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REVIEW ARTICLE

Application of the nano drug delivery system in the treatment of cardiovascular diseases

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ABSTRACT

In the last several decades, cardiovascular diseases (CVDs) have emerged as a major hazard to human life and health. Conventional formulations for the treatment of CVD are available, but they are far from ideal because of poor water solubility, limited biological activity, non-targeting, and drug resistance. With the advancement of nanotechnology, a novel drug delivery approach for the treatment of CVDs has emerged: nano-drug delivery systems (NDDSs). NDDSs have shown significant advantages in tackling the difficulties listed above. Cytotoxicity is a difficulty with the use of non-destructive DNA sequences. NDDS categories and targeted tactics were outlined, as well as current research advancements in the diagnosis and treatment of CVDs. It's possible that gene therapy might be included into nano-carriers in the delivery of cardiovascular medications in the future. In addition, the evaluation addressed the drug's safety.

Keywords: Nano-Drug Delivery System; Cardiovascular Disease; Targeting Strategy; Application Progress; Safety

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1. Introduction

CVDs have become a major public health issue across the world, and their morbidity and death ranks number 1 among all other diseases in the globe[1]. Development of medications for the treatment of CVD is now a primary focus. New ways of treating cardiovascular illness have emerged as a result of the rapid advances in nanoscience and nanomaterials' exceptional performance. To enhance the safety and efficacy of pharmaceuticals, researchers use NDDSs, a family of nanomaterials that can boost drug stability and water solubility, extend the cycle duration, raise the absorption rate of target cells or tissues, and limit enzyme degradation[2]. As NDDSs may be supplied by a variety of methods, such as inhalation or intravenous injection, their bioavailability is improved. More researchers have begun to create nano-drug carrier systems for the detection and treatment of cardiovascular diseases in the last few years.

Furthermore, when the use of nanomaterials in clinical applications develops, the risk of exposure to nanomaterials in blood vessels, blood, and their components increases, which will have a significant influence on human health as a result. Consequently, this paper focused on NDDSs, their targeting methodologies, and their application in CVDs, as well as the safety of nanomaterials.

2. Classifications of NDDSs

To add to this, nanomaterials will have more opportunities to inter-

act with blood vessels, blood, and their components as they become more widely used in clinical applications. This means that nanomaterials will have a greater impact on human health as they become more widely used in clinical applications. Consequently, this paper focused on NDDSs, their targeting methodologies, and their application in CVDs, as well as the safety of nanomaterials.

2.1 Liposomes

Liposomes are lipid vesicles with a cell-like structure generated by an organized phospholipid bilayer[3]. As a form of drug carrier, liposomes demonstrate a number of advantages, such as non-toxicity, non-immunogenicity, and long-term drug release, as well as modifying drug distribution in vivo, enhancing the treatment index, and minimizing the risks associated with drug interactions. In addition to being simple to make, liposomes may also be used to encapsulate hydrophilic and ionic compounds, as well as hydrophobic medicines[4]. Phospholipids and liposomes can be used to encase hydrophobic medications, whereas liposomes can encase hydrophilic pharmaceuticals, such as those carrying genes. Material modifications can change particle size, potential and surface chemistry. These liposomes, known as cationic liposomes, are positively charged, which indicates that they may cause dose-dependent cell death and inflammation, and as a sort of complex, they may interact with negatively charged serum proteins in an untargeted manner. These issues can be addressed by neutral lipids and pH-sensitive liposomes[5].

2.2 Polymer micellar co-delivery system

It is possible to categorize polymer nanoparticles into non-biodegradable materials and biodegradable materials for the delivery of drugs. Poly(lactic-co-glycolic acid) (PLGA), polyvinyl imine (PEI), polycaprolactone (PCL), and polyvinyl alcohol (PVA) are examples of synthetic polymer materials. Biocompatibility, nontoxicity, and teratogenicity are all demonstrated by these polymers. Oligomerization and final products of degradation have no harmful effects on cells and can coexist peacefully with the majority of medications. Polysaccharides, peptides, Chol, and cyclodextrin inclusion complexes are the most common types of natural polymers[6], although there are many others. Amphiphilic block copolymers, which comprise the core of polymer nanoparticles, can be employed to intercept insoluble medicines through self-assembly[7]. Particle size uniformity and drug release control may be improved by the stable structure of polymer nanoparticles, which can effectively withstand the effects of gastrointestinal environment during oral delivery[8]. Drug absorption is enhanced by their small size and wide surface area, which facilitates greater bioavailability. Polymer nanoparticles, however, not all of them are created equal. Since Chitosan, a naturally occurring polymer, is incompatible with biological fluids, it can lead to particle disintegration and lower operating efficiency. Its deficit can be remedied structurally. The conjugate's endocytosis and macrophage phagocytosis mechanisms are unusual since they combine chitosan and polyethylene glycol. Furthermore, the addition of a polypeptide to chitosan can increase its working efficiency[9].

