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REVIEW ARTICLE

Polymeric Nanoparticles as a Next-Generation Platforms for Cardiovascular Disease Management: A Narrative Review

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Abstract

Cardiovascular diseases are a leading cause of death worldwide and involve endothelial dysfunction, oxidative stress, chronic inflammation and tissue remodelling. Conventional pharmacotherapy can be limited by poor bioavailability, rapid clearance, non-specific distribution and dose-dependent toxicity. Polymeric nanoparticles (PNPs) are being investigated as drug-delivery systems designed to protect bioactive compounds and support controlled release or local targeting. Natural and synthetic polymers can be used to encapsulate small molecules, nucleic acids, peptides and imaging probes, offering potential applications in treatment and diagnosis. Stimuli-responsive systems, hybrid materials and ligand-mediated targeting strategies are being studied for cardiovascular conditions, including atherosclerosis, myocardial ischaemia and thrombosis. Nevertheless, immunogenicity, formulation complexity, manufacturing reproducibility, regulatory requirements and variation in patient response remain obstacles to clinical translation. This narrative review considers the design, properties and proposed cardiovascular applications of PNPs, together with biological, physicochemical and translational limitations. Clinical benefits should not be inferred from preclinical evidence alone.

Key words: Cardiovascular diseases; Nanoparticles; Nanoparticle drug delivery system; Atherosclerosis; Polymers.

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Introduction

Cardiovascular diseases (CVDs), including atherosclerosis, heart failure, myocardial infarction (MI) and stroke, remain a major global health burden. Genetic predisposition, metabolic abnormalities and lifestyle factors contribute to endothelial dysfunction, oxidative stress, inflammation, thrombosis and maladaptive remodelling.[1] Management has improved through pharmacotherapy, percutaneous coronary intervention (PCI) and cardiac surgery, including coronary artery bypass grafting and procedures for valvular disease. Although revascularisation can restore perfusion in selected patients, long-term risk reduction depends on guideline-directed treatment with agents such as statins, antiplatelet drugs, β-blockers and renin–angiotensin system modulators.[2] Some cardiovascular medicines are limited by poor solubility, variable absorption, rapid clearance, non-specific distribution or narrow therapeutic windows.[3] Interventions may correct vascular obstruction without fully addressing the underlying inflammatory, metabolic and remodelling processes, providing a rationale for investigation of additional delivery strategies.

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Nanomedicine has emerged as an investigational approach to some drug-delivery limitations by enabling targeted, sustained and efficient delivery of bioactive agents. Among various nanocarrier systems, polymeric nanoparticles (PNPs) are versatile candidates under preclinical investigation. Comprising natural or synthetic polymers, PNPs can encapsulate both hydrophilic and hydrophobic drugs, protecting them from premature degradation and allowing controlled, site-specific release.[4, 5] Their nanoscale dimensions facilitate penetration across vascular and cellular barriers, while surface functionalisation enables selective binding to diseased tissues such as inflamed endothelium or ischaemic myocardium. Notably, PNPs can be engineered as stimuli-responsive carriers that release their therapeutic payloads in response to local microenvironmental cues — such as pH changes, oxidative stress, enzymatic activity, or temperature variations — typical of cardiovascular pathology. This targeted responsiveness is intended to increase local drug concentrations while limiting systemic exposure; these effects depend on the formulation and require verification. Furthermore, PNPs support multifunctional "theranostic" applications, allowing concurrent delivery of drugs, nucleic acids and imaging agents for combined therapy and diagnosis.

The integration of polymer-based nanotechnology with cardiovascular pharmacology may contribute to precision, patient-specific and mechanism-guided therapy.[6, 7] This review elucidates the design principles, functional advantages and therapeutic implications of PNPs in cardiovascular medicine, while distinguishing proposed applications from established clinical benefit.

Overview of cardiovascular diseases

One of the most serious risks to global health is cardiovascular disease, which is the leading cause of death worldwide. According to international health agencies, it was responsible for around 17.6 million fatalities in 2012, with a historical projection of nearly 19.4 million by 2021.[8] This huge increase in death rate is due to both population aging and ongoing exposure to risk factors, which makes CVDs not only a current but also an increasing concern. Aside from mortality, it is responsible for a large proportion of disability, with approximately 400 million disability-adjusted life years addressed in 2012. Between 2000 and 2012, ischaemic heart disease mortality increased from nearly six million to more than seven million, while stroke deaths jumped from approximately five and a half million to nearly seven million. Other diseases, such as hypertension, cardiomyopathies and rheumatic heart disease, are nevertheless prominent in their own countries but contribute less to worldwide mortality, underlining the variety of CVDs and the need for specialised interventions across regions. The age-standardised death rate from CVDs has declined dramatically over the previous four decades, with global estimates indicating a drop of more than 40 % till 2021. In a high-income milieu, breakthroughs in preventive, acute treatment and risk factor management have largely contributed to these gains. More than 80 % of deaths now occur in low and middle-income countries, where access to healthcare and preventive measures is restricted and regional inequities are severe. Eastern Europe and various other parts of Asian countries continue to have far higher death rates than Western Europe and North America. The burden increases dramatically with age, particularly beyond sixty years and males are generally more likely than women to die in middle age.[9]

Female mortality, by contrast, increases markedly after menopause, reducing the gender disparity. Men frequently present with illness at a younger age in specific regions, such as South Asia and sub-Saharan Africa, with serious consequences for economic productivity and family health. These demographic trends underline the importance of age- and gender-appropriate preventive interventions. The increased prevalence of modifiable risk factors is strongly linked to the global rise in CVD burden.[10] Hypertension, diabetes, tobacco use, dyslipidaemia, obesity, physical inactivity and an unhealthy diet remain the most significant factors. Hypertension alone causes millions of deaths each year and is frequently mismanaged in resource-constrained settings. The concentration of these risk factors, particularly in rapidly urbanising populations, has exacerbated the situation, making comprehensive risk factor management critical to lowering future burden.[11] However, reductions in cardiovascular mortality have contributed significantly to increases in life expectancy, particularly in high-income countries, as shown in Figure 1.

