A REVIEW ON CARDIOVASCULAR DISEASE TREATMENT USING NANO DRUG TECHNOLOGY

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https://doi.org/10.26634/jchem.4.1.21053

Date Received: 01/08/2024 *Date Revised: 07/08/2024* *Date Accepted: 20/08/2024*

ABSTRACT

Cardiovascular Diseases (CVDs) pose a significant global health threat, with rising mortality rates attributed to factors like diabetes, obesity, and an aging population. This paper explores the evolving landscape of micro and nanoscale Drug Delivery Systems (DDSs) to enhance cardiovascular treatment efficacy. Various nanoagents, both organic (e.g., liposomes, dendrimers, polymeric nanoparticles) and inorganic (e.g., carbon nanotubes, silver nanoparticles, iron oxide nanoparticles), are classified and examined. The advantages, limitations, and preparation techniques of nanoagents are discussed, emphasizing their potential in targeted delivery, multifunctionality, minimal side effects, and enhanced efficiency. The anatomical details of the heart, layers of heart walls, and heart functions are presented for contextual understanding. The application of nanoagents in treating specific cardiovascular conditions, such as atherosclerosis, hypertension, myocardial infarction, and coronary artery disease, is thoroughly explored. Evaluation methods for nanoagents, including size and morphology analysis, surface charge determination, and molecular weight evaluation, are outlined. This paper concludes by emphasizing the promising role of nano-drug delivery systems in addressing CVD challenges, urging collaborative efforts for successful translational medicine implementation. Future research directions are proposed, highlighting the potential of peptides, antibodies, and selective nanodelivery systems in advancing cardiovascular care. Challenges like pharmaceutical scale-up, regulatory requirements, and patient preparation are acknowledged, underscoring the need for interdisciplinary collaboration to propel nanocardio medicine into clinical practice.

Keywords: Cardiovascular Disease Treatment, Nano Drug Technology, Nanoagents, Atherosclerosis, Hypertension, Myocardial Infarction, Coronary Artery Disease.

INTRODUCTION

Cardiovascular Diseases (CVDs) are a leading global cause of death, with 17.3 million annual fatalities. The escalating diagnosis and treatment costs are driven by rising risk factors such as diabetes, obesity, and aging population (Pala et al., 2020). Hypertension and hypercholesterolemia contribute significantly to CVD morbidity and mortality. To enhance drug efficacy, micro and nanoscale Drug Delivery Systems (DDSs) have been developed. For example, a pH-sensitive gelatine-based microsphere encapsulating halloysite nanotubes improved the bioavailability of carvedilol. Other innovative

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systems utilizing poly (lactide) polycarboxybetaine, cardiac homing peptide, and gold nanoparticles aim to address myocardial hypertrophy and fibrosis. Targeted micro or nano-delivery of therapeutic agents emerges as a promising strategy in CVD treatment, offering efficient reduction of atherosclerosis burden, recovery in ischemic stroke patients, and improved ventricular function in those with myocardial infarction and heart failure.

1. Literature Review

Modi et al. (2022) aimed to explore the usefulness of nanoparticles in vivo, as they can provide insights for future treatments. Nanogels can help create a more favorable environment not only for the sustained delivery of therapeutics but also for better navigation of the therapeutics to targeted sites. If the damage to the myocardium is too severe for drug treatment, nanopatches can help improve cardiac function and healing by serving as a platform for pluripotent stem cell-derived cardiomyocytes to grow for cell-based regenerative therapy.

Kim et al. (2011) investigated a variety of therapeutic drugs and measures that have been produced to delay the progress of the disease and improve the quality of life of patients. Most of the traditional therapeutic strategies can only cure the symptoms and cannot repair or regenerate the damaged ischemic myocardium. Therefore, it is vital to find and explore new technologies and drugs to solve the shortcomings of conventional treatments. Nanotechnology is a new way of using and manipulating matter at the molecular scale, whose functional organization is measured in nanometers. Because nanoscale phenomena play an important role in cell signal transduction, enzyme action, and the cell cycle, nanotechnology is closely related to medical research.

Chandarana et al. (2018) aimed to highlight that cardiovascular diseases claim numerous lives globally, many of which are preventable. With the increase in diets high in saturated fat, salt, and sugar, combined with sedentary lifestyles and a rise in obesity, the incidence of cardiovascular disease is increasing. These contributing factors, along with more advanced diagnostic methods, have produced statistics that clearly indicate a rising trend in the prevalence of cardiovascular disease. Treatment for cardiovascular diseases is largely limited to oral medications or invasive surgery.

