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Review Article

The Role of Nanocarriers in Hypertension

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ABSTRACT

Hypertension remains a major modifiable risk factor for cardiovascular morbidity and mortality worldwide. Despite the availability of numerous antihypertensive drugs, poor solubility, limited bioavailability, and low patient adherence continue to hinder optimal blood pressure control. In recent years, nanocarrier-based technologies have emerged as promising tools to overcome these limitations while also offering new opportunities for early diagnosis. Nanocarriers, including lipid-based, polymeric, inorganic, and hybrid systems, enhance drug solubility, stability, and targeted delivery, allowing for sustained therapeutic effects with reduced adverse reactions. Moreover, advances in nanomaterial-based biosensors, particularly those employing gold and magnetic nanoparticles, have enabled ultrasensitive detection of hypertension-related biomarkers such as microRNAs, supporting earlier and more precise diagnosis. Innovative approaches, including gene therapy, nitric oxide-releasing nanoplatforms, and pressure-responsive smart nanocarriers, further expand the therapeutic scope of nanotechnology in hypertension management. However, despite promising preclinical outcomes, translation into clinical practice remains limited by safety concerns, scalability, and regulatory challenges. Overall, nanocarriers represent a multidisciplinary advancement that holds great potential to revolutionize hypertension care through improved diagnostics, targeted therapy, and personalized treatment strategies.

INTRODUCTION

Hypertension remains a leading preventable contributor to cardiovascular disease (CVD), often progressing silently without symptoms.[1] In 2020, approximately 30.6% of adults worldwide were affected, with nearly three-quarters residing in low- and middle-income countries.[2] Despite global efforts, it continues to be the foremost risk factor for premature mortality, accounting for an estimated 10.8 million preventable deaths and 235 million years of life lost or lived with disability

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annually.[3] In line with the World Health Organization's target to reduce hypertension prevalence by 33% between 2010 and 2030, effective prevention is essential to mitigate end-organ damage and curb CVD progression.[4] Current management strategies emphasize the integration of pharmacological therapy with lifestyle modification as the cornerstone of hypertension control.[5]

Several classes of antihypertensive agents act through diverse mechanisms, yet many suffer from poor water solubility, limited membrane permeability, and low bioavailability, ultimately reducing their therapeutic efficacy. Their pharmacokinetic profiles are often further hindered by extensive first-pass metabolism and efflux via P-glycoprotein (P-gp). Moreover, short half-lives and frequent dosing regimens contribute to poor patient compliance, while unavoidable adverse effects may further discourage adherence.[6,7] Consequently, despite the availability of various pharmacological options, global hypertension control remains suboptimal, which only 19.1% of patients were controlled in 2020, with an even lower rate of 14.6% in low- and middle-income countries where the burden of hypertension is highest.[2] These challenges underscore the urgent need for innovative therapeutic strategies that enhance drug bioavailability, minimize side effects, and improve patient adherence to antihypertensive therapy.

In recent decades, nanoparticle-based systems have emerged as promising platforms for gene therapy and drug delivery.[8] These systems may involve a drug encapsulated within a nanostructured shell, immobilized in a polymeric matrix, or adsorbed onto a coated carrier surface.[7] Nanocarriers enhance drug performance by improving molecular targeting, stability, solubility, and absorption, thereby extending bioavailability and therapeutic efficacy. They also protect active compounds from enzymatic degradation, reduce renal clearance, and minimize systemic side effects. By enabling controlled and site-specific drug release, nanocarriers offer a potential alternative to conventional antihypertensive formulations.[8] This review highlights recent advancements in nanocarrier applications for hypertension, including diagnostic and drug delivery systems, which may reduce morbidity and mortality.

MATERIALS AND METHODS

A comprehensive literature review was conducted to identify the application of nanocarrier in hypertension. Studies were eligible for inclusion if they were published in English and focused on nanocarrier in hypertension, regardless of study design (review, experimental, or observational). Exclusion criteria included studies not focused on diagnostic and/or drug delivery system, those lacking discussion of nanocarrier applications, and duplications.

The search was performed across multiple databases, including Google Scholar, PubMed, PROQUEST, and ScienceDirect, to identify relevant articles published between January 2016 and October 2025. Search terms encompassed "nanocarrier" "nanoparticle," "hypertension," "cardiovascular disease" and "drug delivery system".

After retrieval, duplicate records were removed, followed by title and abstract screening to identify potentially relevant studies. Full-text articles were then reviewed to confirm eligibility. Discrepancies during the selection process were resolved through discussion and consensus.

RESULTS AND DISCUSSION

How Nanocarrier Works

Nanocarriers are colloidal nanoparticles designed to deliver therapeutic agents or other substances to specific target sites. Typically ranging from 1 to 100 nanometers in diameter, those intended for therapeutic applications must remain below 200 nm to ensure passage through microcapillaries. Their key advantages include improved biodistribution, pharmacokinetics, stability, and solubility, along with reduced toxicity and targeted drug release. By modifying surface characteristics, composition, and shape, nanocarriers can achieve enhanced therapeutic efficacy with minimal adverse effects.[9] Collectively, these features underscore their significant potential in advancing drug delivery systems.

