



An Overview About Nanoparticle Used For Target Drug Delivery System (TDDS) To The Heart

Mr. Dhiraj N. Chavhan^[1], Prof. Mukesh M. Nikhade^[2], Mr. Abhishek R. Kale^[3], Mr. Chaitanya M. Masatwar^[4], Mr. Hemanshu S. Rathod^[5],

Jagadambha Institute of Pharmacy & Research Kalamb, Maharashtra 445401, India ^[1-5]

ABSTRACT

More than half a billion people around the world continue to be affected by cardiovascular diseases, which accounted for 20.5 million deaths in 2021 – close to a third of all deaths globally and an overall increase on the estimated 121 million CVD deaths. An essential therapeutic method for a variety of cardiac illnesses is the efficient delivery of medications to the heart. Targeted medication delivery techniques have become more and more promising thanks to Nano carriers. Specific target locations, suitable drug delivery vehicles, and efficient drug delivery systems are key factors in the efficacy of Nano carriers for delivering medications to therapeutic areas in the heart focusing on ligands. Effective targeted medication delivery implies that a drug is specifically deposited in the heart after administration with little impact on other organs. Nano carrier may provide a solution to more effective treatment of disease, with better prognoses and a reduced side effect profile. This review provide a brief overview about Nanoparticle used for TDDS to the heart including their advantages, features, application and future prospective.

Keywords;

Cardiovascular disease, target drug delivery system, Nano-carrier, Nanotechnology, nanomaterial, Nanomedicine.

1. INTRODUCTION

By decade, cardiovascular disease will overtake all other causes of death as the leading cause of morbidity and mortality worldwide, particularly ischemia impairment. At the molecular level, the heart is a worrying organ since it is susceptible to illness in both children and adults. Morphogenesis, muscle function, and heart rhythm are all affected abnormally in human cardiac illness^[1] Direct administration of cardio protective medications to the circulatory system and infarcted myocardium is a potential treatment for heart disease. Targeted medicine delivery to the heart has become more popular as a result of the demand for better treatments^[2].

Successfully directing medicinal chemicals and their initial aggregation to the intended place is referred to as targeted drug delivery. A potential approach of targeted drug delivery that can deliver numerous molecules to particular areas in the body involves combining therapeutic medicines with nanoparticles and establishing appropriate targeting pathways^[3] The DDS must be kept in the physiological system for a sufficient amount of time to target particular cells and tissues and release the delivery medicine while preventing the immune system from destroying it in order to achieve high targeting effectiveness^[4]. Nanoparticles can increase the efficacy and safety of encapsulated payloads by increasing its stability and solubility, facilitating transmembrane transport, and extending cycle durations^[5].

It is always vital to adopt targeted medication delivery systems because they offer special benefits that increase effectiveness and minimize off-target effects. The most popular delivery methods for therapeutic ingredients to target tissues are nanoparticles (NPs). Lipids, polymers, dendrimers, carbon nanotubes, and

metallic nanoparticles are only a few examples of the nanomaterials and structures that may be included into NPs to deliver therapeutic drugs [6,7]. Because to their distinct biological characteristics and biocompatibilities, NPs have attracted a lot of interest in the field of cardiovascular medicine. Nanomaterials have special qualities that set them apart from conventional vectors, such as regulated and prolonged release, decreased drug degradation, adverse effects, and higher in vivo effectiveness.[8]