2.3 Dendritic macromolecules

Synthetic macromolecules may take on a variety of shapes and are frequently branched. Nano-carriers, such as macromolecules structured like spheres, can be utilized to administer and dissolve insoluble medications in a monodisperse environment. In addition to being monodispersed, dendritic macromolecules with a unique branch structure also have a variable molecular weight. In addition, the package has a significant number of pre-made surface functional groups and a hydrophobic environment, making it an ideal drug delivery medium[10]. Dendritic macromolecules are frequently employed in the biomedical and pharmaceutical industries because of their good biological characteristics, however, the presence of a surface cationic charge also restricts their clinical applicability.

2.4 Metal nanomaterials

There are a wide variety of metal nanomaterials that can be separated into/like gold, silver, and

platinum nanomaterials, each of which may be categorized into/like nanoparticles, rods, capsules, nanocuboids, and wire[11]. Gold nanoparticles are employed in photothermal therapy of malignancies and rheumatoid arthritis in addition to being a nano-contrast agent for CT and surface-enhanced Raman spectroscopy. Antibacterial, anti-infection, and anti-tumor are among the various uses for silver nanoparticles that have been demonstrated in several studies. Another option is to use hollow nanostructures to hold therapeutic pharmaceuticals[12] or chemically bind them to the surface of nanoparticles to transport the medications. Gold and silver nanoparticles can be used to treat chronic illnesses, however, the elimination of gold nanomaterials in the human body is too slow, and silver ions are poisonous in vivo.

2.5 Inorganic non-metallic nanomaterials

There are a wide variety of nonmetallic inorganic nanomaterials, such as quantum dots, iron oxide, silicon, and grapheme for example[13]. Fluorescence imaging with QDs, or semiconductor nanocrystals, is the primary focus of QD research, whereas iron oxide nanoparticles are being exploited to develop novel MRI contrast agents. Because of their enormous surface area and porous structure, mesoporous silicon nanoparticles have become increasingly popular in recent years as a therapeutic tool. Drugs and genes can be transported more efficiently in mammalian cells by integrating diverse functional groups into Inorganic nanomaterials. In the meanwhile, they're being touted as a type of joint carrier with room for growth. However, the bio-safety of inorganic non-metallic nanoparticles would be a significant barrier to their clinical use[14].

2.6 Composite nanomaterials

Additionally, several research are focusing on the development of composite nanomaterials with a variety of characteristics. To generate multifunctional NDDSs, for example, metal or inorganic non-metallic nanomaterials are inserted into polymer or lipid nanoparticles. Organic materials are used to decorate or modify metal and inorganic nanomaterials to improve their physical and chemical properties, in vivo kinetic behavior, and biocompatibility, and some NDDSs with special structure and diverse functions can be prepared by combining different metals and inorganic materials.

3. Targeting strategy of the NDDSs

Lesion cells or tissues of CVDs may also be targeted, making them easier to target than tumor tissues that have various physiological hurdles to overcome, according to new studies in the field. If you're using nano-transporter medications, the time it takes for them to enter the bloodstream may be longer than if you were using traditional pharmaceuticals. It is possible to alter the rate of those targeted nano-transporter medications by adjusting pH, temperature, light, ultrasound, or biological enzyme[15].

3.1 Passive target transfer enhanced vascular permeability

High permeability and high retention (EPR) effects are the primary means by which passive targeted transport is accomplished[16]. There are some chemicals or particles that tend to collect in tumor tissues, and this is known as EPR. Normal tissue has a thick and intact microvascular endothelial cell space, making it difficult to pass through the vascular wall NDDSs loaded with drugs of a high molecular weight. Despite its high blood artery density, tumor tissue is structurally weak. High molecular weight NDDSs loaded with drugs can preferentially pass through the vascular wall and stay in the tumor tissue. Nano-drug carriers with a particle size of less than 100 nm have been proven to be able to find and target solid tumor tissues using EPR. The nano-drug carrier can boost the drug's bioavailability by more than ten times when compared to the direct delivery approach[17]. However, it has been revealed that the EPR effect may be exploited to treat a variety of cardiovascular diseases, not just malignancies. To provide one example, the development of AS in some CVDs may be traced to an ongoing inflammation that leads to abnormally high levels of blood vessel permeability—a phenomenon strikingly similar to that seen in solid tumors. For the NDDS to reach the inside of the plaque, vascu-

lar endothelial permeability is a crucial factor in the process. Aside from being consumed by inflammatory cells (monocytes or macrophages), nano-drug carriers entering the blood are also taken up by these cells, allowing medications to be given in a different manner[18].

Nanomaterials are inappropriate for medications with lengthy cycle durations because of their quick clearance from the circulation upon intravenous administration due to their size and surface properties. The nano-system may be covered over using nano-coating technology, and the rate at which the coating agent is administered can be precisely regulated and changed. NDDSs can benefit from this technology in the treatment of cardiovascular disease. Poly (ethylene glycol) (PEG) has been used in particle creation by NDDS developers. A hydrophilic polymer known as PEG may be grafted onto any surface to create an effective coating of water that prevents proteins from adhering to the surface. So that tissue plasminogen activator is protected from plasma inhibitor inactivation and its half-life is prolonged. It is enclosed in nanoparticles that conceal the nanosystem[19].

