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Chapter 8: Polymeric and Solid Lipid Nanoparticles in Cardiovascular Nano-Therapeutics

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Abstract

Cardiovascular Diseases (CVD) rank as the primary global cause of death which results in more than 17 million deaths each year. Atherosclerosis and endothelial dysfunction and plaque instability start to develop in CVD patients because of inflammatory processes. The disease becomes worse because people lead unhealthy lives through their poor eating habits and inactive lifestyles and their use of tobacco and alcohol. Conventional treatments require replacement because of multiple issues that include low drug solubility and rapid systemic clearance and imprecise targeting abilities and off-target toxicity and multiple side effects that include dizziness and stroke and gastrointestinal bleeding and electrolyte imbalance. The drug delivery systems based on nanotechnology provide a new solution which enhances stability and bioavailability and targeted delivery for medical applications. The two most effective platforms for cardiovascular treatment among different nanocarriers are polymeric nanoparticles PNPs and solid lipid nanoparticles SLNs. The chapter investigates the new field of nanoparticles which includes Polymeric Nanoparticles and Solid Lipid Nanoparticles as a method for treating cardiovascular disease. The research studies how these nanoparticles differ from one another through their solubility and stability and bioavailability and capacity to target blood vessels. The research presents both the safety regulations and molecular pathways which these formulations control while discussing their essential elements which must be considered for safety and regulatory approval and control over production. The final section of the document examines current developments and upcoming developments which include hybrid nanocarriers and personalized nanotherapeutics.

Keywords: *Cardiovascular Diseases, Solid Lipid Nanoparticles, Polymeric Nanoparticles, Nanotechnology, Drug release*

1. INTRODUCTION

Cardiovascular diseases (CVDs) represent one of the primary causes of death throughout the world. The WHO reported that 19.8 million people died in 2022 which accounted for 32 percent of worldwide deaths. The majority of deaths which make up 85% of the total fatalities result from heart attacks and strokes. The World Health Organization (WHO) states that CVDs impact low- and middle-income countries at greater rates since this group experiences more than 75% of CVD fatalities due to insufficient healthcare services and prevention programs. The increase in CVD-related deaths occurs at an alarming rate which accounts for 38% of total noncommunicable disease-related deaths that affect people under age 70 in 2021. The statistics demonstrate an escalating emergency because global CVD-related deaths increased from 12.4 million in 1990 to 19.8 million in 2022 which resulted from population aging and avoidable health risks. CVD burden develops through the interaction of metabolic risk factors with behavioral risk factors and environmental risk factors. Metabolic risks drive health problems through various physical conditions which include high systolic blood pressure (SBP) and high fasting plasma glucose (FPG) and high body mass index (BMI) and elevated low-density lipoprotein cholesterol levels and kidney dysfunction. Poor dietary choices and tobacco usage and insufficient physical activity and alcohol consumption create behavioral problems which worsen the situation. Air pollution and suboptimal temperature conditions and household air pollution from solid fuels create environmental risks which contribute to the problem. The Solid fuels household air pollution situation caused a 65.1% decline in attributable DALYs from 1990 to 2022 because of implemented interventions. The dietary risks and rising obesity rates present major obstacles for low and middle income countries located in sub-Saharan Africa and North Africa and South Asia regions.

The cardiovascular system functions as the body's second most important communication system while the nervous system serves as the primary communication system. The main purpose of this system is to transport electrolytes together with nutrients and oxygen throughout the entire body. This process enables all organs to function properly while maintaining stable internal body conditions (Hendgen-Cotta et al., 2014) The cardiovascular system operates as a closed system that enables blood circulation throughout the entire human body. Blood circulation begins in arteries which branch into smaller vessels known as arterioles and eventually reach their smallest form called capillaries. The system consists of two components which include pulmonary circulation that delivers blood to the lungs for oxygen intake and systemic circulation that distributes oxygenated blood to all body organs. The system consists of three essential components which include the heart, blood vessels, and blood. The heart functions as the primary organ responsible for blood circulation. The heart processes approximately 7000 liters of blood every single day. The heart processes waste materials together with electrolytes and gases through a process that transfers these substances between blood and adjacent tissues. The heart functions as a muscular organ which exists between the lungs inside the mediastinum space. The heart operates as a muscular pump which moves blood throughout the human circulatory system. The heart occupies a space which matches the dimensions of an average adult's fist with a width of 9 centimeters and length of 14 centimeters. The heart gets protected by three different layers which