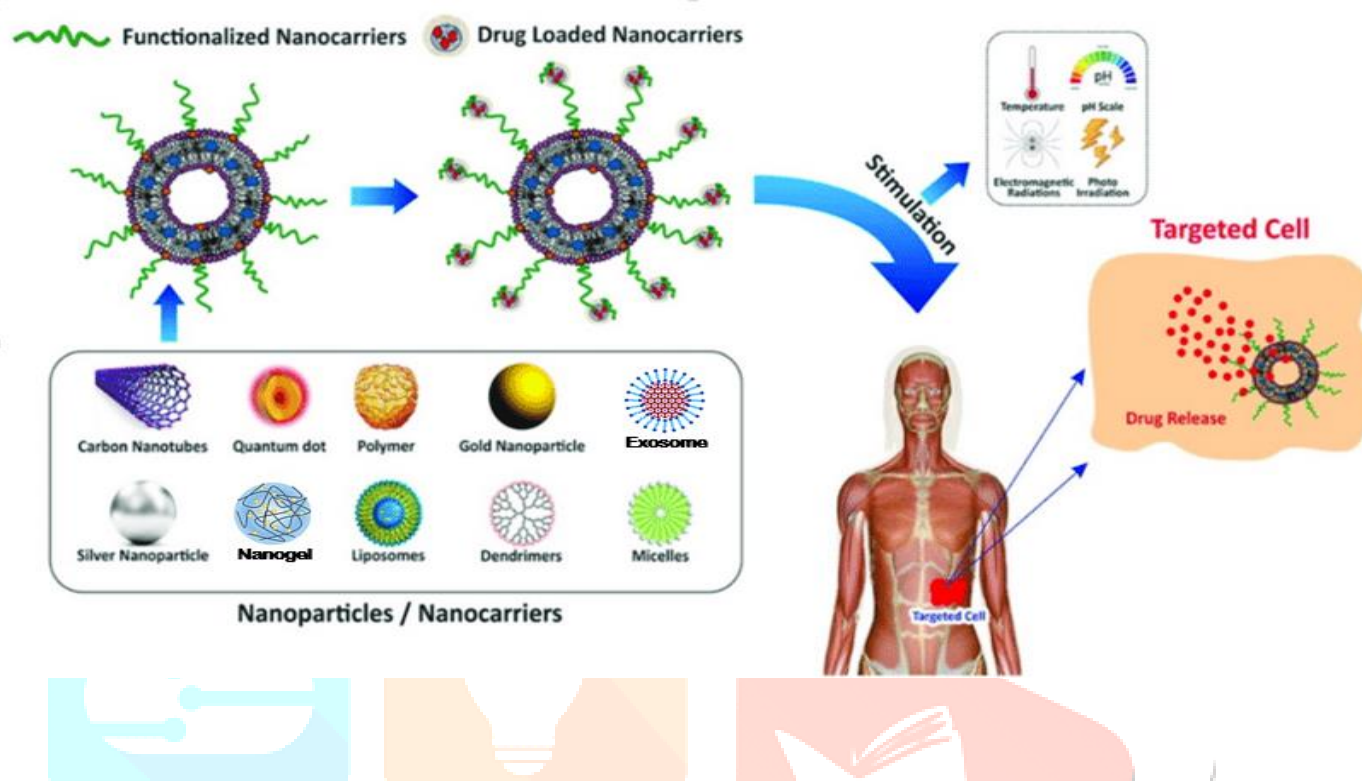


Figure 1; representation of different nanoparticles reaching targeted sites. [9]

2. Advantages of Nanoparticle / Nano-carrier

Nano-carriers, which encompass a range of nanoscale delivery systems such as nanoparticles, liposomes, micelles, and dendrimers, offer distinct advantages when employed in cardiac drug delivery. These advantages contribute to the precision and effectiveness of therapeutic interventions for cardiovascular diseases. Here are the key advantages of Nano-carriers in this context:

2.1 Targeted Drug Delivery:

Nano-carriers can be engineered to target specific cells, tissues, or receptors in the cardiovascular system, ensuring the precise delivery of drugs to the heart. This minimizes off-target effects and enhances drug efficacy while reducing systemic exposure.

2.2 Enhanced Drug Solubility:

Many cardiac drugs have poor solubility, which can limit their effectiveness. Nano-carriers can solubilize hydrophobic drugs, improving their bioavailability and therapeutic action.

2.3 Controlled Drug Release:

Nano-carriers can be designed to release drugs in a controlled and sustained manner. This is particularly advantageous for cardiac conditions that require continuous medication, such as hypertension or heart failure.

2.4 Protection of Therapeutic Agents:

Nano-carriers shield encapsulated drugs from degradation in the bloodstream, ensuring their stability during transit to the heart. This is crucial for drugs susceptible to enzymatic or chemical breakdown.