3.2 Shear-induced targeting

For patients with severe coronary artery disease (CAD), thrombosis or microthrombus formation develops, which leads to stenosis of the blood arteries, which restricts blood flow through the plaque, and therefore raises the fluid shear stress. Compared to the normal vasculature, the blood fluid shear force in the AS plaque stenosis can reach up to 1,000 dyne·cm^2 on a daily basis[20]. As a result, the difference in blood fluid shear force between AS plaque and normal blood arteries may be used to develop blood fluid shear-sensitive nanoparticles to accomplish physicochemical targeting. Lipid nanoparticles were formed into convex, two-sided lenticular nanoparticle vesicles, according to Holme *et al*. As blood flow is increased to the AS plaque, the drug-loaded nanoscale is able to preserve its structural stability, and its configuration change may be leveraged to release the medication. It was based on platelet activation and adherence to plaque blood vessels in AS plaques that prompted the development of a nanoparticle aggregate that may be built locally in plaques[20]. To begin, the researchers synthesized PLGA nanoparticles with a diameter of 180 nm, encapsulated tissue plasminogen activator, and then used spray drying to produce a 3.8 nm PLGA nanoparticle aggregate. PLGA nanoparticles of 180 nm were formed after exposure to the high fluid shear stress of the AS plaque, and these nanoparticles were then able to penetrate the plaque's local thrombus because of the nanoparticles' great penetrability. The thrombolytic impact increased effectiveness while minimizing thrombolysis' negative effects and dosage requirements. Cardiomyopathy is characterized by an endothelial gap that widens and polysaccharide from Ophiopogon japonicus polysaccharides in ischemic myocardium that is twice as high as that of normal rats. Both shear stress and blood flow shear rate of the vascular wall can influence the aggregation of nanoparticles, according to Tan *et al.*[21].

3.3 Magnetically guided

A "pseudo-passive" targeting approach using a magnetically guided nanoparticle seems intriguing. In theory, magnetic nanoparticles may be directed to the illness location by the application of an external magnetic field. CVD patients may benefit from this approach, as evidenced by recent studies. The effects of several nano drug carriers on atherosclerotic plaque imaging were examined[22]. Ultra-tiny, superparamagnetic iron oxide nano-carriers, and extremely small superparamagnetic iron oxide nanoparticles are some of the nanoparticle forms of iron oxide. One collection of ultra-small superparamagnetic iron oxide nanoparticles performed significantly better than others in terms of vascular wall penetration and plaque retention. External magnetic fields may aid in the movement of particles from the cell-free layer, which lacks red blood cells, to the artery wall, some studies have suggested[23]. **Figure 1** illustrates the passive and active targeting strategy.

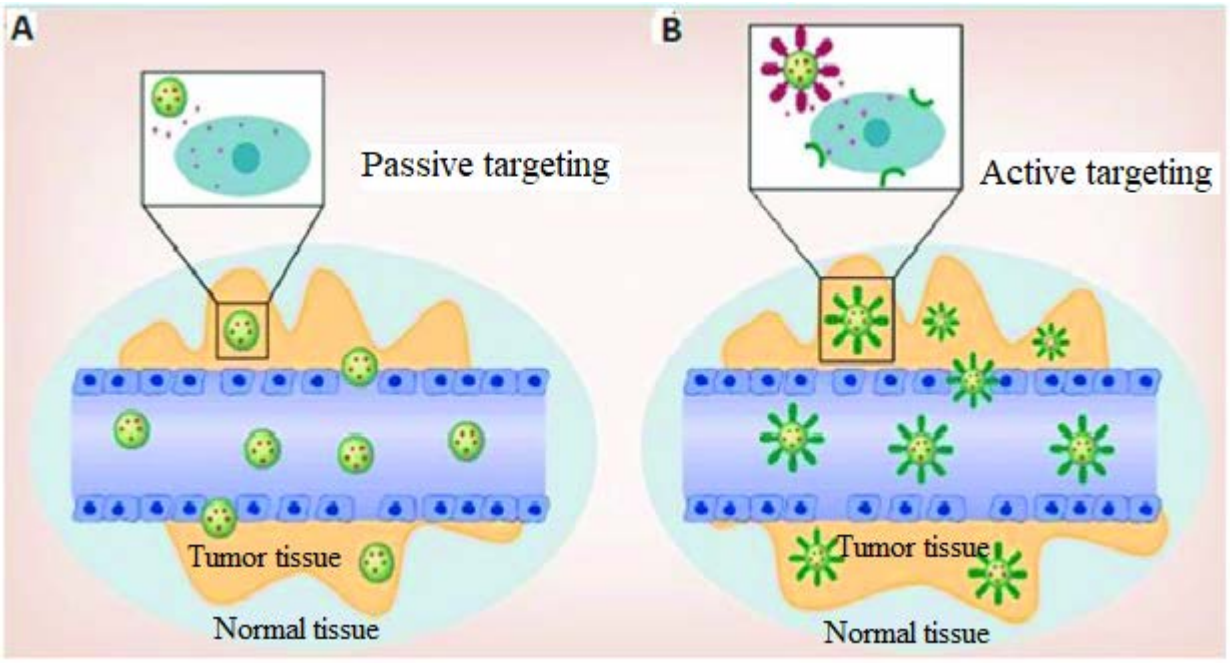

Figure 1. Drug targeting strategy. (**A**) Passive targeting (**B**) Active targeting.