Nanocarriers can be broadly categorized into three types: organic, inorganic, and hybrid systems. Organic nanocarriers are highly versatile, exhibit low toxicity, and can efficiently conjugate various drugs and ligands for targeted delivery. In contrast, inorganic nanocarriers offer tunable physicochemical properties advantageous for controlled delivery and imaging applications. Hybrid nanocarriers integrate two or more components from organic and/or inorganic systems. By combining distinct materials, hybrid nanocarriers harness the complementary benefits of each, resulting in enhanced stability, functionality, and therapeutic performance.[9]

Several drug-loading strategies have been developed for nanocarrier-based delivery systems, including molecular-level, surface, matrix, and cavity loading mechanisms. In molecular-level loading, drug molecules interact with host structures such as small molecules, polymers, or peptides through either physical (e.g., host–guest self-assembly, dendrimer complexes) or chemical (e.g., polymer–drug conjugates) interactions. Surface loading involves the adsorption of drugs, prodrugs, or drug complexes onto the nanoparticle surface. In matrix loading systems, the drug is distributed within the bulk of the carrier material, and release occurs gradually as the matrix dissolves or degrades. Drugs may be incorporated by co-precipitation with excipients (preloading) or by diffusion into preformed matrices (postloading). Finally, cavity loading systems encapsulate drugs within hollow structures, such as vesicles or capsules, where release is triggered by the rupture or pore opening of the carrier shell.[7]

In general, drug-loaded nanocarriers exhibit two primary release profiles: continual and triggered release. In continual release, drug diffusion begins immediately after administration and persists throughout the delivery process. The release rate is influenced by factors such as adsorption affinity, barrier thickness or porosity, and the degradation or dissolution rate of the matrix. In contrast, triggered release occurs only in response to specific stimuli, either external (e.g., light, temperature, ultrasound, or magnetic field) or internal (e.g., variations in pH, enzymatic activity, or redox conditions). This controlled and stimulus-responsive behavior allows for precise spatial and temporal drug delivery, enhancing therapeutic efficacy while minimizing systemic side effects.[7]

Nanocarriers can be designed to achieve targeted drug delivery through several mechanisms. Direct administration of therapeutic nanocarriers to a specific site is often challenging due to the systemic nature of many diseases and the difficulty in localizing pathological regions. A noninvasive alternative involves the use of magnetic nanocarriers guided by an external magnetic field, a technique validated in both in vitro and in vivo studies. While this approach enhances cellular uptake and site-specific accumulation, its

effectiveness depends on multiple factors, including magnetic field strength, particle characteristics, vascularization, tissue depth, and blood flow rate.[9]

Active targeting offers another strategy, in which nanocarriers are functionalized with ligands that specifically bind to receptors on diseased cells, enabling selective retention and cellular internalization. In contrast, passive targeting relies on the enhanced permeability and retention (EPR) effect, where leaky vasculature in diseased or necrotic tissues permits larger nanocarriers to extravasate and accumulate in the interstitial space. Despite its utility, passive targeting is not universally effective, as not all pathological tissues exhibit increased permeability. Moreover, the EPR effect can be hindered by high interstitial fluid pressure, tissue hypoxia, extracellular matrix complexity, limited endosomal escape, and variable endothelial gap sizes, all of which reduce drug penetration and retention efficiency.[9]

Current Applications Of Nanocarriers In Hypertension

This review discusses the application of nanocarriers in hypertension therapy, categorized according to their composition: lipid-based, polymer-based, and inorganic systems. Each type offers distinct physicochemical properties that influence drug loading capacity, release profile, biocompatibility, and therapeutic efficacy in antihypertensive treatment (Table 1). The application of nanocarrier as drug delivery system is depicted in Table 2.

Table 1. Advantages and Limitations of Various Nanocarrier Systems

	Advantages	Limitations
Lipid-based nanocarrier		
Liposome	High biocompatibility and low toxicity; capable of encapsulating both hydrophilic and lipophilic drugs; improved bioavailability and targeted delivery.	Short systemic half-life; potential drug leakage and fusion; scalability and stability challenges.
SLN	Controlled drug release; protection of labile drugs; good biocompatibility and low cytotoxicity.	Limited drug loading capacity; potential particle aggregation; risk of burst release.
NLC	Enhanced stability and entrapment efficiency; higher drug loading than SLN; minimized drug expulsion during storage.	Complex formulation process; possible long-term instability under varying temperatures.
Polymer-based nanocarrier		
Polymeric nanoparticle	High structural stability; controlled and sustained release; tunable surface modification for targeted delivery.	Possible polymer-related toxicity; batch-to-batch variability; complex degradation behavior.
Dendrimer	Precise molecular architecture; high drug-loading capacity; potential for multifunctionalization.	High synthesis cost; dose-dependent cytotoxicity; possible cardiotoxic effects.
Polymeric micelle	Improves solubility of hydrophobic drugs; prolonged circulation; controlled release and passive targeting via EPR effect.	Low stability below critical micelle concentration; limited drug loading for hydrophilic agents.
Polypeptide based nanoparticle	Excellent biocompatibility and biodegradability; protects drugs from enzymatic degradation; prolonged half-life.	Risk of denaturation; limited large-scale reproducibility; potential immunogenicity.
Inorganic nanocarrier		

Gold nanoparticle	High surface functionalization potential; superior optical/electronic properties for biosensing and imaging.	Long-term accumulation risk; cytotoxicity at high concentrations; high production cost.
Silica nanoparticle	High surface area and pore volume; tunable release profile; good thermal and chemical stability.	Poor biodegradability; possible silica-induced inflammation; requires surface modification for safety.
Carbon-based nanocarrier	Exceptional strength, conductivity, and drug-loading potential; efficient cellular penetration.	Hydrophobicity and potential neurotoxicity; biopersistence and unclear metabolism.
Magnetic nanocarrier	Enables targeted delivery under magnetic field; useful for imaging and theranostics; good loading capacity.	Risk of oxidative stress and vascular reactivity; uncertain long-term biosafety.
Hybrid nanocarrier	Combines advantages of organic and inorganic systems; enhanced stability, multifunctionality, and controlled release; customizable for personalized therapy.	Complex synthesis and characterization; potential incompatibility between components; limited clinical data.

