular regions undergoing severe hypoxia, such as infarcted myocardium, local oxidative stress levels are elevated [11]. Polymeric nanoparticles synthesized with thioether or boronic ester backbone links undergo rapid polymer cleavage upon exposure

to local hydrogen peroxide, triggering controlled drug release [11, 14]. Similarly, temperature-sensitive polymeric carriers composed of poly(N-isopropylacrylamide) (PNIPAAm) undergo reversible phase transitions around pathological body temperatures, altering their structural swelling to release anti-arrhythmic or anti-inflammatory drugs directly into inflamed myocardium [11, 12].

4.3. Dendrimeric Architectures: Structural Properties and Poly-L-Histidine Mechanics

Dendrimers are hyperbranched, monodisperse, three-dimensional synthetic macromolecules characterized by a central core, repeatedly branched interior layers (generations), and a dense peripheral surface arrayed with functional terminal groups [13, 14]. Polyamidoamine (PAMAM) and poly(L-lysine) represent common dendrimer classes [13].

4.3.1. Architectural Dynamics and Payload Capacity

The uniform step-wise synthesis of dendrimers provides control over size, molecular weight, and surface charge [13]. Small hydrophobic molecules can be physically encapsulated within the internal hydrophobic cavities, while charged moieties (e.g., nucleic acids, peptides) or targeting ligands can be covalently conjugated to the abundant terminal surface groups [13, 14].

4.3.2. Poly-L-Histidine Structural Mechanics and Endosomal Escape

Poly-L-histidine (PLH) nanocarriers utilize the unique pKa (~ 6.0) of the imidazole ring to achieve stimulus-responsive endosomal escape [13, 14]. Under physiological blood conditions (pH 7.4), the imidazole group remains unprotonated, hydrophobic, and uncharged, maintaining structural integrity and retention of encapsulated gene payloads [13].

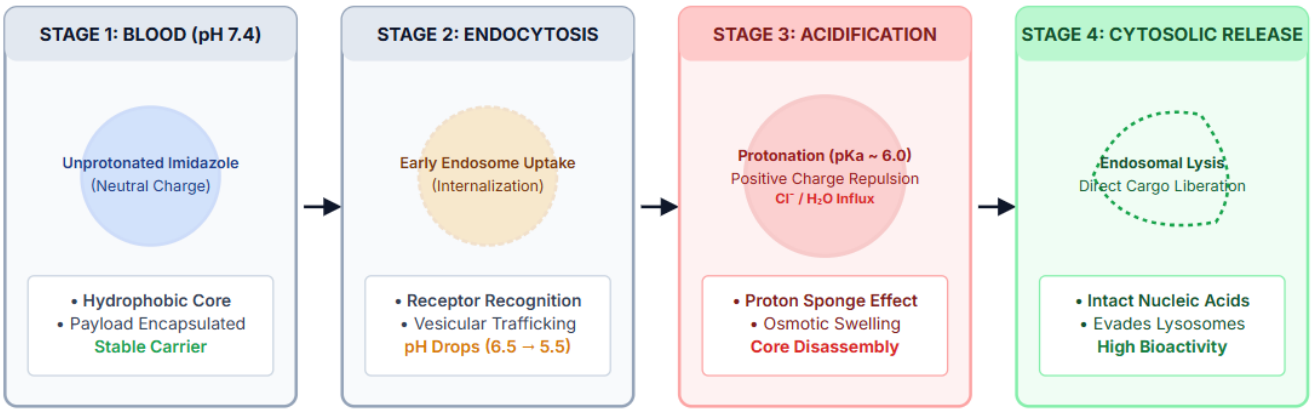

Figure 2. Physical mechanism of poly-L-histidine (PLH) endosomal escape.

In physiological blood stream conditions (pH 7.4), the unprotonated imidazole rings remain hydrophobic, maintaining carrier core stability and payload encapsulation. Upon endocytosis into early endosomes, the environmental pH decreases to 5.0–6.5. This acidification causes rapid protonation of the imidazole nitrogen atoms, inducing electrostatic repulsion, core swelling, and an influx of chloride ions and water (the proton sponge effect). The resulting osmotic pressure ruptures the endosomal membrane, releasing therapeutic nucleic acids (e.g., miRNA, siRNA) directly into the cytosol before lysosomal degradation can occur.