3.4 Active targeted transhipment

Passive targeting may be utilized to build an active targeting approach for CVDs based on their unique pathological characteristics, which has piqued the interest of researchers interested in improving the targeted delivery efficiency of medications to CVD lesions. NDDSs with one or more targets are the primary focus of active targeting in order to facilitate medication delivery to a specific location[24]. In other words, the ability of carriers to target sick tissues or cells will be improved by adding a functional group or active material to the surface of the nano-drug carrier.

3.4.1 Active targeting of vascular endothelial cells

The vascular endothelial cells of CVDs are in an inflammatory activation state at different phases of the disease. One of the main targets for NDDSs is the overexpression of certain small molecules in these cancerous endothelial cells, such as ICAM-1 and VCAM-1. Other small molecules that are overexpressed include integrins and selectins[25]. Liposomal delivery of anti-inflammatory liposomes to the pulmonary vascular system is improved by conjugating lung-specific single-stranded variable fragment/liposome with PECAM-1 (platelet endothelial cell adhesion molecule 1) antibody[26]. Anti-VCAM-1 monoclonal antibody was used to silica nanoparticles in 2013. Before being absorbed by endothelial cells, the nanoparticles were able to attach to inflammatory sites.

The antibody anti-ICAM-1, which actively targets ICAM-1 on the liposome surface and loads contrast chemicals[27] based on the pathological characteristics of elevated ICAM-1 expression in early vascular endothelial cells of AS (gadolinium). Anti-ICAM-1 and ICAM-1 have been proven in studies to have a particular effect on liposomes that activates the targeting of vascular endothelial cells and AS plaques. Liposomes' ability to target AS plaques may be compromised if circulating white blood cells compete for binding to the ICAM-1 site and blood flow shearing occurs. Liposome binding to ICAM-1 was improved by testing liposome particle size, antibody concentration, and lipid concentration ratios.

As an endothelial cell glycoprotein, E-selectin promotes the attachment of monocytes/macrophages and lymphocytes to trigger an inflammatory response, ultimately leading to CVDs such AS (atherosclerosis-related cardiovascular disease)[28]. Also, nano-transport medicines might leverage the target of E-selectin. Human umbilical vein endothelial cells triggered by interleukin-1 (IL-1) and umbilical cord vein endothelial cells not

stimulated by IL-1 (IL-1) were treated with functional liposomes containing mouse H18/7 mAb (an E-selectin-specific antibody). The capacity of functional liposomes to target activated human umbilical vein endothelial cells was shown to be 275 times more than that of the non-activated form of liposomes[29].

When a myocardial infarction or heart failure occurs, AT1 levels increase in myocardial tissue. Polyethylene glycol liposomes (1,428 nm) were developed[30] to deliver medicinal payloads (such as growth factors, cytokines, etc.) in a regulated way. Gly-Arg-Val-Tyr-Ile-His-Pro-Phe (binding sequence of AT1 receptor) is connected to these liposomes, which might lead the nanoparticles to the infarction heart.

3.4.2 Active targeting of macrophages or foam cells

Foam cells, also known as macrophages, play an important part in the development of AS. Some inflammation-related molecules, including as CD44 and interleukin-4 (IL-4) receptors, were overexpressed in an inflammatory environment by mononuclear/macrophages in the early stages of AS. In order to track the course of AS and administer medication, NDDSs can be used for imaging and drug administration into macrophages or foam cells.

When the carboxyl group of the HA skeleton was chemically coupled to 5-cholic acid and the fluorescent dye Cy5.5, nanoparticles (HA-NPs) were generated by self-assembly[31]. It was shown that in comparison to nanoparticles (HGC-NPs) made with chitosan backbones that did not target CD44 receptors, HA-NP could greatly improve the absorption of activated macrophages, and the plaque site of ApoE/mice (AS model) was more targeted. Co-localization experiments showed that HA-NP was mostly found in macrophages in plaques.

Amphiphilicity of the IL-4 receptor peptide was improved by the application of phage library screening technology and chemical bonding to amphiphilic chitosan (with ethylene glycol chitosan as the backbone and 5-cholate attached). Self-assembled nanoparticles having the function of targeting macrophages in AS plaques are then produced.

3.5 Targeting vascular basement membrane collagen

Damaged blood arteries and inflammatory areas have collagen IV (Col IV)-rich vascular basement membranes, according to research. Collagen IV-targeting nanoparticles (Ac2-26 Col IV NPs) were developed in 2013 by Kamaly *et al.* by attaching the 7 amino acid oligopeptides to the PEG end of the PLGA–PEG block copolymer, and using it to package Act-26 (with anti-inflammatory and inhibition of leukocyte extravasation). Act-26 Col IV NPs were shown to limit neutrophil migration and adherence to the inflammatory site and to prevent inflammation development. IL-10 nanoparticles (Col-IV IL-10 NPs) were also created in 2016 by combining PLGA-PEG-Col IV and PDLA-PEG-OMe targeting collagen LV with self-assembly[32]. Col-IV IL-10 NP considerably boosted the plaque's IL-10 content after being administered intravenously to Ldlr/mice and had a greater impact on AS therapy than free IL-10.