NLC: nanostructured lipid carrier; SLC : solid lipid nanoparticle

Table 2. The application of nanocarrier in drug delivery system of antihypertensive agent

Drugs	**Type of Nanoparticle**	**Excipient/ Absorbent used**	***In-vivo study model***	**Result**	**Ref**
Carvedilol	Polymeric nanoparticle	Chitosan	Wistar Rats	Higher bioavailability Stable formulation Good biocompatibility between the preparations and gastric mucosa	[10]
Losartan	Lipid-based	Liposome	Wistar Kyoto rats	Enhanced penetration across the blood–brain barrier	[11]
Nebivolol	Hybrid	Pluronic- and chitosan-coated liposome	-	Improved encapsulation efficiency Improved stability in gastrointestinal condition and interaction with mucin Sustained drug release over 24 hours Minimal toxicity	[12]
Hydro-chlorothiazide	Lipid-based	SLC and NLC	Caco-2 cells	Both exhibit good stability and minimal cytotoxicity NLC formulations demonstrated higher drug entrapment efficiency and more controlled release profiles than SLN formulations	[13]
Irbesartan	Polymer-based	Micelles	-	Sustained and controlled release Minimizing burst release Improving overall drug delivery efficiency	[14]
Ramipril and hydro-	Polymer-based	Dendrimer	-	Faster and complete dissolution compared to pure	[15]

chlorothiazide combination				ramipril or hydrochlorothiazide. Similar pattern of dissolution profile was established with hybrid formulations as compared to individual drug loaded dendrimers.	
Isoliensinine	Polumer-based	PEG-PLGA	AngII-induced mice	Higher cellular uptake and greater inhibition of PCNA-induced proliferation than free isoliensinine. Slower in vivo clearance and better tissue absorption. Suppressed AngII-induced increases in SBP, DBP, and MAP. Good biological safety with no effect on body weight in mice. Stronger antihypertensive effect than free isoliensinin Reduced abdominal aortic PWV and wall thickness	[16]
Verapamil	Lipid-based	Solid lipid nanocarrier	Rats with Isoproterenol-induced myocardial necrosis	Improved hemodynamic parameters and showed cardioprotective effects, also confirmed through histopathological studies and improved pharmacokinetic parameters	[17]
Valsartan	Inorganic	Mesoporous silica nanoparticle	Albino male rabbits	Highest entrapment efficiency Higher bioavailability compared to commercial Diovan tablet Longer sustained blood pressure control	[18]

AngII: angiotensin II; DBP: diastolic blood pressure; MAP: mean arterial pressure; NLC: nanostructured lipid carrier; PCNA: Proliferating Cell Nuclear Antigen; PEG: polyethylene glycol; PLGA: poly(lactic-co-glycolic acid); PWV: pulse wave velocity; SBP: systolic blood pressure; SLC: solid lipid nanoparticle

1. Lipid-based nanocarriers

Lipid-based nanoparticles represent promising carriers for delivering antihypertensive drugs with low solubility and high permeability. These lipid excipients can encapsulate a larger proportion of lipophilic drugs compared to hydrophilic ones. As the drugs are generally solubilized within the lipid matrix, the dissolution step is eliminated, improving bioavailability. Enhanced drug absorption is attributed to several mechanisms, including increased membrane fluidity, modulation of tight junctions, inhibition of P-glycoprotein efflux, alteration of cytochrome P450–mediated intestinal metabolism, and promotion of lymphatic transport that bypasses hepatic first-pass metabolism.[19] Various types of lipid-based nanoparticles employed for antihypertensive drug delivery are discussed in the following section.

A. Liposome

Liposomes are phospholipid-based spherical vesicles consisting of one or more bilayers enclosing an aqueous core, allowing simultaneous delivery of hydrophilic and lipophilic drugs to targeted sites.[9] Their high biocompatibility, low toxicity, minimal immunogenicity, and cell membrane-like properties make them one of the most widely utilized nanocarrier systems. Incorporation of cholesterol strengthens membrane rigidity, while careful phospholipid selection is essential to optimize therapeutic performance.[20] Surface modification, such as polyethylene glycol (PEG) coating, further enhances their circulation time and stability by minimizing immune recognition, resulting in PEGylated or "stealth" liposomes.[9] However, limitations such as short systemic half-life, potential drug leakage or vesicle fusion, and low encapsulation efficiency for certain compounds remain challenges. Large-scale manufacturing is also constrained by difficulties in achieving consistent size, loading capacity, and stability, leading to high production costs.[20] Despite these drawbacks, liposomal systems markedly improve drug bioavailability by protecting therapeutic agents from gastrointestinal and hepatic degradation. Moreover, functionalization with specific targeting ligands enables site-directed delivery, thereby enhancing therapeutic precision and efficacy.[6]

Losartan, an angiotensin receptor blocker, has been successfully delivered to the brain using penetratin- and transferrin-functionalized liposomes prepared via the post-insertion technique. Unlike free losartan solution, which was undetectable in rat brain tissue, the liposomal formulation achieved a significantly higher brain concentration, with an area under the curve (AUC) of 163.304 ± 13.09 and a mean residence time of 8.623 ± 0.66 hours, without any observed toxicity. The liposomes, approximately 150 nm in diameter, effectively facilitated transport across the blood–brain barrier and exhibited an entrapment efficiency of 66.8 ± 1.5%.[11] These findings highlight the potential of liposome-encapsulated losartan as a promising strategy for treating neurogenic hypertension, overcoming the limited brain permeability associated with conventional losartan formulations.