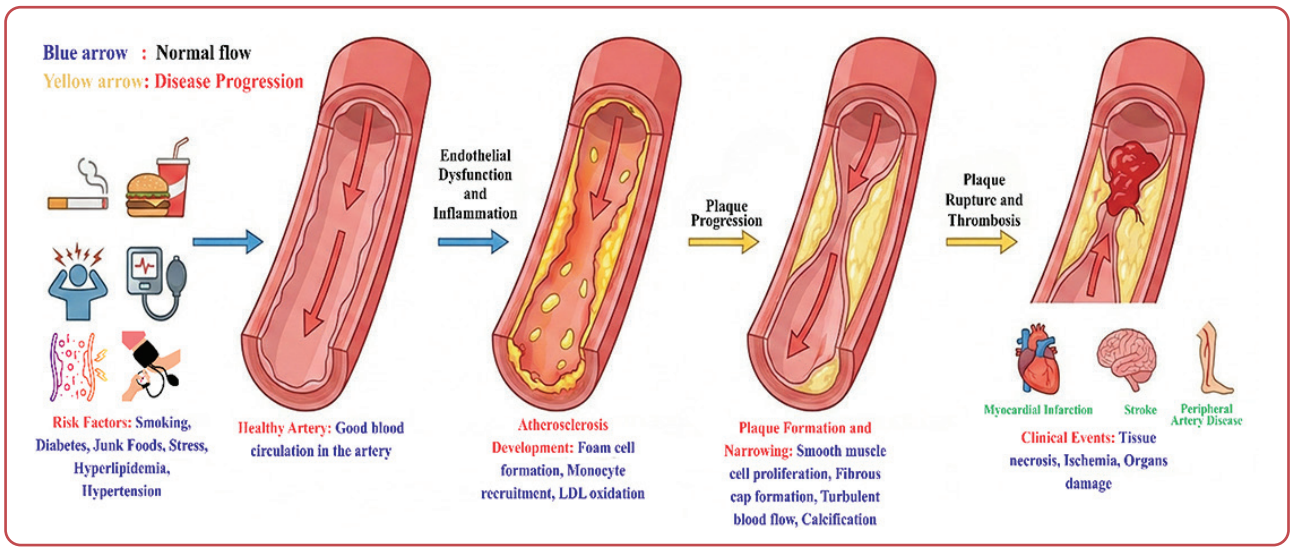


Figure 1: Pathophysiology of cardiovascular disease

The figure illustrates the progressive development of cardiovascular disease, starting with risk factors, atherosclerosis, plaque formation and narrowing and plaque rupture and thrombosis can occur. Blue arrows indicate normal blood flow, while yellow arrows show disease progression.

The improvements in cardiovascular outcomes accounted for more than two years, or nearly forty percent of the rise in life expectancy at age 20. This highlights the importance of CVDs control in determining population health, as well as the potential setbacks if progress pauses in poor and middle-income countries. Despite improvements in age-standardised rates, predictive models indicate that CVDs will remain a major danger for decades to come. Annual cardiovascular death rates are expected to stay considerable under the present health system management, according to risk assessments and long-term projections indicate a persistent worldwide burden.[12] These findings emphasise the importance of ongoing surveillance, stronger preventative strategies and improved healthcare system responses to reduce the persisting global threat posed by cardiovascular disease.

Classification of polymeric nanoparticles

Based on the structural configuration

Nanospheres

It is characterised as the solid polymeric matrix in which the drug is uniformly distributed by a matrix mechanism and can be dissolved, adsorbed or encapsulated within the polymeric matrix, having no distinct core. They are mostly fabricated by emulsion, mini-emulsion and salting out methods for sustained and controlled drug release.[13]

Nanocapsules

They are PNPs with a characteristic core-shell architecture that is fabricated by a reservoir mechanism and the drug is contained within a central liquid or solid core, surrounded by a polymeric shell. This structural arrangement protects the encapsulated medication from external degradation, allows for regulated or prolonged release and aids targeted drug delivery. They are typically created through polymerisation of monomers or encapsulating techniques such as interfacial polymerisation.[14]

Based on polymer origin

Natural polymers

Such types of polymers are extracted from microorganisms, plants and animals. Their intrinsic biocompatibility, biodegradability and low toxicity make them highly valued in nanoparticle frameworks because they lower the possibility of unfavourable immunological reactions.[15] They can successfully facilitate medication encapsulation and cellular interaction because their structure frequently matches elements of the extracellular matrix. Moreover, they can facilitate targeted or prolonged drug release and enhance drug solubility. However, they also have demerits that affect reproducibility and large-scale application, such as limited mechanical strength, batch-to-batch variability and difficulties in chemical modification.[16]

Synthetic polymers

Such types of polymers are chemically synthesised in laboratories. Due to their great degree

of tunability, characteristics including molecular weight, degradation rate, hydrophobicity or hydrophilicity and functional groups can be precisely adjusted. This gives them great versatility for creating drug release profiles for nanoparticles that are predictable. Clinical applications benefit from their superior stability, repeatability and scalability when compared with natural polymers. If synthetic polymers are not well constructed, they might occasionally present problems with toxicity, poor biodegradability and inflammatory reactions.[17]

Stimuli-responsive nanoparticles

pH-responsive

They are explored as smart drug carriers known as pH-responsive PNPs which change their structure and behaviour in response to the acidic or basic medium of various body locations including the stomach, tumour tissues, lysosomes and blood plasma. They can be broadly categorised into two groups: one comprises poly-bases, which expand in an acidic framework, the other comprises poly-acids, which swell in a basic medium.[18] These polymers can be synthetic (polymethacrylic acid, polyglutamic acid, polyhistidine and polydimethylaminoethyl methacrylate) and natural (alginate, chitosan, hyaluronic acid and gelatin). They can be formed as block copolymers, dendrimers, vesicles, hydrogels or micelles. For example, targeted delivery of doxorubicin to tumour tissue, delivery of fluorouracil to the colon[19] or prolonged ocular release can improve therapeutic efficacy and minimise side effects. Figure 2 displays the classification of polymeric nanoparticles along with their preparation methods.