Additional research has focused on nanocarriers that can deliver numerous anti-inflammatory agents to distinct types of cells in the body. Platelet-mimetic discoid morphology and flexibility were integrated with the platelet-mimetic biochemical heteromultivalent interactive functions by dendritic presentation of multiple peptides that bind simultaneously to both activated natural platelets and injured endothelial sites by dendritic presentation of multiple peptides[33].

Nanoparticles' biological and physical features determine whether they are passively targeted or actively targeted. Particle size and distribution, targeting unit kinds, surface chemistry, morphology, and density are all examples of biological and physical features. The development stage, type and location of CVDs and tumors, vascular wall shear rate, blood composition and its fluid type, as well as other elements, will have a significant impact on the targeting efficiency for the body[34]. However, even though the use of active targeted NDDSs in clinical diagnosis and treatment is exceedingly appealing, their development is still hampered by several dif-

ficulties. As a result of these issues, there are two primary aspects: one is the inability to locate an optimal target; the other is the difficulty in designing and preparing effective nanosystems.

4. Multifunctional responsiveness NDDSs

With the principles of the aforementioned two targeting mechanisms, nano-drug carriers could be produced that would have a superior ability to target. These nanocarriers are often constituted of stimulatory responsive materials, which may be released under the stimulation of a specific environment, thereby decreasing release in normal tissue and enhancing drug accumulation at the focal site. When combined with other diagnostic compounds like Volatile organic compounds, Halogen containing compounds and many, nanocarriers can form an integrated diagnosis and treatment system.

5. Application of the NDDSs in the diagnosis of CVDs

Effective CVD prevention and therapy depend on early, quick, and precise identification. There has been an increase in the use of molecular imaging in the diagnosis of cardiovascular diseases in the last few years. Additionally, new contrast agents are essential for real-time high sensitivity and high resolution diagnostics, in addition to the continual invention of various imaging modalities. Nano-contrast agents have the following benefits over traditional contrast agents. There will be improvements in the following areas: (1) in vivo stabilization; (2) controllable physical and chemical properties (like chemical composition and size) and imaging performance; (3) specific identification of specific biomolecules; (4) multimodal imaging capability; (5) potential benefits for personalized treatment and diagnosis. Nano-probes with distinct chemical signal molecules of sick tissues defined by pathological investigations can be used to drive the contrast agent to the lesion location for MRI, X-ray imaging, fluorescence imaging, and contrast-enhanced ultrasound (US) imaging in the early stages of the illness. Also optical coherence tomography (OCT) using AuNPs and Photoacoustic molecular probe are in existence to diagnose CVDs.

5.1 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a non-invasive, safe, and high-resolution imaging technique that is particularly useful for studying soft tissues. However, MRI's sensitivity ranges from 103 to 109 M, which isn't very high. T1-weighted imaging contrast agents, such as gadolinium complexes, are routinely employed in clinical practice; nonetheless, gadolinium has some nephrotoxicity. Non-toxic T2-weighted MRI contrast agents are Fe_3O_4 nanoparticle[35]. In comparison to tinctures, their sensitivity, tissue compatibility, and superparamagnetism are far higher, and they're also more potent. A high signal to noise ratio is achieved by using targeted contrast agents to collect MRI probes at a high concentration (in micrograms to milligrammes) in the target tissue.

Preliminary vascular imaging may be conducted at an early stage of cardiovascular illness, and medications can be provided after the magnetic nanoparticles are infused in the body. Diethylenetriamine pentaacetic acid (DTPA) was used[36] to chelate gadolinium in hydrophilic lipid (amphiphilic) micelles, which were subsequently encased in dendritic polymers and linked with fibrin binding agent. An improved targeting of atherosclerotic plaques and the ability to identify thrombus at an early stage have been achieved by this method. New Zealand white rabbits were injected intravenously with paramagnetic nanoparticles targeting integrin v3 by Winter *et al.* to identify neovascularization in plaques during the early stages of AS[37].

5.2 X-Ray imaging

Nuclear medicine relies heavily on radionuclides for imaging[38]. In addition to being highly sensitive, radionuclides also have the ability to be quantified. Imaging techniques use positron emission tomography (PET) and single photon emittance computed tomography (SPECT)[39]. Radiation-labeled nanoparticles can now be used to track the embolization process and nanomedicine delivery in order to gain more precise imaging. These liposomes were utilized to conduct SPECT, which

can monitor the distribution of pharmaceuticals in the body, as well as enhance drug release. For example, researchers employed 186Re-BMEDA and 99mTc-PEGylate-labeled doxorubicin liposomes. To detect atherosclerotic plaques, CT may be utilized to detect the nanoparticles, which can also be used to predict the prognosis of the disease. Using a venous injection, Galperin and colleagues administered iodine nanoparticle contrast agent (N1177) to animals. In macrophage-rich tissue, the contrast agent was shown to congregate, and the signal of atherosclerotic plaques was greatly amplified, and the enhancement period may continue for more than 30 min. When researchers utilized 11-MUDA (11-mercaptoundecanoic acid), they discovered that gold nanoparticles might concentrate in foam cells of atherosclerotic plaques and boost the contrast of imaging[40].