2.5 Reduction of Side Effects:

By delivering drugs directly to the heart, Nano-carriers reduce systemic exposure, reducing the risk of side effects in other organs and tissues. This is particularly important when dealing with medications that may have cardio toxic effects.

2.6 Combination Therapies:

Nano-carriers can encapsulate multiple drugs, enabling combination therapies that address different aspects of cardiovascular diseases simultaneously. For instance, they can carry anticoagulants, anti-inflammatories, and vasodilators in one formulation.

2.7 Improved Pharmacokinetics:

Nano-carriers can modify the pharmacokinetics of drugs, prolonging their circulation time in the bloodstream and enhancing their therapeutic effect.

2.8 Reduced Dosage Frequency:

Enhanced drug stability and controlled release allow for less frequent dosing, improving patient compliance and overall treatment outcomes.

2.9 Cardiac Regeneration:

Some Nano-carriers can deliver regenerative therapies, such as growth factors or stem cells, directly to damage cardiac tissue, promoting tissue repair and regeneration.

2.10 Diagnostic Applications:

Nano-carriers can serve as contrast agents in cardiac imaging techniques, providing real-time visualization of the heart's structure and function, aiding in diagnostics and monitoring.

2.11 Personalized Medicine:

Nano-carriers enable personalized medicine by tailoring drug delivery systems to individual patient profiles, optimizing treatment outcomes while minimizing side effects and adverse reactions.

2.12 Minimized Toxicity:

Nano-carriers, when designed with biocompatible materials, can minimize toxicity concerns associated with drug delivery systems.

2.13 Less Invasive Routes:

Nano-carriers offer opportunities for less invasive routes of drug administration, such as intravenous, intracoronary, or intramyocardial, minimizing patient discomfort and improving therapy adherence.

In summary, Nano-carriers hold great promise in the field of cardiac drug delivery, allowing for targeted, controlled, and effective therapies for various cardiovascular diseases. Their unique advantages contribute to improved patient outcomes, reduced side effects, and the potential for innovative solutions in cardiac healthcare. However, careful consideration of biocompatibility, toxicity, and clinical translation is essential for harnessing their full potential.

3. NANOPARTICLE USED FOR TDDS TO HEART

Several types of nanoparticles and Nano-carriers have been explored for targeted drug delivery to the heart. These nanoscale delivery systems are designed to improve drug efficacy, reduce side effects, and enhance the therapeutic outcomes for cardiovascular diseases. Some commonly studied nanoparticles and Nano carriers for heart-specific drug delivery include:

- 1) Carbon Nanotube
- 2) Polymeric Nanoparticle
- 3) Dendrimer
- 4) Liposome
- 5) Silver Nanoparticle
- 6) Quantum Dots
- 7) Micelles
- 8) Gold Nanoparticle
- 9) Nano gels
- 10) Exosomes

3.1 CARBON NANOTUBE (CNT)

Heart disease is a leading cause of mortality worldwide, necessitating innovative approaches to improve drug delivery and therapy efficacy. Carbon nanotubes (CNTs), a remarkable nanomaterial, have emerged as a promising solution for enhancing drug delivery to the heart. Their unique properties, including high surface area, excellent biocompatibility, and the ability to transport therapeutic agents to target sites, make CNTs a groundbreaking tool in the field of cardiovascular medicine.

3.1.1 The Features of Carbon Nanotubes (CNT):

High Surface Area:

CNTs possess an extraordinarily high surface area, providing a vast area for drug loading and functionalization. This feature enables the attachment of various therapeutic molecules, such as drugs, peptides, or proteins, to the CNTs' surface, improving drug solubility and stability.

Targeted Drug Delivery:

CNTs can be modified with ligands or antibodies that specifically target heart cells or tissues. This targeted approach ensures that therapeutic agents are delivered precisely to the affected area, minimizing side effects and maximizing the drug's effectiveness.

Controlled Release:

Carbon nanotubes can be engineered to release drugs gradually, allowing for sustained drug delivery over an extended period. This controlled release mechanism is particularly advantageous in treating chronic heart conditions, where continuous medication is required.