Upon receptor-mediated endocytosis into target cardiovascular cells (such as ischemic cardiomyocytes or activated endothelial cells), the nanocarrier encounters the acidic interior of the early/late endosome (pH 5.0-6.5) [13, 14]. At this reduced pH, the imidazole nitrogen atoms undergo rapid protonation, acquiring positive charges [13]. This chemical shift triggers two simultaneous physical processes:

1. Hydrophobic-to-Hydrophilic Transition: The sudden electrostatic repulsion among positive charges destabilizes the hydrophobic core, driving nanocarrier swelling and immediate drug liberation [13].
2. Proton Sponge Effect: The high buffering capacity of the imidazole rings causes an influx of chloride ions and water molecules into the endosome, inducing osmotic swelling, endosomal membrane rupture, and direct cytosolic liberation of delicate nucleic acid payloads (e.g., siRNA, miRNA) before lysosomal enzymatic degradation can occur [13, 14].

4.4. Nanotherapeutic Applications in Vascular Restenosis and Ischemic Angiogenesis

Polymeric and dendrimeric systems have displayed high efficacy across clinical and preclinical cardiovascular scenarios [12, 13].

4.4.1. Prevention of In-Stent Restenosis

Following percutaneous coronary intervention (PCI) and stent deployment, mechanical vascular injury often induces local smooth muscle cell (SMC) hyperproliferation and migration, causing secondary luminal re-narrowing (restenosis) [12]. Delivery of antiproliferative agents (paclitaxel or rapamycin) via PLGA nanoparticles suppresses SMC proliferation while preserving native endothelial cell regeneration [12]. Stent coatings impregnated with PLGA nanoparticles ensure sustained drug release directly into the injured arterial wall over 30 days, significantly lowering restenosis rates [12, 28].

4.4.2. Targeted Gene Therapy and Angiogenesis

Myocardial infarction results in extensive cardiomyocyte loss and irreversible scar formation [13, 14]. Delivery of microRNA mimics (e.g., miRNA-126, miRNA-21) or siRNA targeting prolyl hydroxylase domain protein 2 (PHD2) using arginine-functionalized PAMAM or PLH dendrimers promotes local neovascularization [13, 14]. Downregulation of PHD2 stabilizes hypoxia-inducible factor 1-alpha (HIF-1α), activating endogenous angiogenic pathways, reducing border-zone apoptosis, and preserving cardiac pump performance [13, 14].

5. Inorganic, Biological, and Biomimetic Nanocarriers

5.1. Inorganic Nanostructures: Metallic Nanoparticles, Carbon Nanotubes, and Quantum Dots

Inorganic nanomaterials possess unique physical, optical, electronic, and magnetic properties that distinguish them from organic lipidic and polymeric platforms [15, 16].

5.1.1. Gold and Metallic Nanoparticles

Gold nanoparticles (AuNPs) and iron oxide nanoparticles offer high surface-area-to-volume ratios, facile surface functionalization via thiol chemistry, and tunable physical characteristics [15, 16]. Superparamagnetic iron oxide nanoparticles (SPIONs) serve as dual-action theranostics; under external magnetic fields, SPIONs can be directed to localized sites of vascular injury while simultaneously providing high-contrast magnetic resonance imaging (MRI) of vulnerable atherosclerotic plaques [16, 28].

5.1.2. Carbon-Based Nanomaterials

Carbon nanotubes (CNTs) and graphene oxide sheets feature needle-like structures that enable direct penetration through cell membranes [16]. Functionalized single-walled carbon nanotubes conjugated with anti-inflammatory siRNA efficiently enter plaque macrophages, silencing pro-inflammatory cytokine expression [16].

5.1.3. Quantum Dots

Quantum dots (QDs) are semiconductor nanocrystals (2-10 nm) with exceptional photostability and narrow emission spectra [17, 18]. Functionalized quantum dots loaded with atorvastatin have been employed in rodent and swine models to perform simultaneous near-infrared optical tracking of myocardial ischemia and delivery of cardioprotective payloads to preserve mitochondrial function [17, 18].

5.2. Cell-Derived Extracellular Vesicles and Engineered Exosomes

Extracellular vesicles (EVs), including endosome-derived exosomes (30-150 nm), are naturally occurring membrane-bound lipid vesicles secreted by virtually all eukaryotic cells [19]. Exosomes carry complex biological payloads including functional proteins, lipids, mRNA, and microRNAs and mediate intercellular communication [19].

Exosomes harvested from mesenchymal stem cells (MSCs) or cardiac progenitor cells exhibit innate cardioprotective, anti-inflammatory, and pro-angiogenic activities [19]. Due to their native human cell membrane composition containing self-recognition proteins (such as CD47), exosomes evade mononuclear phagocyte clearance, exhibit long circulation half-lives, and cross tight biological barriers [19]. Functionalizing exosomal membranes with ischemic myocardium-targeting peptides (e.g., CSTSMLKAC) concentrates stem-cell-derived exosomes directly in damaged cardiac tissue, promoting tissue repair and attenuating fibrotic remodeling post-infarction [19].