Temperature-responsive

Such PNPs are transporters which, when exposed to certain temperature thresholds often near physiological values, alter structurally or in solubility. The majority of these systems operate on the lower critical solution temperature concept, which states that the polymer remains hydrated and soluble below the transition temperature but collapses and aggregates beyond it, causing release of the medication.[20] Poly (N-isopropylacrylamide), Poly (N-vinylcaprolactam) and Poly (oligoethylene glycol methacrylate) are examples of common synthetic polymers, whereas modified gelatine, elastin-like polypeptides and certain cellulose derivatives are examples of natural systems. For controlled release, these polymers can be fabricated as vesicles, hydrogels, nanogels, micelles and block copolymers.[21] Their primary uses include tissue engineering with responsive scaffolds, gene delivery for temperature-controlled nucleic acid release and cancer therapy, where moderate hyperthermia triggers drug release. By exploiting pathological temperature changes or providing external heat, these nanoparticles can enable localised, on-demand drug release, thereby improving efficacy and reducing systemic toxicity.

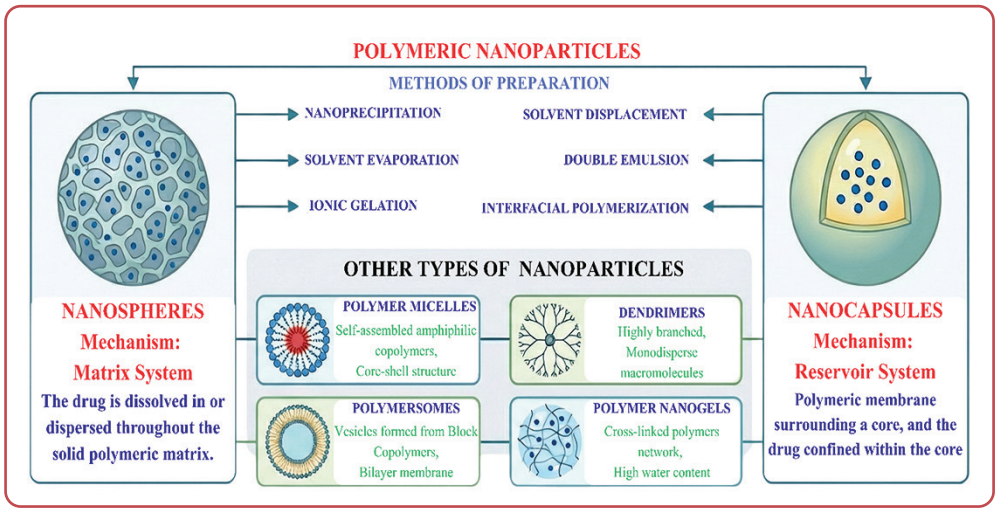


Figure 2: Classification of polymeric nanoparticles based on structure and preparation methods
The figure illustrates the primary division of polymeric nanoparticles into nanospheres (matrix systems) and nanocapsules (reservoir systems). Various preparation methods, other polymeric structures, including polymer micelles, dendrimers, polymersomes and polymer nanogels.

Redox responsive

A smart nano-based drug delivery system can be designed to respond to alterations in oxidative and reductive conditions, typically leveraging differences in glutathione level between intracellular and extracellular milieus. They are frequently engineered to react to reducing agents found inside cells and in diseased tissues, including glutathione, which is present at far greater concentrations there than in blood. In the context of cardiac disease, especially MI, such systems can be designed to release therapeutic agents specifically into infarcted heart tissue, where pathological fibrosis is driven by activated cardiac fibroblasts.[22] Redox-responsive nanoparticles that incorporate glutathione-sensitive linkers or polymer backbones remain stable in circulation but release their medicinal payload when structural cleavage or degradation occurs in the high glutathione milieu of activated fibroblasts.[23, 24]

Enzyme-responsive

Enzyme-responsive nanoparticles are sophisticated nanocarriers that release therapeutic cargo in response to enzyme activity, which is frequently deregulated in cardiac disorders. Enzymes such as proteases, lipases and oxidoreductases are overexpressed following a MI or atherosclerosis, resulting in tissue damage and remodelling. Drugs can be specifically given to sick cardiac tissue using nanoparticles that respond to these enzymes, decreasing systemic toxicity and boosting therapeutic efficacy. Protease-responsive nanoparticles, for example, can release anti-fibrotic or anti-inflammatory drugs in infarcted areas, lipase-responsive carriers can target lipid-rich atherosclerotic plaques and oxidoreductase-responsive systems can adjust oxidative stress during ischaemia-reperfusion injury.[24] These nanoparticles can be used as diagnostic instruments, as aberrant enzymatic activity is a sign of heart damage.

Physicochemical properties relevant to cardiovascular disease

Particle size

Nanoparticle size is a critical consideration in determining their biological performance, particularly in terms of cellular uptake or deposition, tissue penetration and vascular retention. Frequently ranging in size from 10–1000 nm, smaller nanoparticles have the ability to penetrate endothelial layers and therefore further penetrate tissue, which aids drug delivery.[25] The nanoscale size enhances dissolution and greatly contributes to the increased bioavailability of therapeutic agents. Particle size can affect internalisation within cells and also affects pharmacokinetics very small and very large particle sizes can be inefficient for drug therapy delivery. Very small nanoparticles are able to penetrate rapidly, but they can be removed quickly from the systemic circulation and diminish the therapeutic window. Very large nanoparticles potentially have barriers to permeability and transport across biological membranes. Hence, it is beneficial to have a balance in particle size minimise clearance and optimise delivery.[26]

Particle shape

Nanoparticles with spherical shapes (smooth or rough surfaced) are currently of interest due to the ease of uptake by endothelial cells and properties of interest for vascular stent use.[27] Some studies report that nanostructured stents with these geometries promote endothelialisation while also inhibiting smooth muscle cell growth, which may reduce the risk of *in vivo* restenosis. Since, reduced smooth muscle cells proliferation would reduce the chance of restenosis, the reflection on the nanoparticle surface contour as being more similar to cellular and tissue topologies allows for improved biocompatibility and endothelial lining repair potential to occur more naturally, but even with all the positive advancements, creating nanoparticles with the appropriate shape and controlled surface can still be an ongoing challenge and would benefit from further study with systematic data relating shape to beneficial therapeutic outcomes.[28]