B. Solid Lipid Nanoparticle (SLN)

Solid lipid nanoparticles (SLNs) are composed of biocompatible excipients, including a lipid matrix, surfactant, and co-surfactant, that encapsulate the drug within their structure. The lipid components typically consist of fatty acids or alcohols, waxes, steroids, and mono-, di-, or triglycerides. Depending on the formulation and production parameters, the drug can be incorporated into the matrix, core, or shell of the solid lipid. Conventional SLNs, however, may be rapidly cleared by the reticuloendothelial system and present challenges in achieving sustained release, particularly for ionic or hydrophilic drugs.[9] Four structural models have been proposed for SLNs: homogeneous matrix, compound-enriched shell, drug-enriched core, and mixed type, with the final structure determined by the physicochemical properties of the drug and lipid used. Drug release from SLNs typically follows a biphasic pattern, characterized by an initial burst release followed by a prolonged release phase.[19] These nanocarriers can improve drug solubility, permeability, and bioavailability while enabling targeted delivery with minimal toxicity. Nevertheless, SLNs are also limited by potential aggregation, storage instability, and low drug loading capacity for certain compounds.[21]

Lipid-based materials often undergo physicochemical transitions, such as molecular rearrangement within the matrix, leading to a denser and more ordered structure. This

reorganization can alter particle morphology and reduce the available space for drug incorporation, resulting in unfavorable drug localization. The drug-loading capacity of SLNs depends not only on the physicochemical properties of the drug but also on the characteristics of the lipid matrix. In cases where drugs cannot be efficiently embedded within the matrix, they may adsorb onto the nanoparticle surface or cause phase separation. To minimize premature drug release during storage, the formation of a less ordered or "imperfect" matrix is preferred, which can be achieved by incorporating spatially diverse lipid molecules.[21]

A study conducted in India optimized the formulation of verapamil-loaded solid lipid nanoparticles (V-SLNs) using high-shear homogenization and ultrasonication techniques. The resulting nanoparticles exhibited an average size of 218 nm with an entrapment efficiency of 80.32%. The V-SLN formulation demonstrated a biphasic release pattern, characterized by an initial burst followed by a sustained release of 75–80% over 24 hours, consistent with the Korsmeyer–Peppas model. In an isoproterenol-induced myocardial necrosis model, oral administration of V-SLNs significantly improved hemodynamic parameters, including left ventricular end-diastolic pressure, cardiac injury biomarkers, and myocardial tissue integrity. Compared with free verapamil, V-SLNs produced a greater reduction in systolic, diastolic, and mean arterial pressures, while both formulations exhibited antihypertensive effects. Histopathological analyses further confirmed the cardioprotective effects through reduced myonecrosis, inflammation, and edema. Pharmacokinetic evaluation revealed increased $t_{1/2}$, $AUC_{0-\infty}$, and Cmax in the V-SLN group, indicating enhanced bioavailability. Notably, verapamil concentrations from the SLN formulation remained above the therapeutic level for up to 24 hours, whereas free drug was cleared within 8–12 hours.[17] These findings underscore the potential of V-SLNs as an effective oral delivery system for improving verapamil's pharmacological and therapeutic performance.

C. Nanostructured Lipid Carrier (NLC)

Unlike SLN, nanostructured lipid carriers (NLC) incorporate both solid and liquid lipids, typically in a ratio of up to 70:30, along with an aqueous phase containing surfactants.[21] The use of biologically compatible lipids minimizes toxicity and enhances formulation safety. The inclusion of liquid lipids within the solid matrix prevents complete crystallization, resulting in higher drug solubility and improved entrapment efficiency, stability, and loading capacity compared to SLNs. NLCs are generally categorized into three structural types: imperfect matrix, multiple oil/fat/water (O/F/W) type, and amorphous non-crystalline type, depending on the preparation method.[19] In contrast to SLNs, where drugs are primarily dispersed in molecular form, the structural imperfections created by the coexistence of solid and liquid lipids in NLCs generate additional void spaces that accommodate drug molecules in both molecular and amorphous states. This feature not only enhances drug incorporation but also prevents drug expulsion during storage, thereby improving formulation stability.[21]

A study comparing SLN and NLC in the formulation of hydrochlorothiazide demonstrated superior performance of NLCs over SLNs. The NLC formulation achieved approximately 90% drug entrapment compared to 80% for SLNs and released more than 90% of the drug within 300 minutes, whereas SLNs released only about 65%. This improved performance is attributed to the less ordered and less crystalline structure of NLCs,

which facilitates drug diffusion, in contrast to the densely packed lipid matrix of SLNs that restricts drug release. Both formulations exhibited good physical stability after six months of storage at 4 °C; however, SLNs showed greater drug loss (15%) compared to NLCs (<5%), indicating a lower tendency for drug expulsion in NLCs due to the presence of liquid lipids within their solid matrix.13 Cytotoxicity studies using Caco-2 intestinal cells confirmed the safety of both formulations, while cellular uptake assays revealed enhanced internalization and improved intestinal permeability of hydrochlorothiazide with both systems.[13] Overall, these findings highlight the potential of NLCs as a more effective and stable drug delivery system for hydrochlorothiazide compared to conventional SLNs.