Peters et al. (2009) aimed to show that a large majority of cardiovascular nanomedicine research has focused on fabricating designer nanoparticles for improved targeting as a means to overcome biological barriers. For cardiac-related disorders such as atherosclerosis, hypertension, and myocardial infarction, designer micro- or nanoparticles are often administered into the vasculature or targeted vessel with the hope of circumventing problems associated with conventional drug delivery, including negative systemic side effects. Additionally, novel nano-drug carriers that enter circulation can be selectively taken up by immune cells with the intended purpose of modulating inflammatory processes and migrating locally to plaques for therapeutic payload delivery.

2. Advantages

- *Targeted Delivery:* Precise delivery to the site of cardiovascular injury (Yang et al., 2022).
- *Multifunctional:* Integration of treatment, diagnosis, and imaging.
- *Minimal Side Effects:* Avoidance of adverse effects and systemic toxicity.
- *Enhanced Efficiency:* Improved efficacy of drugs or doses.
- *High Penetration:* Increased penetration capability.
- *Ease of Adsorption:* Simple adsorption process.

3. Limitations

- *Cost Challenges:* High costs associated with production scale-up.
- *Stability Concerns:* Issues with long-term stability of drugs.
- *Data Gap:* Lack of clinical trial and safety data.
- *Characterization Complexity:* Tedious methods for characterization and purity assessment.

4. Anatomy of Heart

The heart, a conical, hollow muscular organ within the pericardium, is located in the middle mediastinum. Positioned posteriorly to the sternum, one-third of the heart lies to the right and two-thirds to the left of the midline. Organs associated with the heart include the sternum, costal cartilages, lungs, pleura, esophagus, aorta, veins, thoracic duct, and diaphragm (Kohli, 2020).

4.1 Layers of Heart Walls

- *Epicardium:* The outer layer, formed by the visceral layer of the serous pericardium.
- *Myocardium:* The middle layer, containing excitable tissue and the conducting system (Ravichandran et al., 2014).
- *Endocardium:* Composed of a middle concentric layer and a subendocardial layer.

5. Functions of Heart

- Venous blood returns from the body to the right atrium.
- The right atrium pumps blood through the tricuspid valve into the right ventricle.
- The right ventricle pumps blood through the pulmonary valve to be oxygenated in the lungs.
- Oxygenated blood returns from the lungs to the left atrium.
- The left atrium pumps blood through the bicuspid (mitral) valve into the left ventricle.
- The left ventricle pumps blood through the aortic valve into the ascending aorta to supply the body.

6. Nano Agents Used in CVDs

Physical Properties of Nano Agents: Nanoparticles within the size range of 1 nm to 100 nm possess unique characteristics, including their nanoscale size, distinctive quantum properties, high surface-to-volume ratio, and varied shapes (Watson, 2022).

7. Classification of Nano Particles

Nanoparticles (NPs) can be broadly classified into organic and inorganic structures, typically with sizes of <100 nm. Organic nanoparticles are composed of biodegradable materials, including lipids, liposomes, micelles, proteins, dendrimers, and polymeric vesicles. Inorganic nanoparticles are formed from various minute-sized structures, such as quantum dots, mesoporous silicon, graphene, carbon nanotubes, metals, and metal oxides (Valk et al., 2015).

7.1 Organic Nanoparticles

7.1.1 Liposomes

- Phospholipid bilayer structures (250-400nm).
- Dual hydrophilic and hydrophobic nature.
- Potential for platelet-targeted drug delivery in cardiovascular diseases (CVDs).
- Used in atherosclerosis and thrombosis treatment.
- Challenges include immune system interactions and cost compared to polymer-based systems (Varna et al., 2015).

7.1.2 Dendrimers

- Tuneable size, multiple functional features, good biocompatibility.
- Positive charge, smaller size, and flexible gene delivery vehicles.
- Applications in treating atherosclerosis with sustained release behavior.
- Developed for targeting activated microglial cells after cardiac arrest.
- Promising for post-cardiac arrest syndrome treatment (Shen et al., 2021).

7.1.3 Polymeric Nanoparticles

- Biodegradable materials with potential reabsorption in the body.
- Includes poly(lactide) (PLA), poly(lactide-co-glycolide) copolymers (PLGA), and more.
- Quercetin encapsulation in PLGA for atherosclerosis prevention (Serpooshan et al., 2015).
- Attractive for nanomedicine due to manipulative qualities.

7.1.4 Magnetic Nanoparticles

- Considered as safe MRI contrast agents and drug delivery carriers (Fan et al., 2020).