Improved Pharmacokinetics:

CNTs can enhance the pharmacokinetics of drugs by increasing their circulation time in the bloodstream. This prolonged presence of drugs in the body increases their chances of reaching the heart and exerting their therapeutic effects.

Biocompatibility:

CNTs exhibit excellent biocompatibility, reducing the risk of adverse reactions or toxicity. Extensive research has demonstrated that properly functionalized CNTs can be safely used in drug delivery systems.

3.1.2 Applications of Carbon Nanotube in Heart Disease

Ischemic Heart Disease:

CNTs can carry drugs that promote angiogenesis, helping to restore blood flow to ischemic heart tissue. They can also transport anti-inflammatory agents to reduce inflammation in damaged heart muscles.^[10]

Heart Failure:

CNT-based drug delivery systems can deliver drugs that improve contractility and reduce oxidative stress in the heart, addressing key aspects of heart failure management.^[11]

Arrhythmias:

CNTs can be utilized to transport anti-arrhythmic drugs, ensuring precise and controlled release at the arrhythmogenic sites in the heart.^[12]

3.2 POLYMERIC NANOPARTICLE

Heart diseases, including coronary artery disease, heart failure, and arrhythmias, continue to be leading causes of morbidity and mortality worldwide. Effective treatment often requires precise drug delivery to the heart tissue. Polymeric nanoparticles have emerged as a promising platform for delivering therapeutic agents to the heart, offering controlled release, targeted delivery, and improved drug stability.

3.2.1 Composition and Structure:

Polymeric nanoparticles used in heart drug delivery are typically composed of biocompatible and biodegradable polymers. Common choices include poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and chitosan. These nanoparticles can be engineered to have specific sizes and structures, such as core-shell or multi-layered designs, to optimize drug encapsulation, release kinetics, and targeting capabilities.

3.2.2 Applications in Heart Disease**Ischemic Heart Disease:**

Polymeric nanoparticles can carry drugs that promote angiogenesis, helping to restore blood flow to ischemic heart tissue. They can also transport anti-inflammatory agents to reduce inflammation in damaged heart muscles.^[13]

Heart Failure: Nanoparticles can deliver drugs that improve cardiac contractility and reduce oxidative stress, addressing key aspects of heart failure management^[14].

Arrhythmias: Polymeric nanoparticles can transport anti-arrhythmic drugs to specific sites in the heart, ensuring controlled and targeted release at arrhythmogenic foci.^[15]

3.3 DENDRIMER

Dendrimers are highly branched, three-dimensional macromolecules with a well-defined and symmetric structure. They consist of a central core, repeated branching units, and terminal functional groups. This architecture allows for precise control over size, molecular weight, and surface properties, making dendrimers ideal carriers for therapeutic agents.

They are Nano-sized, radially symmetric molecules with well-defined, homogeneous, and monodisperse structure that has a typically symmetric core, an inner shell, and an outer shell. For example, dendrimer NPs loaded with simvastatin acid were designed with the ability to adsorb to the surface of red blood cells, providing reactive oxygen stress (ROS) and shear stress dual-sensitive bionic systems.^[16] Dendrimers with drug delivery capability and the availability of multiple functional groups can be used for stabilizing drugs, improving the solubility of therapeutic agents, and improving the sustained/controllable release of drugs/bioactive agents. The developed devices with prolonged release characteristic therefore shown superior atherosclerosis treatment effects and great in vivo safety. After cardiac arrest, dendrimer-N-acetylcysteine conjugate Nano systems were created to target activated microglial cells and increase survival rates, neurological recovery, and short-term motor deficits^[17,18]. These Nano systems provide potentially effective methods for treating post-cardiac arrest syndrome^[19].

3.3.1 Application in Heart Disease

Anti-inflammatory Therapies:

Dendrimers have been used to deliver anti-inflammatory agents to mitigate the inflammatory response often associated with myocardial infarction and heart failure^[20]

Gene Therapy:

Dendrimers can facilitate the delivery of therapeutic genes to cardiac cells, potentially offering a revolutionary approach for treating genetic cardiovascular disorders.^[21]

Cardioprotective Agents:

Dendrimer-based carriers have been explored for delivering cardioprotective drugs, which can reduce ischemia-reperfusion injury during cardiac surgeries^[22].