Zeta potential

The zeta potential is an essential characteristic of the stability and biological interactions of nanoparticles. Particles that have a zeta potential in the range of 20–30 mV are seen as stable,[29] due to satisfactory electrostatic repulsion; whereas particles with a zeta potential below ± 10 mV would be expected to aggregate and therefore be unstable. Electrostatic interactions are particularly important in regulating the adhesion of nanoparticles to endothelial cells or vascular tissues. Cationic nanoparticles, when compared with neutrally or negatively charge nanoparticles, show promise for enhanced cellular uptake

and increased adhesion to vessels and thus creating better opportunities advancing for drug delivery. However, excessive surface charge induces cytotoxicity, damaging endothelial cells that are key components of vascular homeostasis. Negative effects from nanoparticles with high charge include oedema formation and thrombus formation. As a result, the zeta potential must be carefully optimised for successful drug delivery by balancing stability, cellular uptake and safety.[30]

Drug encapsulation and release kinetics

Sustained and controlled drug release is an important property of nanoparticle-based delivery systems that allows therapeutic concentrations at the target location to be maintained for longer period of time. This property is critical in many cardiovascular applications like restenosis, where prolonged anticancer therapy allows antioxidant activity to provide continued vascular protection and suppress pathological cardiac remodelling.[31] The sustained release slope improves the consistent nature of the release so that it can minimise frequency of dosing which decrease systemic exposure and risk of local toxicity associated with burst release. However, if release kinetics are not well-controlled, nanoparticles are prone to very rapid degradation and uncontrolled drug release, leading to excessive local concentration and toxic effects.[32] Therefore, the preparation of formulations with consistent release control following drug release is important so that therapeutic efficacy can be optimised and patient safety can be ensured.

Surface functionalisation

The surface-functionalisation of nanoparticles has a prominent role in controlling their biological interactions and circulation time and targeting efficacy. PEGylation and conjugating specific ligands are common practices to impart a "stealth" effect which limits opsonisation by plasma proteins and extends the length of systemic circulation.[33] Ligand-mediated functionalisation allows for active targeting and allows ligands to bind selectively to receptors on endothelial cells so site-specific drug targeting is facilitated and off-target effects are reduced. These modifications offer increased therapeutic efficacy and will avoid premature elimination from systemic circulation. However, there are still issues related to reproducibility, limiting non-specific-binding and long-term biocompatibility.

Types of polymers and their biodegradability

Natural and synthetic polymers are typically used for surface-modified drug delivery with nanoparticles due to their intrinsic biocompatibility and adjustable degradation profiles.[34] Biodegradability is advantageous as these polymers will degrade into nontoxic metabolites, leading to enhanced safety and limited accumulation in tissues over long time periods. Furthermore, the ability to provide continual and local drug delivery is highly desirable in application areas such as cardiovascular disease, where the main goal is to prevent restenosis through the constant maintenance of therapeutic levels. Poly(lactic-co-glycolic acid) (PLGA) is widely used as a biodegradable polymer, but its use in a nanoparticle formulation does not itself establish regulatory approval; drug deposition and vascular responses depend on the specific formulation.[35] In extreme cases, lack of degradation of the drug can result in incomplete drug release, low drug effectiveness and local toxicity.

Crystallinity and glass transition

The ability to design nanoscale drug carriers can change the structural characteristics of formulations, such as crystallinity and the glass transition temperature, which defines the range of motion between molecules in the polymeric matrix and determines whether a drug delivery system is rigid or flexible by controlling molecular mobility.[36] The design characteristics of a drug carrier influence its release profile, which is important for successful drug delivery. If crystallinity and the glass transition can be controlled adequately in the composition of a drug carrier, it can provide a time-dependent sustained release profile. This is advantageous because cardiovascular therapies often require sustained drug activity and prolonged delivery effect.[37] However, producing drug carriers at the nanometre scale is technically demanding; even small changes in the production process will yield different batches. Without the capability to reproduce the same formulations, drug delivery reliability is affected, hence nanoscale design must be tightly controlled to demonstrate predictable and safe therapeutic outcomes. These characteristics are summarised in Table 1.

Mechanisms of delivery

Drugs are delivered by PNPs through a coordinated sequence of actions that maximise thera-

Table 1: Properties, mechanistic roles and therapeutic implications of polymeric nanoparticles in cardiovascular disease

Property	Feature	Mechanistic role	Potential cardiovascular relevance	Potential advantages	Limitations	Ref.
Particle size	10–100 nm	Influences cellular uptake, tissue penetration and arterial-wall retention	Small size may facilitate penetration across endothelial layers and improve local drug delivery and dissolution	Improved cellular uptake, penetration and bioavailability	Very small particles may be cleared rapidly, whereas larger particles may penetrate poorly	[38, 39]
Particle shape	Spherical particles with smooth or rough surfaces	Influences endothelial uptake and interactions with stents	Nanostructured stents may promote endothelialisation while limiting smooth-muscle-cell proliferation	May better resemble tissue topography and promote endothelial repair	Preparation may be difficult; evidence for shape-specific effects is limited	[40, 41]
Zeta potential	20–30 mV for stable particles; 10 mV for unstable particles	Electrostatic interaction with endothelial cells and tissues	Cationic particles may increase cellular uptake but uncontrolled surface charge may damage tissue	May increase vascular adhesion and cellular uptake	Risk of oedema and thrombosis	[42, 43]
Drug encapsulation and release kinetics	Sustained or controlled release	Maintains local therapeutic drug concentrations	Prolonged local drug release may benefit restenosis treatment	May reduce dosing frequency and local toxicity	Burst release and uncontrolled degradation may cause toxicity	[44, 45]
Surface functionalisation	PEGylation and ligand conjugation	May reduce clearance and facilitate targeted delivery	Reduced opsonisation may prolong circulation; ligands may facilitate endothelial targeting	Potentially improved delivery and reduced clearance	Reproducibility, non-specific binding and biocompatibility remain concerns	[46, 47]
Polymer type and biodegradability	Natural or synthetic polymers with variable degradation profiles	Breakdown into metabolites	Sustained drug release may help suppress restenosis; PLGA deposition may affect vascular stenosis	Biocompatibility and availability of established polymers	Incomplete release or uncontrolled degradation may cause toxicity	[48, 49]
Crystallinity and glass transition	Nanoscale particles may differ in crystallinity and glass transition	Alter molecular mobility, matrix stiffness and drug release	Controlled crystallinity and glass transition may alter release profiles	Potential for sustained drug release	Batch-to-batch variation and limited reproducibility	[16]