2. Polymer-based nanocarriers

A. Polymeric nanoparticles

Polymeric nanoparticles are solid colloidal systems composed of biodegradable polymers and can be classified as either reservoir-type (nanocapsules), in which the drug is dissolved or dispersed within a polymeric core, or matrix-type (nanospheres), where the drug is uniformly entrapped within the polymer matrix. In both types, drugs may also be adsorbed or covalently attached to the nanoparticle surface. These nanocarriers can be synthesized from natural polymers such as chitosan, gelatin, albumin, collagen, and alginate, or from synthetic polymers including poly(lactic-co-glycolic acid) (PLGA), PEG, polyglutamic acid, and polycaprolactone. Compared with other nanocarrier systems, polymeric nanoparticles offer enhanced structural stability, higher drug-loading capacity, prolonged systemic circulation, and controlled drug release. Additionally, their versatile design allows for the development of multifunctional systems capable of co-delivering multiple therapeutic agents.[9] Drug release behavior from polymeric nanoparticles is influenced by several factors, including preparation method, particle size, surfactant type, polymer molecular weight, and polymer architecture.[19]

Isoliensinine, a bibenzyl isoquinoline alkaloid derived from Lotus Plumule (Nelumbo nucifera Gaertn.), exhibits antihypertensive and anti-proliferative effects on vascular smooth muscle cells. Encapsulation into PEG-PLGA nanoparticles (PEG-PLGA @isoliensinine) significantly enhanced cellular uptake, prolonged circulation, and increased tissue absorption—up to fivefold higher than the free drug ($P < 0.05$). In angiotensin II–induced hypertensive mice, PEG-PLGA @isoliensinine effectively reduced systolic, diastolic, and mean arterial pressures, pulse wave velocity, and aortic wall thickness, outperforming both free isoliensinine and valsartan. These effects were associated with inhibition of vascular cell proliferation and PI3K/AKT signaling. Histological evaluation confirmed the absence of organ toxicity, supporting its high biosafety.[16] Overall, PEG-PLGA @isoliensinine represents a promising nanocarrier-based approach to enhance the efficacy of traditional Chinese medicine for hypertension therapy.

B. Dendrimers

Dendrimers are highly branched macromolecules composed of a central core from which multiple layers of branching units extend, terminating in active surface groups. They can be synthesized from various building blocks such as nucleotides, sugars, and amino acids. Drug molecules may be encapsulated within the internal cavities of dendrimers through hydrophobic, hydrogen bonding, or other chemical interactions, or covalently attached to the terminal functional

groups.[9] Dendrimers facilitate drug delivery by several mechanisms, including core encapsulation, surface conjugation, ligand or antibody functionalization for targeted transport, and controlled release modulation based on surface chemistry and dendrimer generation.[6]

Poly(amidoamine) (PAMAM) dendrimers are among the most widely utilized dendrimers due to their controlled stepwise synthesis, which enables precise structural modification for specific applications. These nanocarriers enhance the solubility, dissolution rate, and bioavailability of hydrophobic drugs. A study investigating G4.0 and G3.5 PAMAM dendrimers as carriers for the combination of ramipril (RAPL) and hydrochlorothiazide (HCTZ) demonstrated that dendrimer-based formulations achieved faster and more complete dissolution than the pure drugs, with hybrid formulations showing similar dissolution profiles to those of individually loaded dendrimers.14 However, another study assessing G6 PAMAM dendrimers in control and diabetic rat hearts following ischemia–reperfusion injury revealed dose-dependent impairment of cardiac and vascular function in healthy rats after both acute and chronic administration. Chronic daily injections significantly ($P < 0.01$) reduced cardiac recovery in non-diabetic animals, while only coronary flow was affected in diabetic rats. Moreover, G6 PAMAM completely abolished the cardioprotective effects of pacing postconditioning in healthy hearts.[15] These findings indicate that, despite their promising drug delivery potential, the cardiotoxic effects of PAMAM dendrimers warrant careful consideration in future therapeutic applications.

C. Polymeric micelles

Micelles are colloidal aggregates formed when detergents are dispersed in water. Their formation depends on the surfactant concentration, known as the critical micellar concentration (CMC); below this threshold, micelles do not form. In addition to conventional amphiphilic micelles, polymeric micelles can be produced in selective solvents using amphiphilic block copolymers, one segment being solvent-soluble and the other insoluble. The insoluble block forms the hydrophobic core, while the soluble block forms the hydrophilic shell, resulting in stable nanoscale structures.[9] Owing to their unique core–shell architecture, polymeric micelles have been widely investigated as nanocarriers for therapeutic agents, including drugs and nucleic acids. They enhance the solubility of hydrophobic compounds, improve bioavailability, and enable controlled and targeted drug delivery.[22]

A study on irbesartan formulated with ethylene oxide–propylene oxide (EO–PO)–based polymeric nanomicelles demonstrated a significant enhancement in the drug's solubility compared to its plain solution. The EO–PO block copolymer micelles effectively encapsulate hydrophobic drugs, thereby improving their dispersion in aqueous environments. The molecular characteristics of the EO–PO copolymer, including block composition and size, influence drug-loading capacity and micellar stability. Optimizing these parameters, along with factors such as polymer concentration, drug-to-polymer ratio, and formulation conditions, allows modulation of the drug release profile. The optimized formulation exhibited sustained and controlled release of irbesartan, minimizing burst release and improving overall drug delivery efficiency.[14] Such polymeric micelle-based strategies provide a promising approach for enhancing the bioavailability and therapeutic performance of poorly water-soluble drugs like irbesartan.

D. Polypeptide/protein-based nanoparticles

Proteins possess distinctive structural and functional properties that make them valuable in both biological and industrial applications, including as fundamental materials for nanoparticle synthesis. Protein-based nanoparticles offer notable advantages as drug delivery systems due to their biocompatibility, stability, and ability to enhance drug activity. Their nanoscale size enables cellular internalization through endocytosis, while their protein matrix protects the encapsulated drug from enzymatic degradation, immune recognition, phagocytosis, and rapid renal clearance, ultimately prolonging drug half-life and therapeutic efficacy. Various proteins have been explored for nanoparticle fabrication, such as silk fibroin (from Bombyx mori), human serum albumin, gliadin (a major wheat gluten protein), legumin (from soybean or Pisum sativum L.), 30Kc19 protein (derived from silkworm hemolymph), lipoprotein, and ferritin.[23]