5.3 Fluorescence imaging

Optics is a strong imaging approach that has no radiation, no invasion, great resolution and good controllability, but it has a low penetrating ability. Fluorescein is commonly used to create fluorescence signals in fluorescence imaging. It is common to utilize near infrared fluorescence (NIRF) probes due to their high penetrating power and safety. Small animal live imaging systems and clinical tumor transformation have utilized them. Nano-drug carriers, such as liposomes, metal, or non-metallic nanoparticles, can encapsulate NIRF to enable optical imaging of blood arteries at present. A growing amount of focus has been placed on its use in cardiovascular disease imaging. They created diagnostic and therapeutic nanoparticles by combining near infrared light activated therapy (NILAT) with macrophage-targeted magnetic nanoparticles (MNP). Within 24 hours of injection, the nanoparticles had spread across the study region. Using profilin-1 as a target[41] injected atherosclerotic mice with profilin-1-targeting magnetic iron oxide nanoparticles (PF1- Cy5.5-DMSA-Fe3 O4 NPs). Carotid atherosclerotic plaques contained magnetic iron oxide nanoparticle aggregates. Fluorescence intensity measured in vitro was found to be in good agreement with the MRI signal from animals injected with PC-NPs.

5.4 Ultrasound imaging

Ultrasound imaging provides a number of advantages to fluorescence imaging, including the fact that it is less invasive, more convenient, and can be used in real time. Materials that can be targeted to certain vascular indicators have been produced. To give one example, vascular ultrasound nanoparticles that target VEGFR2 increase drug localization in blood vessels by increasing the clarity of ultrasound imaging of tumor blood vessels. VEGFR2 is an endothelial growth factor receptor 2 (VEGFR2). Streptokinase-carrying perfluorocarbon nanoparticles were created by Marsh and colleagues for the diagnosis and treatment of thrombus[42]. Ultrasonic imaging may be performed on the drug-loaded particles, which are made using the evaporation/dispersion approach and have a diameter of around 250 nm.

5.5 Multi-modal bioimaging

A mixture of diverse imaging technologies, known as multi-modal imaging technology, may now be used to achieve synergistic effects, resulting in more complete and accurate images for the diagnosis and treatment of cardiovascular diseases. For example, 64Cu-labeled SPIO-loaded doxorubicin nanoparticles can be employed for MRI and PET imaging, for example[43]. According to one study, gold nanoparticles mixed with Cy5, sputum, and folic acid can provide trimodal optical imaging as well as MRI and CT imaging in mice[44]. Cardiovascular nanomedicine's future development will take a fresh turn in the direction of multimodal imaging and diagnostic and therapy integration.

6. Application of the NDDSs in the treatment of CVDs

6.1 The NDDSs in AS

AS is the most prevalent kind of CVD, and it frequently results in a stroke or heart attack. Endothelial dysfunction is the first step in the development of AS. Ischemic cardiomyopathy can be caused by plaque-induced coronary artery narrowing, whereas acute myocardial infarction might be

caused by plaque rupture. Peptideases and macrophages can be candidates for intervention in the pathophysiology of plaque instability because of increased vascular permeability, increased PECAM expression, and macrophage aggregation. In order to maximize the concentration of lesions and decrease side effects, the medicine can be administered to atherosclerotic plaques using a nano-drug carrier. With these nano-drug carriers, you can regulate lipoprotein levels and reduce inflammation as well as prevent the formation of new vessels. In order to stop the formation of AS, reduce plaque area, or stabilize susceptible plaques, these therapeutic options are employed[45].

6.2 The NDDSs in hypertension

Today, a wide variety of medications are used to treat hypertension, including ATEN inhibitors, vascular angiotensin antagonists, central sympathetic nerve agents, adrenergic receptor blockers, diuretics and vasodilators, among other classes of medication[46]. Antihypertensive therapeutic medications have evident flaws such as short plasma half-lives, limited bioavailability and toxic and side effects such as upper respiratory tract abstraction, angioedema, reflex thyrotomy, excessive hypotensive effects, etc. Nano-drug carriers, on the other hand, can offer the advantages listed above. Olmesartan has been developed into a nanoemulsion system by certain researchers. The nanoemulsion group exhibits greater blood pressure-lowering effects, a longer maintenance period, and nearly three times the dosage decrease than the standard dose group[47].

6.3 The NDDSs in pulmonary hypertension

Increased pulmonary vascular resistance and raised pulmonary artery pressure are the hallmarks of pulmonary hypertension. Pulmonary hypertension is commonly treated with vasodilators such as prostaglandin I, endothelin receptor antagonist, type 5 phosphodiesterase inhibitor, and others. The therapeutic potential of these vasodilators is limited, however they have demonstrated some results. In order to address this issue, nano-mediated drug delivery systems have become increasingly relevant. In nanoparticle form, bosentan is an Endothelin receptor antagonist that is seven times more soluble than bosentan that hasn't been treated[48].