Dendrimers represent a promising avenue for improving drug delivery to the heart, offering precision, control, and versatility in targeting cardiac tissues. While there are many challenges remain in terms of biocompatibility, toxicity, and clinical translation, ongoing research and innovation hold great potential for dendrimer-based cardiac therapies. As our understanding of dendrimer technology continues to evolve, we may witness significant breakthroughs in the treatment of cardiovascular diseases, ultimately leading to improved patient outcomes and a healthier global population.

3.4 LIPOSOMES

A liposome is a small artificial vesicle (about 50-200nm in size), spherical in shape, having at least one lipid bilayer^[23]. They are very biocompatible because their structure resembles the phospholipid bilayer found naturally in cell membranes. Hydrophilicity and hydrophobicity together allow liposomes to function as efficient drug delivery vehicles. Based on the size and quantity of bilayers, liposomes may be divided into three categories. A liposome's characteristics can be attributed to a variety of elements, including lipid content, surface charge, technique of formation, and variable size^[24]. Multilamellar vesicles (MLV) have many bilayers of lipid, while small unilamellar vesicles (SUV) have just one. Large unilamellar vesicles (LUV) resemble SUVs.^[24] Poly(ethylene glycol) (PEG) can be added to liposomes to manipulate their surface and give the carrier "stealth"-like characteristics.^[25] The "stealth liposomes" have a longer half-life in circulation, less absorption, and less liver or phagocyte clearance.^[24] Moreover, particular regions of the liposomal surface can be targeted by attaching antibodies or other targeting moieties to it.^[26] Due to the processes of platelet aggregation in myocardial infarction, atherosclerosis, and thrombosis, platelet-targeted liposomal drug delivery may prove to have potential therapeutic application^[27] In regard to applications in cardiovascular medicine, liposomes have the potential to be utilized to treat peripheral artery disease and intermittent claudication.^[28]

Comparatively speaking, liposomes have been around for a while, but polymer-based systems are probably going to be therapeutically useful sooner. There are certain drawbacks, nevertheless, as shown in other liposomal drug delivery applications. Among concerns include the systems' short-term instability, which leads to medication release that happens too soon. Additionally, they are frequently more costly and less effective than certain polymer-based systems because to the requirement for higher excipient-to-drug ratios.^[29]

3.4.1 Application in Heart Disease

Doxorubicin:

Liposomal doxorubicin formulations have been developed to reduce cardiotoxicity while maintaining anticancer efficacy.^[30]

Antioxidants:

Liposomes have been used to deliver antioxidants, such as coenzyme Q10 and vitamin E, to combat oxidative stress in cardiac tissues.^[31]

Sirna Therapies:

Liposomes have been investigated for delivering small interfering RNA (siRNA) to silence genes associated with cardiac diseases, offering a potential gene therapy approach^[32]

Liposomes have emerged as a promising tool in drug delivery to the heart, offering targeted and controlled release of therapeutic agents while minimizing side effects. Ongoing research and advancements in liposomal technology are paving the way for more effective treatments for cardiovascular diseases.

3.5 SILVER NANOPARTICLE

Between 1 and 100 nm in size, silver nanoparticles are actively studied nanostructures. They are mainly utilized for novel and improved biological applications, including medication delivery, tissue scaffolding, wound dressings, and protective coatings. Additionally, Nano-silver's remarkable accessible surface permits the coordination of several ligands, opening up a world of possibilities for the surface functionalization of silver nanoparticles. Silver nitrate (NO_3^-) is commonly utilized for its antibacterial properties^[33].

Apart from this, AgNPs are used to treat CVS disease because they have the ability to produce a variety of effects, including cytotoxic, apoptotic, phagocytic, vasodilation/vasoconstriction, angiogenic/antiangiogenic, and most of these effects depend on the concentration, size, biological target, and exposure time^[34-42].