Chitosan, a natural polysaccharide obtained through the deacetylation of chitin, the primary component of crustacean shells, has been widely explored as a biopolymer in drug delivery systems due to its biocompatibility, biodegradability, mucoadhesiveness, non-immunogenicity, and low toxicity. Carvedilol-loaded chitosan nanoparticles (CAR-CS-NPs) were formulated using the ionic gelation method with sodium tripolyphosphate (TPP) as the crosslinking agent and optimized via a Box–Behnken design (BBD). The optimized nanoparticles exhibited a mean particle size of 102.12 nm and a drug entrapment efficiency of 71.26 ± 1.16%. Compared to the marketed formulation, which showed a rapid and nearly complete release (91.67%), the CAR-CS-NPs demonstrated a biphasic release profile with an initial burst within the first 2 hours followed by sustained release over 72 hours, reaching a cumulative release of 71.79%. This release pattern, consistent with the Higuchi diffusion model, suggests prolonged drug availability and reduced dosing frequency, thereby minimizing plasma concentration fluctuations. Furthermore, pharmacokinetic studies revealed that CAR-CS-NPs achieved higher bioavailability than the marketed tablet, with a 1.82-fold increase in Cmax and a 9.76-fold increase in AUC(0→24), confirming their potential as an effective delivery system for poorly water-soluble drugs like carvedilol.[10]

3. Inorganic nanocarriers

A. Gold nanoparticles

Gold nanoparticles exist in various anisotropic forms, including nanostars, nanorods, nanocages, nanoshells, and nanoprisms. Among their distinctive features, the unique optical properties are particularly significant, making them highly attractive for biomedical applications. These optical characteristics facilitate the conjugation of diverse biomolecules, such as enzymes, carbohydrates, fluorophores, peptides, proteins, and genes, to the nanoparticle surface, thereby enabling efficient intracellular delivery and overcoming biological barriers that typically hinder molecular transport.[9]

One promising application of gold nanoparticles (AuNPs) in hypertension management is their integration into miRNA detection systems through AuNP-based biosensing technology, which enables early and accurate diagnosis. The exceptional conductivity, high stability, large surface area, and strong light interaction of AuNPs significantly enhance biosensor sensitivity, allowing detection of miRNAs at ultra-low concentrations. Unlike conventional diagnostic methods that are often complex and equipment-dependent, AuNP-based biosensors provide a simplified, label-free detection process that

minimizes errors and streamlines analysis. Incorporating AuNPs increases target miRNA loading capacity and signal amplification, achieving detection limits in the zeptomole range with a wide dynamic range spanning several orders of magnitude. The use of magnetic composites such as MrGO@AuNPs further improves mass transfer, reduces detection time, and enhances operational efficiency. Moreover, AuNPs facilitate multiplex detection of various miRNAs through their unique optical signatures and allow operation under ambient conditions, eliminating the need for specialized temperature control. Overall, AuNP-based biosensors represent a powerful, cost-effective, and scalable diagnostic platform with high sensitivity and specificity for miRNA detection. Continued efforts in clinical validation, standardization, and regulatory compliance are essential to translate this technology into practical applications for early and personalized hypertension diagnosis.[24]

B. Silica nanoparticles (mesoporous silica nanoparticles/MSNs)

Mesoporous silica features a highly ordered honeycomb-like porous structure that allows efficient incorporation of large quantities of drug molecules. Owing to its structural simplicity, availability, and versatility, it has gained significant attention in biomedical applications. This material can encapsulate both hydrophobic and hydrophilic drugs and can be further functionalized with ligands for targeted delivery. Its key attributes, high surface area, large pore volume, biocompatibility, substantial drug-loading capacity, and thermochemical stability, make it an excellent drug carrier.[9] Moreover, mesoporous silica enhances drug solubility by transforming crystalline drugs into stable amorphous forms without affecting their lattice energy. The extensive surface area promotes strong adsorption of therapeutic agents while providing steric protection from external degradation. Additionally, its tunable pore size and modifiable surface chemistry enable precise control over drug release kinetics, establishing mesoporous silica as a highly promising platform for controlled and targeted drug delivery.[18]

Mesoporous silica nanoparticles have demonstrated significant potential as carriers for controlled and targeted drug delivery. Valsartan-loaded mesoporous silica nanoparticles (M-MSNs) showed a high drug entrapment efficiency (59.77%), attributed to strong ionic interactions between valsartan and the silica matrix. Compared with the commercial valsartan formulation (Diovan®), M-MSNs demonstrated a 1.28-fold increase in bioavailability. In vivo blood pressure measurements indicated that while the Diovan tablet maintained efficacy for approximately 360 minutes, the antihypertensive effect of M-MSNs persisted for up to 840 minutes, confirming their enhanced pharmacokinetic and therapeutic performance.[18]

C. Carbon-based nanocarriers

Carbon nanotubes (CNTs) possess unique biological and physicochemical properties that make them highly promising materials for drug delivery applications. Their exceptional features, including a high aspect ratio, ultralight weight, extensive surface area, and nanoscale needle-like structure, contribute to their efficiency as delivery vehicles. Additionally, CNTs exhibit remarkable chemical, thermal, mechanical, and electrical stability. Their needle-shaped morphology facilitates cellular uptake via endocytosis, allowing them to penetrate biological barriers and deliver therapeutic agents effectively. Functionalization of CNTs enhances their water solubility and extends their circulation time in the bloodstream, improving biocompatibility. In

contrast, non-functionalized CNTs remain hydrophobic and exhibit potential toxicity, underscoring the importance of surface modification for safe biomedical use.[9]

Administration of multiwalled carbon nanotubes (MWCNTs) at very low doses into the brain has been shown to significantly reduce blood pressure and heart rate. This effect is attributed to the upregulation of neuronal nitric oxide synthase (nNOS) expression in the medullary cardiovascular center, leading to decreased sympathetic nerve activity. Moreover, MWCNTs have been observed to promote acetylation and nuclear translocation of nuclear factor-κB (NF-κB) in brain cells, further influencing cardiovascular regulation and contributing to the observed hypotensive response.[25] These findings suggest that MWCNTs may serve as a potential neuromodulatory nanomaterial for regulating cardiovascular function, although further studies are required to ensure their safety and clinical applicability.