- Iron oxide superparamagnetic nanoparticles for treating acute myocardial infarction (AMI).
- Enables magnetic orientation for enhanced local thrombolysis.
- Broad application in occlusive vascular diseases.

7.2 Inorganic Nanoparticles

7.2.1 Carbon Nanotubes

- Graphite sheets rolled into tubular forms.
- Preferred as drug carriers due to addressing solubility and bioavailability issues.

7.2.2 Silver Nanoparticles (AgNPs)

- Synthesized by various methods.
- Exhibits antibacterial, antifungal, antiviral, anti-inflammatory, and osteoinductive effects (Katsuki et al., 2017).
- Promising agents for cancer therapy.

7.2.3 Iron Oxide Nanoparticles (INPs)

- Superparamagnetic iron oxide nanoparticles (SPIONs) for various biomedical applications.
- Used in enhanced resolution contrast agents for MRI, targeted drug delivery and hyperthermia (Munjal, 2018).

7.2.4 Silica Nanoparticles

- Mesoporous or nonporous silica NPs with amorphous structure.
- Promising for drug delivery systems with controlled release profiles.
- Methods include Stober, sol-gel, spray drying, and more.

7.2.5 Gold Nanoparticles

- Used for delivery of cardio protective drugs.
- Less toxic, low immunogenicity, and stable.
- Examples include Simdax conjugated on gold nanoparticles for cardioprotective effects (Spivak et al., 2013).

8. Preparation Techniques of Nanoagents

8.1 Spray Drying

- Polymer dissolved in volatile organic solvents (e.g., dichloromethane, acetone).
- Drugs are dispersed in the polymer solution with high-speed homogenization.
- Dispersion atomized in hot air stream, forming microspheres (1-100μm).
- Feasible under aseptic conditions (Brahamdutt et al., 2018).

8.2 Solvent Evaporation

- Polymer dissolved in organic solvent (e.g., dichloromethane, chloroform).
- Mixture emulsified in an aqueous solution containing surfactant.
- Formation of stable oil-in-water (o/w) emulsion.
- Organic solvent evaporated by reducing pressure or continuous stirring.
- Particle size influenced by stabilizer type, homogenizer speed, and polymer concentration.

8.3 Single Emulsion Technique

- Microparticulate carriers of natural polymers (proteins, carbohydrates).
- Dissolution or dispersion of natural polymers in aqueous medium.
- Dispersion in non-aqueous medium (oil), followed by cross-linking.
- Cross-linking achieved by heat or chemical cross-linkers (e.g., glutaraldehyde).

8.4 Double Emulsion Solvent Technique

- Formation of w/o/w emulsion for water-soluble drugs, peptides, proteins, vaccines.
- Aqueous protein solution dispersed in lipophilic organic phase.
- Homogenization or sonication before addition to an aqueous solution of polymer.
- Formation of double emulsion, followed by solvent removal (evaporation/extraction).

8.5 Spray Freeze Drying

- Spray freezing of solution into a liquid nitrogen bath.
- Vacuum freeze-drying to sublime water and obtain a

dried powder.

- Three-step operation with control over residual moisture, mass density, and particle size.
- Manipulation of parameters like cryogenic liquid temperature, solution composition, and atomizer type.

9. Evaluation of Nanoagents

9.1 Size and Morphology

- *Photon Correlation Spectroscopy (PCS):* It measures particle size using radiation scattering technology.
- *Scanning Electron Microscopy (SEM):* It determines particle shape, morphology, and sizes.
- *Transmission Electron Microscopy (TEM):* It provides higher resolution for size, distribution, and morphology.
- *Freeze Fraction Electron Microscopy (FFEM):* It examines fractured samples at room temperature.
- *Atomic Force Electron Microscopy:* It measures the entire three-dimensional structure of nanoparticles.

9.2 Specific Surface

Specific surface is determined with the Sorptometer using the formula A = 20206 / D] x d, where A is the specific surface, D is density, and d is the diameter of the particle.

9.3 Surface Charge and Electrophoretic Mobility

Surface charge is measured by determining the velocity of particles in an electric field.

9.4 Density of Nanoparticles

Density of nanoparticles is determined using a gas pycnometer with helium or air.

9.5 Molecular Weight

Molecular weight and its distribution for the polymer are evaluated using Gel Permeation Chromatography (Ni et al., 2013).

9.6 Nanoparticle Recovery and Drug Incorporation Efficiency

Nanoparticle recovery (%) is calculated as [Concentration of drug in nanoparticle / Concentration of nanoparticle recovered] $\times$ 100.