are known as pericardial membranes which include fibrous pericardium, parietal pericardium, and visceral pericardium which is also called epicardium. The outer sac consists of tough fibrous material while the middle layer covers both the diaphragm and major blood vessels and the fluid that exists between the parietal and visceral layers helps to minimize friction throughout heart operation. These membranes create an enclosure around the heart muscle (myocardium) which constructs the four heart chambers according to endocardium's thin interior lining. (*Cardiovascular System - an Overview | ScienceDirect Topics*, n.d.).

The cardiac cycle is a sequence of pressure changes in the heart that moves blood through its chambers and the body. These changes happen because of electrical signals in the myocardium, causing the heart muscle to contract. Valves in the heart guide the blood flow, ensuring it moves smoothly from one chamber to the next (Pollock & Makaryus, 2022a). The cardiac cycle or cardiac rhythm happens in 0.8 seconds, which involves the relaxation and contraction of both the atria and ventricles (Cardiac Cycle | Anatomy and Physiology II, n.d.).The cardiac cycle has two phases: diastole and systole. Diastole is when the ventricles relax and fill with blood, starting when the aortic or pulmonic valve closes and ending when the mitral or tricuspid valve closes. Systole is when the ventricles contract, pushing blood into the arteries, starting with the mitral or tricuspid valve closing and ending with the aortic or pulmonic valve closing. This happens in both the right and left sides of the heart, with different pressures (Pollock & Makaryus, 2022b). The vascular system maintains cellular homeostasis by ensuring cells receive essential nutrients and oxygen while removing metabolic waste. Arteries deliver blood containing oxygen and nutrients, such as vitamins and minerals, to capillaries, where these substances diffuse into tissues to support cell growth and function (Pugsley & Tabrizchi, 2000).

The term cardiovascular disease describes multiple medical conditions which impact both the heart and blood vessels. The medical field uses blood tests to identify these conditions by measuring cardiac markers. Cardiac troponins serve as the most reliable biomarkers because they detect heart muscle damage with high sensitivity and specificity according to Vasatova and colleagues 2013 study. The World Health Organisation reports that Cardiovascular diseases represent the primary global cause of death, resulting in approximately 17.9 million fatalities each year. Heart attacks and strokes account for more than 80% of deaths which occur due to cardiovascular diseases(CVD). One third of these deaths occur among individuals who have not yet reached 70 years of age Cardiovascular Diseases n.d. report. The regions of Central Europe, Eastern Europe and Central Asia report the highest cardiovascular disease CVD death rates across the globe. The majority of men experience higher CVD death rates than women, but this pattern exists in almost 30% of North African, Middle Eastern and Sub-Saharan African countries. The year 2019 recorded high blood pressure as the most significant global CVD risk factor which resulted in 10.8 million deaths. (Di Cesare et al., 2024).