D. Magnetic nanoparticles

Magnetic nanocarriers generally consist of a magnetic core, with metal nanoparticles typically exhibiting stronger magnetic properties than their metal oxide counterparts.[9] Recent research has expanded to other magnetic nanostructures, particularly spinel ferrites, which can enhance magnetic characteristics such as anisotropy and coercivity while maintaining the inherent advantages of iron oxide nanoparticles. Cobalt ferrite ($CoFe_2O_4$) nanoparticles are among the most extensively studied spinel ferrites owing to their superior theranostic potential and tunable magnetic properties. These nanoparticles demonstrate excellent physicochemical characteristics, making them suitable for diverse biomedical applications, including magnetic hyperthermia therapy, imaging, biosensing, magnetic separation, and drug delivery. Beyond the medical field, $CoFe_2O_4$-based magnetic nanoparticles have also been utilized in environmental remediation, catalysis, data storage, and optical technologies.[26] However, their application in hypertension therapy remains limited, requiring further investigation to establish their safety and therapeutic efficacy.

A study investigating Fe_3O_4@PEG nanoparticles (with a ~30 nm core and ~51 nm hydrodynamic diameter) in Wistar–Kyoto (normotensive) and spontaneously hypertensive rats (SHR) demonstrated that nanoparticle administration significantly reduced blood pressure in hypertensive rats compared to SHR controls. Gene expression analysis revealed upregulation of endothelial nitric oxide synthase (eNOS), inducible NOS (iNOS), antioxidant response regulator (NRF2), and metal transporter (DMT1) genes in the aorta, with similar increases in NOS and iron metabolism–related genes observed in the liver. Vascular reactivity studies showed enhanced femoral artery contractions in response to noradrenaline and reduced endothelium-dependent relaxation in treated SHRs relative to controls. Notably, higher nanoparticle accumulation in the aorta and liver of hypertensive rats compared to normotensive counterparts suggests potential for targeted delivery in hypertension therapy. However, despite the observed blood pressure reduction, the impaired endothelial relaxation raises safety concerns.[27] The authors emphasize that iron oxide nanoparticles should be applied cautiously in hypertensive conditions, as their long-term vascular effects remain inadequately understood.

4. Hybrid nanocarriers

Hybrid nanocarriers are advanced delivery systems composed of two or more nanomaterial types, which may be organic, inorganic, or a

combination of both. Examples include lipid–polymer and ceramic–polymer hybrids. By integrating distinct nanomaterials, hybrid nanocarriers combine the advantageous properties of each component, thereby enhancing stability, functionality, and therapeutic performance. The selection of an appropriate hybrid system depends on factors such as the drug's physicochemical characteristics, target site, physiological barriers, and the desired stability and solubility profile. Ultimately, the primary objective in designing hybrid nanocarriers is to maximize drug bioavailability while minimizing adverse effects, offering a versatile platform for efficient and targeted drug delivery.[9]

Liposomes loaded with nebivolol hydrochloride and coated with either chitosan or pluronic F127 demonstrated enhanced stability in simulated gastrointestinal fluids and strong in vitro interaction with mucin, indicating improved absorption, residence time, and cellular contact. Among the two, pluronic-coated liposomes exhibited significantly higher encapsulation efficiency than chitosan-coated liposomes ($p < 0.05$). Additionally, polymer-coated formulations achieved greater cumulative drug release over 24 hours compared to uncoated liposomes, likely due to the stabilizing effect of the polymer matrix. No aggregation was observed after four weeks of storage, and cytotoxicity studies in Caco-2 cells confirmed low toxicity.[12] These findings suggest that polymer-coated liposomes represent a promising nanocarrier platform for oral delivery, offering improved drug stability and bioavailability over conventional formulations.

Emerging Strategies and Innovations

1. Gene therapy

Gene therapy involves the introduction of exogenous genetic material into target cells through gene transfer technologies to correct genetic abnormalities and achieve therapeutic benefits. In recent years, its application in cardiovascular medicine has expanded rapidly, offering a promising strategy for the treatment of cardiovascular diseases. One of the most effective delivery methods for gene therapy is the use of nanocarrier-based formulations.[28] In a study by M. N. Repkova et al., an antisense oligonucleotide targeting the ACE gene was conjugated with polylysine and immobilized onto titanium dioxide nanoparticles. When administered to rats with inherited stress-induced arterial hypertension (ISIAH) via intraperitoneal injection or inhalation, the nanoparticle formulation produced a significant reduction in systolic blood pressure of 20–30 mmHg compared to control groups, with minor differences attributed to dosage and pharmacokinetic variations.[29] In a subsequent study, silicon–organic nanocarriers were utilized instead of titanium dioxide due to their superior colloidal stability and lower aggregation tendency during storage. Antisense oligo-deoxyribonucleotides directed against angiotensin-converting enzyme and angiotensin II type 1 receptor (AT_1R) mRNA were electrostatically immobilized on these nanocarriers and administered to hypertensive ISIAH rats, resulting in a comparable systolic blood pressure reduction of approximately 30 mmHg.[30] Although gene therapy for hypertension remains in its early stages and requires further investigation, its prospects are highly promising, as emerging nanocarrier systems offer significant advancements in targeted and efficient genetic delivery.