PNPs: polymeric nanoparticles; PEG: polyethylene glycol; PLGA: poly(lactic-co-glycolic acid).

peutic effectiveness and minimise systemic adverse effects.[50] The process begins with active compounds being encapsulated, adsorbed or conjugated within the polymeric matrix.[51] This increases the apparent solubility of poorly water-soluble drugs and protects them from hydrolytic or enzymatic degradation. After administration, circulation and stability are influenced by nanoscale particle size and surface characteristics: particles in the optimal size range avoid rapid renal clearance, while surface modifications such as PEGylation provide a "stealth effect" by reducing opsonisation and immune recognition, thereby extending systemic half-life.[52] Targeting then occurs by two complementary mechanisms. Passive targeting exploits the enhanced permeability and retention effect, enabling accumulation in inflamed or diseased tissues with leaky vasculature and impaired lymphatic drainage, while active targeting involves functionalisation of nanoparticles with ligands, antibodies, peptides or aptamers that bind receptors overexpressed on pathological cells such as vascular smooth muscle cells, endothelial cells and macrophages

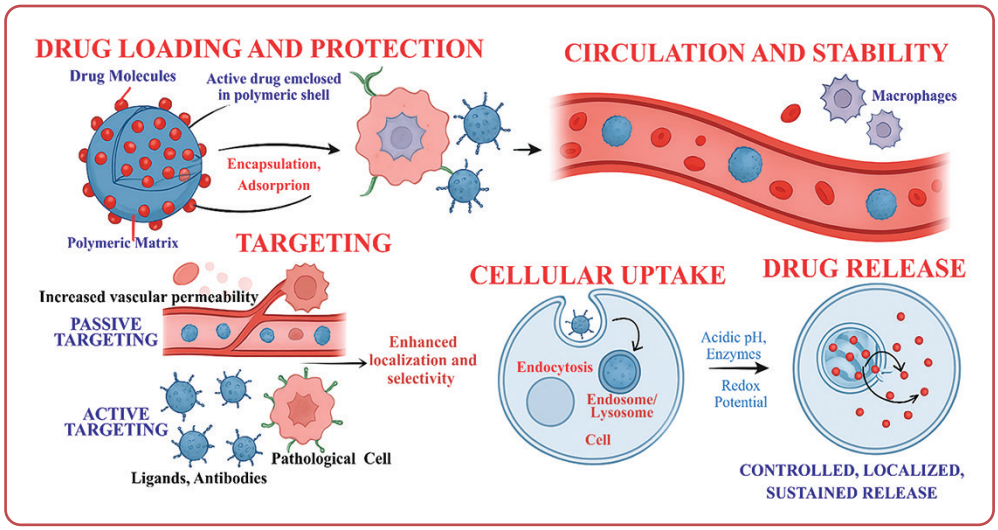


Figure 3: Schematic representation of the drug delivery mechanism via polymeric nanoparticles
Polymeric nanoparticles protect loaded drugs and use surface modifications to achieve prolonged circulation by evading immune recognition and specifically target disease sites through passive enhanced permeability and active ligand-binding mechanisms. Cellular uptake via endocytosis leads to controlled, localised drug release triggered by internal stimuli within endosomes.

to enhance site selectivity and cellular localisation.[53] Upon reaching the target, nanoparticles are primarily internalised by cells via endocytic processes and transported to endosomal and lysosomal compartments. In these compartments, controlled drug release can be triggered by the local microenvironment, for example acidic pH, enzyme activity or redox potential, via diffusion from the nanoparticle matrix and by polymer degradation.[54] Compared with conventional drug delivery methods, such localised and sustained release can improve therapeutic outcomes, reduce systemic toxicity, increase drug uptake and maintain therapeutic concentrations at the diseased site, as shown in Figure 3.

In medicinal applications, PNPs have become versatile carriers with several advantages. They can be manufactured at scale using flexible and cost-effective fabrication techniques and can improve the stability of labile medicinal ingredients.[55] Such nanoparticles may deliver higher local drug concentrations to the site of action than conventional oral or intravenous administration. Their capacity to tune release kinetics through polymer selection renders them useful in areas such as targeted antibiotic delivery, cancer therapy, vaccine development and contraceptive delivery. Their adaptability also permits incorporation into broader biomedical applications, for example tissue engineering.

Applications of polymeric nanoparticles in cardiovascular disease

Atherosclerosis

Atherosclerosis is a prolonged continuous condition in which cholesterol and other lipids accumulate in the arterial wall, forming plaques that solidify and narrow the vascular lumen, thereby reducing blood flow and predisposing to major events such as myocardial infarction.[56] The earliest features are endothelial dysfunction and lipoprotein retention within the arterial intima. oxidised lipoproteins trigger an inflammatory response that recruits monocytes and T lymphocytes to the vessel wall. Monocytes differentiate into macrophages that take up lipids, forming foam cells and releasing enzymes and cytokines that promote plaque development. Smooth muscle cells migrate into the intima and synthesise extracellular matrix, forming a fibrous cap over the lipid core. Plaques may accumulate and become unstable; rupture exposes thrombogenic material and provokes thrombosis.[57] Superficial endothelial erosion can also lead to thrombus formation. Systemic factors such as interleukin-1, interleukin-6 and clonal haematopoiesis increase inflammation and accelerate disease progression. Various pharmacological approaches target these processes; for example, simvastatin and atorvastatin have been formulated with PLGA

and PEG polymers in preclinical studies to enhance delivery to macrophages and plaques, to reduce LDL uptake, suppress inflammation and promote plaque stabilisation.