2. PATHOPHYSIOLOGY

The plaque formation in Atherosclerosis starts with the accumulation of Low density lipoprotein (LDL) in the atrial wall (inner wall of the blood vessel). This causes oxidative attack on LDL resulting in monocytes gathering around and getting converted into macrophages, eventually leading to the absorption of oxidized LDL by macrophages after which they become foam cells (*[Atherosclerotic Plaque Formation] - PubMed*, n.d.). The atherosclerotic plaque consists of lipids that triggers inflammatory reaction leading to non uniform flow with bringing the onset of CVD (*Atherosclerosis - StatPearls - NCBI Bookshelf*, n.d.; Pahwa & Jialal, 2023). Atherosclerosis is observed due to continuous lesion of atrial wall called intima due to the retention of lipids by proteoglycan matrix that sticks to the wall. This results in the progression of the disease by inducing chronic inflammation, worsening the damage and driving the disease forward. It starts with small fatty streaks in the arteries and later on grows into hardened plaque. This damage of the intima in other words can be described as endothelial dysfunction where, as discussed earlier, the LDL gathers within vascular wall and modifies into oxidized LDL (ox LDL) that being a crucial immunogen triggers an immune response. The process of LDL release starts the release of Bioactive phospholipids which activate the cells to connect with signaling proteins through their integrin receptors that bind to intracellular adhesion molecule 1 and vascular cell adhesion molecule 1 and endothelial cell-leukocyte adhesion molecule 1 to create pathways for inflammatory immune cells that produce inflammation inside the intima. The immune cells together with mast cells produce chemical substances known as cytokines which have the ability to either increase or decrease the process of inflammation and they influence the behavior of immune cells through their movement and growth and death and the development of changes in the artery wall structure. The process causes atherosclerosis because it creates plaques which have the potential to develop into more severe conditions. (Hansson, 2009) (Fig.8.1).

This plaque hardens gradually and is prone to rupture which can lead to arteries break open causing serious health concerns. The plaque has a thin fibrous cap with few smooth muscle cells (SMCs) and lots of fats, with plenty of macrophages and T lymphocytes. They also contain tissue factors that can trigger blood clotting. The core of the plaque aka necrotic core is filled with cholesterol crystals and macrophages making it unstable. There are several factors that can lead to rupture like matrix metalloproteinases (MMPs) that with it's enzymatic activity and weaken the can, high blood pressure, macrophage calcification and iron deposition, making the plaque even more dangerous and increasing the risk of thrombosis or clot formation (Pahwa & Jialal, 2023).

Coronary circulation coordinates the vascular resistances to match the blood flow with myocardial oxygen demand (Cagnina et al., 1999). Myocardial infraction can be described as the myocytes (heart muscle cell) death due to blocked blood flow and lack of oxygen (Ischemia) for prolonged duration. If the ischemia continues for about 10 to 15min, lower cellular glycogen levels, loosened myofibrils (heart muscle fibers) and damage to the cell membrane (sarcolemma) can be observed. Coronary occlusion (blocked arteries) can result in abnormal functioning of the mitochondria in a span of 10 mins. Subsequently, Myocyte necrosis can be

observed which can be described as the heart cell death due to lack of blood supply and it has a tendency of spreading from subendocardium (inner heart layer) to subepicardium (outer heart layer) over the following hours. Though such necrosis is irreversible but this process can be slowed down by providing extra blood flow (Thygesen et al., 2018) . When cells experience ischemia, they immediately show changes in the structure and function due to low energy supply. To understand what causes cell death, researchers focus on whether these changes can be reversed. Key signs of irreversible injury are failure to fix mitochondrial function and damage to the plasma membrane. Studies show that mitochondrial abnormalities comes from problems with long chain acyl CoA metabolism, which blocks aenine nucleotide translocation and increases inner mitochondrial membrane permeability due to excess Ca2+ ions. These issues can only be reversed if cells are reoxygenated before a massive buildup of intracellular Ca2+ ions, that usually occurs when phospholipids are lost from other cell parts (Farber et al., 1981) . The heart works as a heterocellular organ because it contains different types of cells which include cardiomyocytes endothelial cells vascular smooth muscle cells pericytes fibroblasts neurons and all resident and invading immune cells. Myocardial infarction (MI) was mainly blamed on cardiomyocyte necrosis. The recent study shows that myocardial ischemia/reperfusion injury develops from destruction of the coronary microcirculation system which contains the heart's tiny blood vessels. (damage from lack of oxygen and blood flow, worsened when blood flow returns) (Heusch, 2024).