2. NO donor

Nitric oxide (NO) exhibits dual biological roles, functioning both as an enzyme inhibitor and as an antioxidant capable of protecting cells from

cytokine-induced damage and apoptosis. It can also react with reactive species such as superoxide or lipid-derived radicals to form peroxynitrite ($ONOO^-$), which subsequently interacts with various biomolecules. Through these mechanisms, NO participates in numerous physiological and regulatory processes, including modulation of cardiovascular activity and neuronal signaling. Given its extensive biological influence, the NO pathway has become an important target for cardiovascular therapy. However, the therapeutic application of NO gas is hindered by its extremely short half-life, rapid and non-specific diffusion, and poor tissue accumulation, all of which limit its clinical efficacy. Uncontrolled spatial and temporal NO release may reduce its therapeutic benefits and even cause toxicity from localized overaccumulation. To overcome these challenges, nanocarriers have been developed to deliver NO in a controlled and sustained manner, prolonging its half-life while minimizing adverse effects on healthy tissues. Moreover, nanotechnology enables the integration of NO therapy with other treatment modalities, such as chemotherapy and photothermal therapy, for synergistic effects.[31]

Dr. Chen and colleagues developed NanoNO, a nanoscale delivery platform capable of sustained NO release. The released NO forms a concentration gradient around blood vessels, contributing to tumor vessel normalization and modulation of the tumor microenvironment. The PEG coating on NanoNO prevents opsonization and clearance by monocytes and macrophages, thus prolonging systemic circulation. Meanwhile, the PLGA matrix regulates the gradual release of NO from the dinitrosyl iron complex donor. With an average particle size of approximately 120 nm, NanoNO demonstrated enhanced tumor accumulation through the enhanced permeability and retention effect, suggesting its strong potential as a platform for controlled NO-based therapy.[32]

3. Smart nanocarriers

Most nanomedicines currently under development rely on intravenous administration, which necessitates hospital-based delivery and limits their suitability for chronic conditions such as hypertension. Exploring non-invasive delivery routes represents a promising alternative, offering advantages such as ease of administration, reduced infection risk, and lower systemic toxicity. Khadka et al. reviewed recent advances in smart wearable patch systems that combine biosensing technologies with stimuli-responsive drug delivery platforms to enable closed-loop, on-demand therapy. These systems integrate nanocarriers responsive to various stimuli, such as temperature, light, electrical signals, mechanical stress, or environmental factors, to regulate drug release in real time based on physiological cues.[33] Although primarily discussed in the context of metabolic and chronic diseases, this approach is directly applicable to hypertension management. Incorporating blood pressure sensors with nanocarrier-based antihypertensive delivery in wearable patches could enable feedback-controlled release of vasodilators or other antihypertensive agents during hypertensive episodes, offering a more personalized and responsive therapeutic strategy.

Researchers have developed hydrostatic pressure-responsive multivesicular liposomes (PSMVLs) encapsulating amlodipine besylate, a calcium channel blocker aimed at reducing pulmonary artery pressure. These liposomes are designed to rupture and release the drug under elevated hydrostatic pressures (≥25 mmHg), mimicking conditions characteristic of pulmonary hypertension or high-altitude pulmonary edema (HAPE). In vivo studies demonstrated that PSMVLs preferentially accumulated in lung tissue and exhibited rapid, pressure-triggered drug

release, leading to improved respiratory function and reduced pulmonary edema compared with conventional liposomes or free drug. This work establishes a novel concept of self-regulated, pressure-sensitive nanocarriers capable of on-demand drug release in response to pathological pressure changes.[34] Although the formulation exhibited physical instability at room temperature, requiring storage at 4 °C, the same pressure-responsive mechanism holds promise for treating systemic hypertension, where elevated body fluid pressure also plays a critical pathological role.

Challenges and Limitations

Over recent decades, significant progress in nanomedicine has enhanced the solubility, release profile, absorption, and bioavailability of poorly soluble drugs. Nonetheless, several challenges persist before nanotechnology can be fully translated into clinical practice. Nanocarrier-based delivery systems may modify drug toxicity or induce adverse effects of their own. For instance, selenium nanoparticles have demonstrated anti-atherosclerotic effects in ApoE-/- mice; however, prolonged exposure has been associated with increased oxidative stress, aggravated hyperlipidemia, and organ damage.[35] Hence, careful evaluation of the benefit–risk balance is essential in the design and development of nanomedicines to ensure both therapeutic efficacy and safety.

While the safety and efficacy of nanocarrier have been demonstrated in rodent studies, comprehensive evaluation in large mammalian models relevant to human physiology remains limited. Moreover, differences in disease progression and pathophysiology between animal models and humans often hinder direct clinical translation, indicating that nanoparticles still face significant barriers before widespread therapeutic application. In addition to biological challenges, issues related to large-scale production, stability, and regulatory approval persist. To date, only a few nanocarrier-based formulations, such as liposomal doxorubicin for cancer, have received FDA approval for cardiovascular or related applications. This highlights the urgent need for standardized manufacturing practices, robust safety assessments, and stronger collaboration between academia and industry to accelerate the clinical translation of nanomedicines.

CONCLUSION

Nanocarrier technology has emerged as a versatile platform with transformative potential in both the diagnosis and treatment of hypertension. In drug delivery, nanocarriers enhance solubility, stability, and bioavailability of antihypertensive agents while enabling controlled and targeted release, thereby improving therapeutic efficacy and patient adherence. In diagnostics, nanomaterial-based biosensors offer highly sensitive and rapid detection of hypertension-related biomarkers, paving the way for earlier and more precise disease monitoring. Despite these advances, the clinical translation of nanocarrier-based approaches remains limited by challenges in large-scale production, safety validation, and regulatory standardization. Continued interdisciplinary collaboration and translational research are essential to fully harness nanocarriers' potential in achieving personalized, efficient, and accessible hypertension management.

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