5.3. Lipoprotein-Based Nanocarriers and Reconstituted High-Density Lipoproteins

High-Density Lipoproteins (HDLs) are endogenous nanostructures (8-12 nm) responsible for transporting excess cellular cholesterol from peripheral tissues back to the liver for excretion [20]. Synthetic or reconstituted HDL (rHDL) nanocarriers assembled from recombinant apolipoprotein A-I (ApoA-I) and phospholipids mimic these endogenous dynamics [20].

Reconstituted HDL nanocarriers naturally target macrophages within atherosclerotic plaques via scavenger receptor class B member 1 (SR-B1) and ATP-binding cassette transporters (ABCA1/ABCG1) [20]. Upon binding, rHDL promotes reverse cholesterol transport, extracting stored cholesterol esters from foam cells [20]. When loaded with statins or anti-inflammatory drugs, rHDL acts as a dual therapeutic platform: the encapsulated drug suppresses local inflammation, while the particle shell removes excess plaque lipid deposits [20, 28].

5.4. Comparison of Cardiovascular Nanocarrier Platforms

A comparison of the hydrodynamic dimensions, structural architectures, drug encapsulation profiles, pharmacological advantages, and toxicological liabilities across all major cardiovascular nanocarrier platforms is detailed in Table 2.

Table 2. Physicochemical Attributes, Pharmacological Advantages, Toxicological Limitations of Cardiovascular Nanocarrier Systems

Nanocarrier Platform	Diameter Range	Structure & Payload Capacity	Advantages	Limitations	References
PEGylated Liposomes	80-150 nm	Spherical lipid bilayer with an aqueous core; encapsulates hydrophilic payloads in the interior and lipophilic drugs in the bilayer.	Prolonged systemic circulation half-life; attenuates drug cardiotoxicity; passive accumulation in ischemic tissue.	Accelerated blood clearance (ABC) phenomenon upon repeated dosing; risk of lipid peroxidation during long-term storage.	[4–6]
Solid Lipid Nanoparticles (SLNs) & NLCs	50-200 nm	Solid lipid core stabilized by surfactants (SLN) or spatially disordered liquid/solid lipid blends (NLC).	High physical stability; scalable high-pressure homogenization manufacturing; controlled lipid matrix erosion.	Potential drug expulsion during matrix crystallization in SLNs; limited loading for highly hydrophilic payloads.	[27, 28]
Polymeric Micelles	10-50 nm	Amphiphilic block copolymer core-shell structures; hydrophobic core sequesters poorly soluble molecules.	Superior penetration into dense arterial walls and atheromatous plaques due to ultra-small hydrodynamic radius.	Risk of premature dissociation upon dilution below critical micelle concentration (CMC) in systemic blood flow.	[7, 8]
Biodegradable Polymeric Nanoparticles (PLGA/PLA)	50-200 nm	Polymeric matrix (nanospheres) or core-shell (nanocapsules) systems degrading hydrolytically.	Programmable zero-order release kinetics over days to weeks; protection of fragile nucleic acid and protein payloads.	Local microenvironmental acidification caused by glycolic and lactic acid degradation byproducts; residual solvent toxicity.	[12, 28]
Dendrimers (PAMAM, Poly-L-Histidine)	2-10 nm	Hyperbranched, monodisperse 3D macromolecules with dense peripheral functional groups.	Precise valency; high density surface functionalization; pH-triggered endosomal escape via imidazole protonation.	Charge-dependent membrane disruption and hemolysis induced by unmodified cationic surface groups.	[13, 14]
Inorganic Nanostructures (SPIONs, AuNPs, QDs)	2-50 nm	Metallic, metal oxide, or semiconductor cores with functionalized outer organic shells.	Multi-modal theranostic capabilities combining real-time magnetic resonance or optical tracking with drug delivery.	Reticuloendothelial system accumulation; lack of biological degradation; potential heavy-metal cytotoxicity and ROS generation.	[15, 16, 17, 18]

Nanocarrier Platform	Diameter Range	Structure & Payload Capacity	Advantages	Limitations	References
Extracellular Vesicles & Exosomes	30-150 nm	Cell-derived lipid bilayer membranes embedded with native biological surface proteins (e.g., CD47).	Low intrinsic immunogenicity; native ability to cross biological barriers; inherent cardioprotective protein and miRNA cargo.	Heterogeneity in biogenesis; low purification yields; complex standardization under Good Manufacturing Practice guidelines.	[19]
Reconstituted High-Density Lipoproteins (rHDL)	8-12 nm	Recombinant apolipoprotein A-I (ApoA-I) complexed with phospholipids forming discoidal/spherical nanostructures.	Endogenous targeting to plaque macrophages via SR-B1 and ABCA1; active mobilization of stored arterial cholesterol.	High manufacturing costs associated with recombinant protein expression; rapid hepatic uptake.	[20, 28]