Formation of blood clot (Thrombus) inside a blood vessel that ultimately restricts or obstructs the blood flow through the circulatory system is known as Thrombosis. It can take place in arteries or veins and have a varied clinical implication. This condition includes myocardial infraction, ischemic stroke and venous thrombosis. Venous Thromboembolism (VTE) involves deep vein thrombosis and pulmonary embolism (Wendelboe & Raskob, 2016).The formation is influenced by alterations of the vascular wall, blood flow and blood content. Though the occurrence of atherosclerosis and it’s plaque disruption can be considered as key factors in atherothrombosis especially for the onset of VTE. Autopsies and various scan results shows that atherothrombosis dosen’t always block the arteries completely or causes obvious symptoms. Infact clinical studies found that around 40% of DVT cases show none of the symptoms. This implies that the growth of the clot determines whether it will lead to chronic conditions like atherothrombosis or venous thromboembolism (VTE) (Yamashita & Asada, 2023). Thrombosis is commonly observed at the venous valves, that are critically responsible for aiding blood circulation in the legs but are also prone to stasis and hypoxia. Autopsy studies have showed that the venous valvular sinus is a common site for the initiation of thrombosis. Slowed blood flow in such areas take around 27 minutes to clear after venography (imaging), This stasis is a part of Virchow’s triad,(along with the vessel damage and clotting tendency) leads to low oxygen and high red blood cell concentration, making the area prone to clotting. Animal studies show a drop in blood flow in the case of oxygen level drop (Esmon, 2009). Recent studies in genetically modified mice show two separate ways platelets can be activated: one triggered by exposed collagen and the other by thrombin from tissue factor, either from the vessel wall or in the blood. Depending on the type of injury or disease, one pathway may be more active, but both lead to the same result—platelet activation and clot formation. The endothelium

produces three substances- Nitric Oxide, prostacyclin, and CD39 (prevents blood clots). Collagen and tissue factor present beneath endothelium helps keep the circulatory system sealed. At the time of damage in the endothelium collagen and tissue factor come into contact with blood and initiates the formation of clots (Shibata et al., 2008).

Collagen activate platelets by accumulating them and tissue factors creates thrombin which also activates platelets and turns fibrinogen into Fibrin. This enables the creation of a platelet plug. It involves enzymes activated in a chain reaction, speeding up clot formation. Some key clotting factors (II, VII, IX, X, and proteins C and S) depend on vitamin K, which is needed for their production in the liver. Under normal conditions they are removed by the fibrinolytic system. If clot grows too large or persists (due to continued stimulus, poor resolution, or obstruction), it can be pathologic, causing ischemia, embolism, etc (ALEXANDER, 1962).

As the name suggest Heart failure is the dysfunction of heart for pumping blood to the organ leading to severe health concern and even death. When the heart doesn't pump blood effectively, body to display symptoms like shortness of breath, swelled ankles and lethargy and tiredness. Other signs includes swelling of neck vein swelling, lung crackling sound, buildup of fluid in tissues, resulting due to damaged heart muscles, faulty heart valves, abnormal rhythm of heart leading to fluctuation in the pumping and pressure of Blood and it’s flow (Schwinger, 2021a).