Significant advancements in the diagnosis, treatment, and prevention of cardiovascular disorders are being produced by all these potentially advantageous applications and impacts of NPs, whether they are linked at distinct ligands or adapted in devices as indicators or detectors. However, under both normal and pathological settings, the side effects that NPs may have on the circulatory system and biodistribution must be addressed. These effects may change how NPs are transported across vessel walls, how they are delivered to specific organelles, and how they affect vascular cells in other ways.^[43-47,37-39]

3.5.1 Application of AgNP in cardiac drug delivery

Antioxidants:

AgNPs can deliver antioxidants like coenzyme Q10 to the heart, combating oxidative stress, which is a contributing factor in many cardiac diseases^[48].

Antithrombotic Agents:

AgNPs can be functionalized to carry antithrombotic drugs to prevent blood clots in the coronary arteries^[49].

Cardiac Imaging:

AgNPs with imaging capabilities, such as MRI contrast agents, can be employed for cardiac imaging and diagnosis^[50].

Silver nanoparticles hold significant potential in revolutionizing cardiac drug delivery by offering targeted, controlled, and effective therapies for heart-related conditions. Their unique properties, including antibacterial activity and controlled drug release, make them versatile carriers for therapeutic agents.

3.6 QUANTUM DOTS

Quantum dots (QDs) are nanoscale semiconductor particles with unique optical and chemical properties that have attracted considerable attention in various fields, including drug delivery. They are considered efficient fluorescent labels used in a drug delivery system for monitoring the metabolism process of drugs in the body owing to the unique physicochemical characteristics^[51]. Targeted delivery of therapeutic agents to the heart is essential for improving the treatment of heart diseases. Quantum dots, due to their tunable size, exceptional optical properties, and surface functionalization capabilities, hold significant promise for enhancing drug delivery to the heart.

3.6.1 Applications of Quantum Dots in Cardiac Drug Delivery

Targeted Drug Delivery:

Quantum dots can be functionalized with cardiac-specific ligands or antibodies, enabling them to target receptors or biomarkers on cardiac cells. This targeted approach enhances drug delivery precision and minimizes side effects^[52].

Imaging and Diagnostics:

Quantum dots serve as versatile contrast agents for cardiac imaging techniques like fluorescence imaging, magnetic resonance imaging (MRI), and computed tomography (CT). Their exceptional brightness and tunable fluorescence properties enable early detection and diagnosis of cardiac diseases^[53].

Therapeutic Payload:

Quantum dots can encapsulate therapeutic drugs, genes, or peptides, enhancing their stability and targeted delivery to the heart. This is particularly important for treating conditions like heart failure, where precise drug localization is crucial ^[54].

Cardiac Regeneration:

Quantum dots can be utilized to deliver regenerative therapies, such as stem cells or growth factors, directly to damage cardiac tissue, promoting tissue repair and regeneration ^[55].

Quantum dots hold tremendous potential in revolutionizing drug delivery to the heart, offering precision, real-time imaging capabilities, and targeted therapies for cardiac diseases.

3.7 MICELLES

A hydrophilic "head" and a hydrophobic "tail" are the common configurations of amphiphilic molecules that make up micelles. In an aqueous solution, micelles are created with the polar part facing the micelle's exterior and the nonpolar region forming the micelle's core. Micelles are capable of delivering hydrophilic and hydrophobic substances. ^[56]

3.7.1 Application of Micelles in drug delivery to Heart**Antioxidants:**

Micelles have been used to deliver antioxidants, such as coenzyme Q10 or vitamin E, to combat oxidative stress in cardiac tissues ^[57].

Anti-Inflammatory Agents:

Micelles can encapsulate anti-inflammatory drugs for targeted therapy in conditions like myocarditis or post-infarction inflammation ^[58].

Gene Therapy:

Micelles have been explored as carriers for delivering therapeutic genes to treat genetic cardiovascular disorders ^[59].

3.8 GOLD NANOPARTICLE

The advanced features of colloidal gold nanoparticles (AuNPs), including their large surface-to-volume ratio and the ability to modify their charge, hydrophilicity, and activity through surface chemistries, make them attractive as non-toxic drug delivery vehicles. ^[60]

Heart failure and coronary artery disease are two examples of cardiovascular illnesses that continue to be a major global cause of morbidity and death. To improve treatment results, it is essential to deliver drugs to the heart effectively. Due to their distinct physicochemical characteristics, gold nanoparticles (AuNPs) have become a viable drug delivery vehicle to help with the difficulties associated with identifying and treating cardiac conditions.