5.4.1. Hydrodynamic Dimensions and Vascular Extravasation Dynamics

Selecting an optimal nanocarrier platform in cardiovascular pharmacology requires balancing particle hydrodynamic radius, particle stability, payload loading efficiency, and clearance kinetics. As shown in Table 2, polymeric micelles (10-50 nm) and reconstituted high-density lipoproteins (8-12 nm) possess small hydrodynamic dimensions that facilitate deep penetration into dense atheromatous plaques, navigating the arterial extracellular matrix more efficiently than larger lipidic constructs. Conversely, liposomes (80-150 nm) and solid lipid nanoparticles (50-200 nm) take advantage of acute microvascular hyperpermeability in ischemic myocardium following infarction, where endothelial fenestrations expand up to several hundred nanometers.

5.4.2. Structural Stability and Kinetic Release Control

While polymeric micelles offer high solubilization capacity for lipophilic drugs, their dynamic stability depends strictly on maintaining systemic blood concentrations above the critical micelle concentration. In contrast, solid polymeric nanoparticles composed of poly(lactic-co-glycolic acid) (PLGA) provide structural rigidity, enabling zero-order drug release across extended therapeutic windows. Synthetic dendrimers and poly-L-histidine constructs introduce responsive delivery dynamics, utilizing localized tissue acidosis or endosomal acidification to trigger immediate structural disassembly and cytosolic payload release.

5.4.3. Biocompatibility, Immunogenicity, and Industrial Scalability

Biological and biomimetic nanocarriers, including extracellular vesicles and reconstituted high-density lipoproteins, possess high biocompatibility profiles due to surface recognition markers like CD47, which limit mononuclear phagocyte system clearance. However, industrial translation of cell-derived vesicles remains restricted by low purification yields and batch variability. Synthetic platforms like PLGA nanoparticles and PEGylated liposomes benefit from established, reproducible manufacturing techniques, making them practical candidates for immediate clinical implementation.

6. Challenges, Safety, and Future Scope

6.1. Nanotoxicology and Long-Term Biocompatibility

Despite promising preclinical efficacy, translational approval of cardiovascular nanotherapeutics requires addressing safety and toxicological concerns [15, 17, 22, 27]. Non-biodegradable inorganic carriers (e.g., carbon nanotubes, quantum dots, metallic nanoparticles) raise toxicity concerns regarding tissue accumulation, delayed clearance, oxidative damage, and potential heavy-metal ion release [15, 16, 18]. Cationic dendrimers and polymers can disrupt cell membranes, inducing hemolysis and unexpected vascular inflammation [13, 22]. Thorough toxicological evaluations mapping clearance pathways, tissue distribution, organ accumulation, and immune responses over extended periods remain critical [22, 27].

6.2. Scale-Up and Quality Control

Translating nanocarriers from bench-top research to commercial production requires industrial scalability and batch-to-batch reproducibility [12, 27, 29]. Nanoparticle formulations often require complex multi-step chemical syntheses, organic solvents, and delicate surface conjugation chemistry [12]. Small shifts in particle size distribution, surface charge (zeta potential), polydispersity

index, or drug loading efficiency can alter pharmacokinetic profiles and biodistribution in human patients [22, 27]. Implementing continuous microfluidic synthesis platforms and continuous quality monitoring will be required to meet Good Manufacturing Practice (GMP) standards [27, 29].

6.3. Regulatory Standards

Regulatory frameworks for complex nanomedicines require clear categorization standards [22, 29]. Clear therapeutic superiority over existing low-cost generic drugs is necessary to justify the higher manufacturing costs of nanotherapeutics [28, 29]. Future developments will focus on patient-tailored nanomedicines, utilizing theranostic systems to identify specific biomarkers in real time before initiating targeted drug release [16, 28].

7. Conclusion

Nanocarrier-based drug delivery systems can overcome the main limitations of conventional treatments including poor aqueous solubility, rapid systemic clearance, off-target toxicity, and limited tissue localization. Structural platforms spanning liposomes, solid lipid nanoparticles, polymeric nanoparticles, dendrimers, inorganic nanostructures, exosomes, and biomimetic high-density lipoproteins enable controlled and site-specific therapeutic delivery to diseased cardiovascular tissue. Incorporating targeted surface ligands and microenvironment-responsive mechanisms ensures precise drug accumulation within atherosclerotic plaques, ischemic myocardium, and injured vascular beds. Preclinical evidence shows that nanotherapeutic strategies improve drug efficacy, reduce required dosages, attenuate cardiotoxicity, and stimulate myocardial repair.

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