Finding the key problem can help choosing the accurate treatment such as fixing valves, managing heart rhythm, or using medications. Root causes of heart failure includes high blood pressure , diabetes, family history, obesity, lung conditions, infections, or exposure to heart-damaging substances like cocaine, alcohol, or cancer drugs (e.g., anthracyclines like doxorubicin) (Cardinale et al., 2015). Heart failure worsens over time. Coronary artery diseases can be considered as the onset of Heart failure, which results in reduces blood flow to the heart. The body tries to compensate for this by boosting the pumping, when these efforts crash gradually, harmful malfunctions occur. The body activates the sympathetic nervous system which, increases the heart rate and blood vessel narrowing, but this reduces the heart’s responsiveness over time, causing heart muscle thickening and overworking. The renin-angiotensin-aldosterone system (RAAS) also starts, which narrows the blood vessels and retaining sodium and water, which strains the heart further (Opie et al., 2006; Schwinger, 2021b). The lethargic reaction (lowered heart output) triggers hormones like epinephrine, norepinephrine, endothelin-1, and vasopressin, which tighten blood vessels, increasing the heart’s workload. This raises calcium levels in heart cells, boosting contraction but preventing relaxation, increasing oxygen needs. Over time, this overwork kills heart cells, reducing the heart’s ability to pump (ejection fraction, or EF), leading to fluid buildup in the lungs and poor blood flow to organs like the kidneys, which worsens sodium and water retention. In extreme conditions blood vessels narrow, and heart fills excess fluid overloads the heart (Kemp & Conte, 2012; Schwinger, 2021b).

3. NANOTECHNOLOGY IN CARDIOVASCULAR THERAPEUTICS – AN OVERVIEW

The 20th century marked the beginning of modern cardiology through three major technological breakthroughs which included X-ray discovery in 1895 and sphygmomanometer development between 1896 and 1905 and electrocardiograph invention in 1902 which enabled doctors to perform tests without harming patients (Röntgen, 1896). Current cardiovascular disease (CVD) treatment is evidence-based, relying on randomized clinical trials to validate therapies. The treatment of acute myocardial infarction (AMI) involves early reperfusion techniques which include balloon angioplasty and stents and the use of coronary care units, which results in a patient mortality rate of approximately 5% according to Antman 2011 and Braunwald 2012.

Open heart surgery procedures which include surgical aortic valve replacement and coronary artery bypass grafting present excessive danger to elderly patients who have serious health problems and patients who cannot undergo surgery because of their existing health conditions. Patients who undergo traditional medical treatments experience severe body harm which leads to extensive healing delays through their medical condition and results in psychological distress for more than 65% of elderly patients who experience delirium which negatively impacts both their immediate recovery and extended recovery period (Table.2). The medical field has restricted options for diagnosing and treating progressive heart failure which occurs with either preserved or reduced ejection fraction because of difficulties in delivering necessary medications through their approved administration methods (Samanidis 2024) The standard biomarkers which consist of CK-MB and myoglobin fail to demonstrate cardiac specificity because they produce incorrect results during non-CVD conditions which include muscle injury .The use of CT/SPECT imaging technology is restricted for vulnerable populations because the method includes radiation exposure and contrast allergy risks and low image quality problems which affect kidney patients The high expenses and limited availability of MRI technology make it unfeasible for people who have medical implants The use of statins leads to muscle pain and liver damage while beta-blockers make users feel fatigue and depression and anticoagulants increase bleeding dangers because many drugs operate within narrow therapeutic ranges and produce toxic effects through amiodarone which damages the pulmonary system and statins which require additional PCSK9 medications to achieve their intended results Netala et al 2024 The 58 percentage of atherosclerotic CVD patients who take statins experience nonadherence to treatment between 43 and 67 percentage after they start using medication because of side effects and costs and trust issues while doctors fail to prescribe generic drugs and appropriate evidence-based medication amounts The healthcare system approved only 50 percent of PCSK9 prescriptions which created disparities in device allocation for LVADs and transplants based on racial and gender and geographical differences (McClellan et al., 2019). We will examine how nanotechnology applies to CVD treatment because it has multiple applications in the medical domain. Nanomedicines serve as tools for CVD prevention and diagnosis and they enable drug delivery for treatment purposes. These nanostructures exhibit distinct operational characteristics compared to their standard physical and biological properties because they contain elements such as lipids and silicon and gold. The particles at this tiny dimension can precisely bind to molecular structures because they can penetrate cell membranes and tissue