Myocardial infarction

Myocardial infarction is described as an acute injury of the myocardium that is identified by a rise or fall in cardiac troponin levels, with at least one value above the 99th percentile upper reference limit, together with clinical evidence of acute ischaemia. Type 1 MI is caused by plaque disruption with thrombosis, Type 2 MI is caused by an imbalance between oxygen supply and demand in the absence of acute thrombosis, Type 3 MI is sudden cardiac death and Types 4 and 5 MI are procedure related, concerning percutaneous coronary intervention and coronary artery bypass grafting.[58] MI results when blood supply to the heart muscle is lost, most often because an atherosclerotic plaque ruptures and the ensuing ischaemia damages and kills cardiomyocytes. Although revascularisation restores blood supply, it may also exacerbate injury through ischaemia–reperfusion damage. Apoptotic and necrotic cell death pathways are activated, mitochondrial dysfunction with ATP depletion occurs and excessive reactive oxygen species production leads to oxidative stress.[59] Tissue damage is further amplified by inflammatory responses characterised by leukocyte recruitment and cytokines including TNF-α and IL-6. Epigenetic factors such as DNA methylation, histone modifications and noncoding RNAs regulate these processes and can intensify injury; together these events increase infarct size and impair cardiac function.[60] Methotrexate, docetaxel and various growth factors have been incorporated into PLGA, PCL and polydopamine polymeric carriers for experimental treatment of MI, with drug delivery to the infarcted myocardium intended to provide sustained release to suppress inflammation and fibrosis. Figure 4 demonstrates the role of polymeric nanoparticles in the treatment of cardiovascular diseases.

Thrombosis

Thrombosis denotes the development of a blood clot within a blood vessel, predominantly in arteries and veins, that impedes blood flow and leads to various cardiac complications. Three primary factors contribute to thrombosis: abnormal blood flow, increased coagulation tendency and vessel wall rupture. Arterial thrombi are largely composed of platelets, are often precipitated by rupture of an atherosclerotic plaque and can result in myocardial infarction and stroke.[61] Venous thrombosis arises from coagulation abnormalities and stagnant blood flow, producing clots rich in fibrin and red blood cells that can embolise to the lungs and cause pulmonary embolism. Thrombosis represents a significant cardiovascular concern because thrombi vary in composition and structure according to the type of vessel and its haemodynamic conditions. Virchow's triad—stasis, endothelial injury and hypercoagulability—explains why thrombosis occurs when the balance between procoagulant and anticoagulant systems is disturbed.[62] Venous stasis reduces oxygen delivery and blood flow, producing local hypoxaemia; this upregulates plasminogen

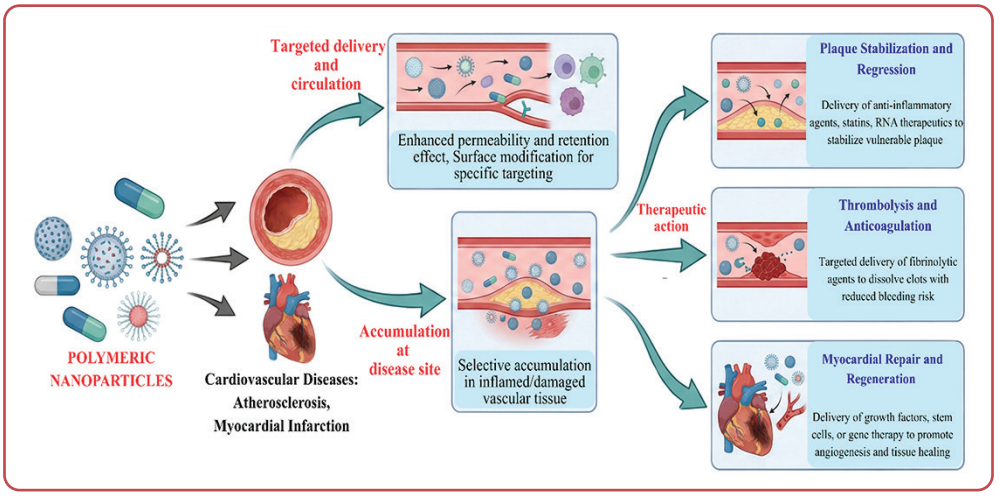


Figure 4: Polymeric nanoparticles in cardiovascular disease treatment

The figure illustrates the role of polymeric nanoparticles in targeted delivery and accumulation at the disease site. They exert therapeutic effects through plaque stabilisation, thrombolysis and myocardial repair by delivering specific agents and provide controlled drug release, enhanced stability and reduced systemic toxicity.

activator inhibitor-1 and tissue factor, enhancing coagulation and suppressing fibrinolysis. Moreover, stasis impairs clearance of leukocytes, coagulation factors and activated platelets, thereby promoting thrombus formation. Endothelial injury accelerates platelet adhesion and leukocyte recruitment and promotes release of von Willebrand factor and P-selectin.[63] Complement activation and neutrophil extracellular traps further promote coagulation and inflammation increases thrombotic risk via cytokines such as interleukin-1β and interleukin-6. Genetic and acquired risk factors, including immobility, factor V Leiden and deficiencies of protein C or protein S, increase susceptibility. Heparin- and streptokinase-loaded PLGA and chitosan formulations have been investigated for thrombosis treatment.

Hypertension

Hypertension is defined as a chronic rise of blood pressure (systolic pressure ≥ 140 mm Hg or diastolic pressure ≥ 90 mm Hg) and is a major risk factor for cardiovascular, cerebrovascular and renal disorders.[64] Lifestyle modification is the cornerstone of care; first-line pharmacological treatments include diuretics, ACE inhibitors, angiotensin receptor blockers and calcium channel blockers. Alternatives are being expanded by device-based therapies such as renal denervation. Because of gaps in knowledge, diagnosis, treatment and follow-up, control rates remain low despite the condition being preventable and treatable.[65] Genetic, environmental, vascular, renal and neurohormonal factors all contribute to hypertension. Impaired renal pressure natriuresis and kidney dysfunction are central to its development and are frequently exacerbated by obesity, excessive salt consumption and inflammation.[66] Sympathetic overactivity contributes to activation of the renin-angiotensin-aldosterone system, drives renal salt retention and contributes to hypertension associated with obesity and sleep apnoea.[67] Endothelial dysfunction, low nitric oxide levels, insulin resistance and metabolic disorders contribute to increased vascular resistance, while excess cardiac output maintains elevated pressure. Altered autonomic tone and cortical–hypothalamic dysregulation reinforces chronic hypertension, supporting its characterisation as a systemic condition rather than one confined to the circulatory system.[68] Several angiotensin-converting enzyme inhibitors, calcium channel blockers, aldosterone antagonists and beta blockers are used in the treatment of hypertension and act principally by reducing vasoconstriction. Drugs such as captopril, enalapril and nifedipine have been formulated with chitosan and PLGA in sustained-release preparations intended to improve absorption; such preclinical polymeric nanoparticle studies report outcomes including sustained release and effects described as reactive oxygen species scavenging and enhanced vasodilation, but these findings do not establish clinical benefit.