6.4 The NDDSs in myocardial infarction

Apoptosis, calcium overload, and reactive oxygen species have all been linked to reperfusion therapy, which is most commonly employed in the early stages of a myocardial infarction. Apoptosis and necrosis of cardiomyocytes are promoted by the opening of the MPTP and the rise in mitochondrial outer membrane permeability as a result of these factors[49]. Growth factors, cytokines, and other small molecular substances are mostly used in clinical practice to treat myocardial ischemia. The drawbacks of these pharmaceuticals are the same as those of the standard medications listed above. In ischemic heart disease, high blood permeability and an abundance of monocytes can be utilized to deliver medications through the targeting ability of nano-carriers.

6.5 The NDDSs in other CVDs

Additionally, the nano-drug delivery method works effectively in the treatment of various cardiovascular diseases. Allogeneic angiopathy of the coronary arteries is an inflammatory process of proliferation that threatens the long-term effectiveness of heart transplantation. Using methotrexate or paclitaxel-coated lipid nanoparticles, researchers administered them intravenously to rabbits receiving an ectopic heart transplant and fed them a cholesterol-rich diet[50]. Insufficient oxygen supply and unstable myocardial energy metabolism are the primary causes of myocardial ischemia, a condition that can't sustain the heart's regular functions. Thin film dispersion was used to make liposomes coated with phenytoin (PHT, a non-selective VGSC inhibitor). PHT-encapsulated liposomes partly suppressed I/R injury-induced CD43+ inflammatory monocyte growth and decreased infarct size and left ventricular fibrosis after intravenous injection of the rat myocardial I/R injury model[51].

After an angioplasty, an arteriotomy, or the implantation of an endovascular stent, the blood arteries might become stenotic and blocked again, a condition known as vascular restenosis. Catheter-intervention methods may be employed to pump

drug-loaded nanoparticles into the damage site to enable angioplasty and topical delivery in one step. Through the compromised endothelium, the nanoparticles can infiltrate the artery wall, locate, and then slowly release the medicine[52]. A high concentration of medicine in the lesion vessel may be maintained for a long length of time, which is advantageous to maximizing the drug's action and preventing vascular restenosis as well.

7. Application of the co-loaded nano-system in the CVDs

When two or more medications are administered to a patient at the same time, we say that we are using drug combination therapy. This treatment has been widely utilized in the medical community to treat a variety of diseases. The synergistic effect of medications, or the therapeutic benefit of numerous drugs which is larger than that of a single drug, is typically a factor in the use of this combination treatment. Recent years have seen the development of several co-loaded nano-systems that carry medications and/or genes, particularly siRNA, for the treatment of cardiovascular disease.

8. Application of RNAi in the treatment of CVDs

RNA interference (RNAi) is a gene-specific silencing process that is present in eukaryotic cells and an essential tool for preventing the spread of alien genes and viruses. When RNAi was initially identified in *C. elegans*, it was later shown to be present in human cells[53]. A variety of RNA interference mechanisms exist, including miRNA, siRNA, Piwi-interacting RNA, and long non-coding RNA (lncRNA) (lncRNA). Cell-specific genes may be silenced using RNAi technology, which involves introducing double-stranded RNA (dsRNA) into cells, degrading mRNA homologously complementary to the dsRNA and limiting its expression. Development of RNAi research has led to it becoming a therapeutic development tool for the treatment of CVDs[54]. Additionally, RNA interference therapy for the treatment of CVD has its own set of obstacles, including toxicity, targeting, temporal impact, and effective delivery method, which restrict its broad usage in the clinic and are urgently needed to be resolved and improved[55]. RNA interference in the cardiovascular system is expected to take a new turn.

9. Co-loaded gene and drug nano-system

In order to overcome the difficulties in the delivery process and realise the full potential of RNAi-based therapies, safe and effective nano delivery devices are essential. The liposome vector was used to contain the apolipoprotein B (ApoB) siRNA. When the liver ApoB mRNA was tested after 48 hours, the silencing rate was over 90%. When ApoB protein and blood cholesterol levels began to fall 24 hours after therapy, the effects lasted until day 11 of treatment[56]. Researchers have created and packaged small interfering RNA (siRNA) against the PDGF-B mRNA expression vector using chitosan nanoparticles, and then employed therapeutic ultrasound to transfect the vascular smooth muscle cells (vSMC) of rabbit artery wall injured by balloon catheter. According to the findings, the nanoparticles dramatically decreased intimal vSMC PCNA and PDGF-B mRNA expressions as well as local intimal thickness and area when applied to cells. The infarcted myocardium expresses considerably more Nox2-NADPH. Nox2-siRNA was delivered to the post-MI heart via acid-degradable polyketal particles[57], which decreased both siRNA degradation and inflammation.