9.7 Swelling Index

Swelling index is calculated using the formula, Swelling Index = (Mass of Swollen Microspheres - Mass of Dry Microspheres) $\times$ 100.

9.8 Angle of Contact

Angle of contact is measured to determine the wetting properties of a micro-particulate carrier.

10. Application of Nanoagents in Cardiovascular Diseases

Nanoparticles are being increasingly explored for the treatment of various cardiovascular diseases (CVDs).

10.1 Atherosclerosis

- Use of non-stimuli-responsive nanoparticles, such as PLGA, cyclodextrin, and chitosan (Lee et al., 2019).
- Pitvastatin delivered by PLGA nanoparticles inhibits plaque rupture.
- Core-shell nanoparticles based on self-assembly of cyclodextrin and statins for enhanced targeting.

10.2 Hypertension

- Nanoemulsion system improves the plasma concentration of Olmesartan.
- Nitric oxide (NO) controlled release systems based on hydrogel or glass hybrid nanoparticles.
- Cationic liposomes reduce β1-adrenergic receptor expression, controlling blood pressure.

10.3 Pulmonary Arterial Hypertension (PAH)

- Bosentan-loaded nanoparticles show higher solubility and effectiveness.
- PLGA nanoparticles incorporating Bera Prost decrease pulmonary vascular resistance and inhibit vascular remodeling.

10.4 Myocardial Infarction (MI)

- Superparamagnetic iron oxide nanoparticles guide and monitor stem cell therapy (Chen et al., 2019).
- Chitosan-alginate nanoparticles deliver placental growth factor for improved cardiac function.
- Silica nanoparticles loaded with adenosine reduce infarct size and side effects.

10.5 Coronary Artery Disease (CAD)

- Nanoparticles enhance drug circulation, solubility, and targeted delivery.

- Liposomal bisphosphonate alendronate decreases neointimal formation.
- Polymeric nanoparticles (PLGA) for plaque destabilization.

10.6 Other Cardiovascular Diseases

- Nanoparticles for targeted delivery of tissue plasminogen activator (t-PA) and thrombolytic drugs (Absar et al., 2013).
- Magnetic nanoparticles enhance drug accumulation at thrombosis sites.
- Fullerene nanoparticles decrease brain ischemia or reperfusion injury.
- Nanocarriers for periadventitial drug delivery in open vascular reconstructions.
- Neuroprotective drug delivery across the blood-brain barrier for ischemia/reperfusion damage.
- Oxygenated nanocarriers for prolonged release during organ transplantation.

Conclusion

Cardiovascular Diseases (CVDs) are a major global health concern, significantly contributing to morbidity and mortality. Despite the availability of various treatment options, challenges persist, and newer therapeutic approaches are continuously sought. Natural compounds, herbal medications, and Traditional Chinese Medicine (TCM) have gained attention for their perceived advantages and fewer side effects.

However, these alternatives lack robust scientific support, hindering their integration into clinical settings. Studies are actively seeking innovative technologies for the diagnosis and treatment of CVDs. While conventional treatments target different pathways, they have limitations and adverse effects. Nano-drug delivery systems offer a promising alternative for efficient and controlled drug delivery to injured heart tissue, addressing some of these limitations.

Nanoparticles play a crucial role not only in drug delivery but also in the diagnosis and imaging of CVDs. Nanoimaging techniques provide advantages such as simple diagnosis and real-time tracking during therapy, which are not achievable with conventional imaging methods. Despite promising results in preclinical studies, the clinical translation of cardiovascular nanoformulations is still under development. Challenges include pharmaceutical scale-up, release efficiency, regulatory requirements, safety, and Good Manufacturing Practice (GMP).

Further research and development of nanocarriers for CVDs demand rigorous studies. Natural products derived from drugs, along with nanoformulations showing cardioprotective activity, await research and clinical translation. Successful implementation of translational medicine in CVDs using nanoparticles requires collaborative efforts from bioengineers, pharmacists, chemists, biologists, and clinicians.

Challenges to overcome include institutional and industrial interests, infrastructure availability, patient preparation for treatment, outcome monitoring, patient registration in clinical trials, and addressing country-specific factors like compensation and affordability. Future research is expected to focus on peptides and antibodies for detecting CVD markers and developing selective nanodelivery systems. The trajectory of nano-cardiovascular medicine aims to evaluate the clinical effects of novel nanosystems to enhance the quality of life for individuals affected by cardiovascular diseases.

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