In-stent restenosis (ISR)

Restenosis denotes pathological re-narrowing of an artery that has already undergone surgery to restore patency, for example through angioplasty, stenting or surgical reconstruction. It is caused by inappropriate tissue growth, fibrosis and thrombus formation, which gradually lowers the vessel lumen, impedes blood flow and may result in the recurrence of symptoms. When this process occurs inside a vascular stent, it is called ISR.[69] ISR can result from an excessive vascular healing response caused by arterial damage after stent insertion. Mechanical disruption of the endothelium exposes the subendothelial matrix, leading to platelet adhesion, activation and the release of pro-thrombotic and pro-inflammatory mediators such as thromboxane A2, platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β) and interleukins.[70] These mediators set off a local inflammatory cascade, attracting leukocytes, mast cells and bone marrow-derived progenitor cells to the wounded location. Concurrently, vascular smooth muscle cells transition from contractile to synthetic phenotypes, increasing migration and proliferation within the intimal layer. The synthetic SMCs secrete extracellular matrix components, resulting in the progressive formation of neointimal hyperplasia, which is a major mechanism of ISR and causes luminal constriction. Delayed re-endothelialisation and chronic inflammatory responses in drug-eluting stents can result in neo-atherosclerosis, which is defined by lipid-laden macrophage infiltration and necrotic core development inside the stented segment.[71] This multifactorial cascade, which includes endothelial damage, inflammation, smooth muscle cell proliferation and extracellular matrix deposition, results in restenosis following stent placement. Drugs such as paclitaxel loaded in PLGA and PEG polymers have been investigated for restenosis treatment; a protein, described as collagen, binds to the deteriorated and injured artery and may be used as a substrate to inhibit smooth muscle cell growth for controlled drug delivery.

Stroke

Stroke is a sudden focal neurological deficit caused by vascular injury to the central nervous system, including cerebral infarction (ischaemic stroke) and intracerebral haemorrhage.[72] It is not a single disease, but rather a collection of several risk factors, disease processes and mechanisms that compromise cerebral blood flow or integrity. Stroke pathophysiology comprises multiple vascular and neuronal pathways that cause brain injury. Ischaemic stroke is caused by thrombotic or embolic blockage, which results in decreased blood flow, oxygen deprivation, necrosis, excitotoxicity, oxidative stress, calcium overload, inflammation and blood-brain barrier disruption.[73] Haemorrhagic stroke is caused by vascular rupture, which produces toxic effects such as blood accumulation, mechanical pressure and neural damage. Conventional risk factors include hypertension, diabetes, atrial fibrillation, hyperlipidaemia, smoking and inactivity, although genetic predisposition, neuroinflammation and environmental variables all play important roles.[74] The interaction of vascular dysfunction, immune cell activation (microglia, astrocytes and leukocytes), cytokine and chemokine release and cellular stress cascades make stroke a complex and diverse disease. Despite breakthroughs in thrombolysis and mechanical thrombectomy, therapeutic constraints and partial replication pose a challenge to establishing tailored and effective therapies.[75] ROS-responsive PEG–PTT carriers containing glyburide have been proposed for stroke, with blood–brain barrier penetration and reduced oedema proposed as potential advantages. The reported nanocarrier approaches are summarised in Table 2.

Table 2: Drug-loaded polymeric nanoparticles and reported therapeutic outcomes

Drug class	Examples	Polymer or formulation	Targeted condition	Proposed mechanism	Reported or proposed outcomes	Ref.
Statins	Simvastatin, atorvastatin	PLGA and PEG	Atherosclerosis	Targeting of macrophages and plaques may reduce LDL uptake and inflammation	Potential plaque stabilisation and improved drug stability with reduced toxicity	[76, 77]
Taxanes	Paclitaxel	PLGA and PEG–lipid PNPs	Restenosis	Collagen IV binding at injured arterial sites may support controlled release and inhibit smooth-muscle-cell proliferation	Reported 50 % reduction in restenosis and improved tolerability	[48, 78]
Sulfonylureas	Glyburide	ROS-responsive PEG–PTT nanoparticles conjugated with AMD3100	Stroke	ROS-triggered changes may facilitate penetration across the blood–brain barrier; CXCR4 targeting may reduce oedema	Reported reduction in oedema and ROS with improved neurological recovery	[79]
Thrombolytic agents	Heparin, streptokinase	PLGA and chitosan	Thrombosis	Encapsulation may protect the drug from degradation and prolong circulation; VCAM-1 has been proposed as a target	Potential reduction in bleeding risk and faster clot lysis	[80, 81]
Antihypertensive agents	Captopril, enalapril, losartan, nifedipine	PLGA and chitosan	Hypertension	Sustained release may improve absorption; ROS scavenging may promote vasodilatation	Potentially improved bioavailability, blood-pressure control and stability	[82]

Anti-inflammatory agents	Methotrexate, docetaxel, growth factors	PLGA, PCL and polydopamine	Myocardial infarction	Sustained local delivery to injured myocardium may reduce inflammation and fibrosis and support tissue repair	Potential reduction in infarct size and improvement in remodelling and cardiac repair	[83]
Antioxidants	Resveratrol, quercetin, curcumin, cherry extracts	PLGA and chitosan	Coronary artery disease	Proposed increases in eNOS activity and reductions in ROS	Potential reduction in oxidative stress with vasodilatation and cardioprotection	[84]

PNPs: polymeric nanoparticles; PLGA: poly(lactic-co-glycolic acid); PEG: polyethylene glycol; PCL: polycaprolactone; ROS: reactive oxygen species; BBB: blood–brain barrier; CXCR4: C-X-C chemokine receptor type 4; VCAM-1: vascular cell adhesion molecule 1; MI: myocardial infarction; eNOS: endothelial nitric oxide synthase.