3.8.1 Application of Gold nanoparticle in drug delivery to Heart**Targeted Drug Delivery:**

AuNPs can be functionalized with ligands or antibodies that specifically bind to cardiac cell receptors, enabling precise drug targeting and reducing off-target effects ^[61].

Imaging and Diagnosis:

AuNPs are utilized as contrast agents in imaging techniques like computed tomography (CT) and photoacoustic imaging, allowing for non-invasive cardiac imaging and diagnosis ^[62].

Therapeutic Payload:

AuNPs can carry various therapeutic agents, such as drugs, genes, or peptides, to the heart. These agents can treat conditions like heart failure, myocardial infarction, and arrhythmias ^[63].

Photothermal Therapy:

Gold nanoparticles can be used for photothermal therapy, where they absorb near-infrared light and convert it into heat, selectively destroying cardiac tissue or drug-resistant cells ^[64].

Gold nanoparticles represent a valuable asset in advancing drug delivery to the heart, offering precise targeting, imaging capabilities, and versatile therapeutic cargo delivery. As researchers continue to explore and optimize AuNP-based drug delivery systems, they have the potential to play a pivotal role in personalized cardiac medicine. Gold nanoparticles can enhance patient outcomes, minimize side effects, and provide innovative solutions for the treatment of heart-related conditions, ultimately contributing to the improvement of cardiac healthcare.

3.9 NANOGELS

Strong, inflated, cross-linked polymer nanoparticles known as nanogels can be employed as biodegradable, extremely effective drug delivery vehicles. Their unique qualities, such as their capacity to encapsulate a wide range of therapeutic agents, controlled drug release, and targeted delivery capabilities, have made them a potential class of nanomaterial for cardiac drug administration.^[65] Hydrogel nanoparticles having a three-dimensional network structure are called nanogels. They are made of hydrophilic polymers, which are able to hold and absorb enormous volumes of biological fluids or water. Nanogels are the best options for drug delivery applications because of their special structure.

3.9.1 Application of Nanogel in Drug Delivery to Heart

Cardioprotective Agents:

Nanogels can deliver cardioprotective agents to reduce ischemia-reperfusion injury and improve cardiac function after myocardial infarction^[66].

Anti-Inflammatory Therapies:

Functionalized nanogels have been used to deliver anti-inflammatory drugs, mitigating inflammation associated with various cardiac conditions^[67].

Gene Therapy:

Nanogels can serve as carriers for gene therapies, delivering therapeutic genes to treat genetic cardiovascular disorders^[68] Nanogels hold significant promise in enhancing drug delivery to the heart, offering precision, controlled release, and targeted therapies for cardiovascular diseases

3.10 EXOSOMES

Exosomes are small, lipid bilayer-enclosed vesicles secreted by a variety of cells, including cardiomyocytes and stem cells. They play a pivotal role in cell-to-cell communication by transferring proteins, nucleic acids (including RNA and DNA), and lipids between cells. Exosomes have gained attention for their potential as drug delivery vehicles^[69].

3.10.1 Application of Exosomes in Drug Delivery to Heart

Cardiac Regeneration:

Stem cell-derived exosomes can be used to deliver regenerative therapies, such as miRNAs or growth factors, directly to damage cardiac tissue to promote tissue repair and regeneration^[70,71].

Anti-Inflammatory Therapies:

Exosomes can deliver anti-inflammatory agents to mitigate inflammation in cardiac conditions like myocarditis or post-infarction inflammation^[72].

Gene Therapy:

Engineered exosomes can serve as carriers for gene therapies, delivering therapeutic genes to treat genetic cardiovascular disorders^[73].

CONCLUSION:

Nanoparticles represent a cutting-edge approach to heart drug delivery, offering precise targeting, controlled release, and improved drug stability. As research in nanomedicine advances, nanoparticle-based drug delivery systems hold the potential to revolutionize the treatment of heart diseases, providing patients with more effective and safer therapeutic options.

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