SiRNA can be delivered to the proper cells at the right time in nano-doses created by several pharmaceutical firms. Alnylam Pharmaceuticals' ALN-PCS or placebo were given intravenously into healthy individuals with serum LDL values of 3 mmol/L or higher[58]. A siRNA, ALN-PCS, is integrated in lipid nanoparticles to block PCSK9 production. A single intravenous injection of ALN-PCS decreased human PCSK9 protein levels by 70%, while LDL was lowered by 40%.

Using a combination of nanotechnology, gene interference technology, and the packaged chemicals, the therapeutic impact is far superior than a single therapy due to the synergistic effect. A medicine called Carvedilol, which inhibits adrenergic

receptors in several organs concurrently, is extensively used and effective. Cardiovascular hypertrophy can be effectively prevented by silencing p53 in the DNA. However, cancer can spread to other organs as a result. These bioactive compounds were successfully encapsulated with stearic acid modified carboxymethyl chitosan (CMC) nanopolymers linked to a homing peptide for distribution in vivo to hypertrophied cardiomyocytes.

10. Safety of the NDDSs

Although nanomaterial NDDSs are becoming more common, their unknown toxicity and lack of systematic research into the materials themselves limit their continued use. The surface effect, small scale effect, quantum scale effect, and macroscopical quantum tunnelling effect will all become apparent when the particle size reaches the nanoscale scale[59].

Only a few research have looked at the potential dangers of NDDS on the cardiovascular system. Because of this, cardiovascular system tissue has been identified as a primary NDDSs target, which can have a significant influence on illness prognosis. Nanomaterials have been shown to enter the bloodstream via the respiratory, digestive, skin, and other mucous membranes, where they interact with the blood, immune system, and other tissues, including plasma proteins and immune proteins, blood cells and immune cells, and so on.

Toxicological studies of the health effects are the primary focus of the NDDS safety evaluation. Nanomaterials' cardiovascular toxicity has been linked to a number of adverse consequences, including oxidative stress, inflammation, apoptosis, blood aggregation, and cardiac signal transduction, in animal and cell studies[60]. Inflammation and oxidative stress are two of the most important pathways for cardiovascular damage caused by nanomaterials, according to this research.

Hypertension, myocarditis, AS, acute myocardial infarction, and heart failure can all be exacerbated by an inflammatory response to a variety of factors. When nano-carriers are not removed in a timely manner, they can reach all organs via blood, triggering a sequence of cytokines, which in turn raises the risk of cardiovascular events if they aren't eliminated[61].

As a result of nanomaterials' many surface atoms and high reactivity, free radicals and reactive oxygen species (ROS) can be generated, posing a threat to antioxidant systems[62]. DNA and proteins, which are macromolecular molecules, can be damaged by oxidative stress, resulting in decreased cell development, irregularities in the cell cycle, and even cell death.

Caenorhabditis elegans was used to test the biological safety of pH-responsive carrier system (FFPFF self-assembling into a nanosphere structure, FFPFF Nps), which was designed for anti-tumor drug delivery and the results showed that exposure to high doses of FFPFF Nps did not have a significant impact on the survival rate, growth, development, movement, and reproduction of *Caenorhabditis elegans*. The preliminary evaluation of the overall biological model of *Caenorhabditis elegans* shows that FFPFF Nps has good biological safety[63]. Potential toxicities that are associated with nanocarriers, mechanisms of toxicity, major target organs, and factors influencing these toxicities have also been discussed[64]. Nanoparticles, due to their nanosize, easily traverse through biological barriers and may be accumulated in the body, where the ingredients incorporated in the formulation development might accumulate and/or produce toxic manifestation, leading to cause severe health hazards. Therefore, the toxic profile of these delivery systems needs to be evaluated at the molecular, cellular, tissue and organ level[65].

The research of nanomaterial-induced cardiovascular system injury is still in its infancy across the world. Nanoparticle physicochemical factors (shape, size, size distribution, surface structure, electrochemical properties) and the toxic effects of the cardiovascular system are poorly understood in terms of their link to the physiochemical parameters. More study into the cardiovascular system hazardous effects and processes of ordinary nanomaterial exposure is therefore needed by scientists in order to better utilise nanomaterials' good properties to avoid, mitigate, or eliminate potential detrimental health consequences. Nanomaterial safety evalua-

tion technologies and standards would also have theoretical and technological foundations provided by this study.

11. Conclusion

In conclusion, the nano-carrier, as an efficient, specific and controllable intracellular drug delivery method, has shown unique advantages in the diagnosis and therapy of CVDs. It can effectively solve the problems of targeting, local drug delivery, controlled release, sustained release, and reducing toxicity while it is developing toward the multifunctional and integrated direction of diagnosis and therapy. With the innovation of nanotechnology and the deepening studies on molecular pathological mechanism of CVDs, the application of NDDSs will be promoted, and new techniques and methods will be provided for clinical diagnosis and therapy. In addition, since the study on these nano-carriers is in its infancy, many problems still remain unclear. The main challenge is how to solve the biocompatibility of nano-drug-loaded particles themselves or their degradation products, which is need to be solved in the field of nano-biomedicine in the future.

Conflict of interest

The authors declared no conflict of interest.

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