Challenges

Biological limitations

PNPs confront significant biological challenges that restrict their therapeutic potential in cardiovascular disorders. The reticuloendothelial system reduces systemic circulation via rapid immune identification, opsonisation and clearance. Crossing specialised barriers, such as the vascular endothelium, thrombus sites, or the blood-brain barrier, remains difficult and patient-specific characteristics such as age, gender and comorbidities influence drug distribution and treatment response.

Physicochemical limitations

Designing PNP formulations is complex from a physicochemical perspective. Particle size influences circulation and penetration, with small particles causing rapid clearance and large particles impeding transport. Surface charge and shape influence cellular uptake, but if not tuned correctly they can cause cytotoxicity or thrombosis. Controlled and sustained drug release is critical, since uncontrolled release can cause toxicity. Synthetic polymers offer tunability but may be inflammatory or toxic, whereas natural polymers are biocompatible but exhibit variability.

Manufacturing and scalability

Large-scale production of PNPs remains problematic owing to difficulties in maintaining consistent size, shape and drug loading. Batch-to-batch variability, particularly in crystallinity and glass transition characteristics, undermines reproducibility and quality. High production costs and a lack of standardised, cost-effective fabrication procedures further impede clinical translation and widespread availability.

Clinical challenges

Despite encouraging preclinical outcomes, translation into human applications is limited. Differences between animal models and human physiology diminish predictive accuracy, while the long-term safety, biodegradation and toxicity profiles of particular polymers are often unknown. Clinical approval is delayed by onerous regulatory criteria. Furthermore, cardiovascular disorders are heterogeneous, necessitating disease-specific solutions rather than general nanoparticle systems.

Patient related issues

Patient characteristics have a considerable impact on the success of polymeric nanoparticles. Obesity, smoking and poor diet all influence disease progression and nanoparticle function. Moreover, differences in healthcare access and pricing in low- and middle-income nations compound the worldwide cardiovascular burden, making equitable adoption of sophisticated nanotherapies an urgent concern.

Translational limitations

PNPs and related encapsulation platforms offer meaningful opportunities for improving CV delivery. However, several translational limitations must be considered before these systems can be reliably implemented in routine clinical practice. Safety and toxicity remain primary concerns because nanocarrier behaviour is strongly influenced by polymer chemistry, surface charge, degradation products and formulation excipients. Depending on these characteristics, PNPs may provoke immunogenicity, complement activation, or inflammatory responses and in some settings

may contribute to infusion related reactions. In addition, off target accumulation, particularly in the liver, spleen and kidneys, can lead to organ specific toxicity, while repeated or prolonged exposure raises questions regarding chronic tolerability and potential bioaccumulation. A second major barrier is the pharmacokinetic (PK) and biodistribution complexity of nanomedicines, which often differs markedly from conventional small molecule formulations. NPs fate can be shaped by protein corona formation, opsonisation and uptake by the reticuloendothelial system, creating nonlinear PK profiles and substantial interindividual variability. Moreover, CV pathology itself is heterogeneous: vascular permeability, plaque architecture, ischaemic tissue perfusion and inflammatory status vary widely across patients and disease stages, which may result in target delivery being inconsistent and penetration or retention at the intended site can be difficult to predict. These factors can complicate translation of promising preclinical results to humans, where coexisting multimorbidity conditions (eg, diabetes, renal impairment) and concomitant medications may further alter distribution, clearance and therapeutic window.

Moreover, successful clinical implementation is constrained by manufacturing and regulatory requirements. Scale up demands control of critical quality attributes including particle size distribution, polydispersity, surface charge, drug loading, release kinetics, sterility and long-term stability, because relatively small batch to batch variations may alter biodistribution, efficacy and safety. Collectively, these considerations increase development time and cost and highlight the importance of designing PNPs systems with safety, manufacturability, reproducibility and regulatory strategy integrated from the earliest stages.

Future perspectives

The future of PNPs in cardiovascular therapy is to improve their biological performance, physicochemical design and clinical translation. Advanced strategies must overcome immune clearance and effectively cross obstacles such as the endothelium, thrombi and blood-brain barrier, while individualised techniques based on age, gender and comorbidities will improve precision. Optimising particle size, charge and shape, as well as developing hybrid polymers that combine the biocompatibility of natural materials with the tunability of synthetics, will result in safer and more efficient drug administration. Equally crucial is the development of scalable and reproducible production processes that use technologies like microfluidics and automated synthesis to reduce variability and costs. To accelerate approval, translational development will rely on improved preclinical models that mirror human cardiovascular illness, long-term safety studies and streamlined regulatory processes. Finally, integrating patient-related approaches ensures affordability, accessibility and lifestyle compatibility which are critical in reducing the disproportionate burden of CVDs in low and middle-income populations and establishing PNPs as next-generation cardiovascular therapeutics.

Conclusion

In cardiovascular treatments, PNPs represent a investigational platform because they provide multipurpose platforms that may address some limitations of traditional drug delivery. Their variable physicochemical properties allow for precise control of drug encapsulation, release kinetics and bio-distribution, while surface functionalisation allows for active and passive targeting of pathological sites such as inflamed endothelium, atherosclerotic plaques, ischaemic myocardium and thrombotic lesions. Preclinical findings suggest possible improvements in drug delivery, reducing systemic toxicity and enabling site-specific interventions for a broad range of cardiovascular diseases. However, obstacles such as immune clearance, interpatient heterogeneity, large-scale repeatability and severe regulatory constraints continue to impede clinical translation.

Future advancement will be dependent on the integration of improved biomaterials, hybrid natural-synthetic polymers and smart stimuli-responsive systems with scalable manufacturing methods such as microfluidics and continuous-flow synthesis. Furthermore, developing predictive in vitro and in vivo models that closely resemble human cardiovascular pathophysiology will be critical for expediting clinical translation. PNPs may contribute to cardiovascular nanomedicine by bridging these scientific and translational divides. This would enable the transition from experimental structures to clinically feasible therapeutics that require testing before any population-level benefit can be inferred.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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