barriers without causing any known harmful effects as shown in Figure 8.2. The particles require extensive research to determine their long-term effects, but they have proven to be valuable resources that enable controlled cellular and molecular interactions and specific manipulations at those levels. Researchers commonly use Superparamagnetic iron oxide nanoparticles (SPION) and small superparamagnetic iron oxide (USPIO) nanoparticles to investigate atherosclerotic plaque. During 1990s superparamagnetic nanoparticles were coated with polymers and biological molecules to enhance their absorption and ability to target specific tissues. Later on lipid coated perfluorocarbon emulsions with gadolinium and high density lipid nanoparticles were used primarily for MRI scans. These methods were refined by making them even more accurate. Since 2005, advanced nanosystems with multiple functions have been developed for combined imaging methods like PET-CT, PET-MRI, and MRI-fluorescence (Bejarano et al., 2018). By early 2020's FDA approved Lipid based NP was introduced to mimic certain cells like macrophages or platelet members for biocompatibility and targeting. Such particles excelled in the nucleic acid delivery such as siRNA against IL-11 or BRD4 to block fibrotic pathways post-MI, reducing ECM buildup in rat models. Biomimetic AuNPs delivered inhibitors like JQ1 to epigenetic targets in heart failure, improving function in preclinical studies (Montano-Peguero et al., 2025)

As mentioned above nanomedicine has been developed into a multidisciplinary, and it enables us to design or extract such substances that have durable surface coating, faster electronics, sensitive biosensors, targeted therapeutics nanovectors, and diagnostic. The primary goal of nanomedicine requires accurate disease diagnosis through noninvasive methods which produce no errors or side effects.((PDF) Nanomedicine For The Diagnosis and Treatment of Cardiovascular Disease, Current Status and Future Perspective. Cardiovascular Disease. *(Concept Press. 2013.*, n.d.). Application of nanomedicine can be subcategorized: In vivo diagnostics, in vitro diagnostics and medical devices. Nanotechnology can easily perform invitro diagnosis which is usually a conventionally difficult task. Nanotechnology can aid in creating effective, efficient and affordable medical devices. Techniques commonly used to monitor CVD for diagnostic purposes are ECG (electrocardiography), chest xray, echocardiography, cardiac catheterization and blood tests. These techniques confines only to capture the changes in the appearance of tissues during crucial symptoms arises. Nanotechniques (*(PDF) Nanomedicine For The Diagnosis and Treatment of Cardiovascular Disease, Current Status and Future Perspective. Cardiovascular Disease. (Concept Press. 2013.*, n.d.).

Nanocrystals (NCs) are tiny particles that measure less than 1,000 nm and serve to enhance the distribution of drugs that have limited ability to dissolve in water. The use of NCs in cardiovascular diseases enables better drug delivery because they increase the amount of active drug that enters the bloodstream. The first approved NC product for this purpose was Tricor®, a fenofibrate NC formulation, approved on 5 November 2004. Fenofibrate is a drug used to treat hypercholesterolemia, which is a condition with high levels of cholesterol and low-density lipoproteins (LDL) in the blood, which leads to plaque formation in arteries. Fenofibrate belongs to Class II of the Biopharmaceutical Classification System (BCS), which indicates that it does not dissolve well in water but it can traverse cell membranes effectively. The drug

becomes less effective through oral administration because its low solubility prevents proper absorption. To address this, Tricor® was developed by Abbott Laboratories using pearl mill technology, creating fenofibrate NCs smaller than 30 nm. The NCs demonstrated improved drug solubility because they delivered 9% higher oral bioavailability than micronized fenofibrate, which consists of larger particles. Tricor® proves to be effective for patients because it maintains its effectiveness whether they eat food or remain in a fasted state. The use of Tricor® leads to lower cholesterol levels and reduced LDL levels, which decrease the likelihood of atherosclerotic plaque development that results in strokes and heart attacks.

The study conducted by Gite et al. conducted experiments which used media milling method to encase fenofibrate NCs inside polyvinyl alcohol (PVA) material. The NCs dissolved completely within 30 minutes which exceeded the dissolution speed of Tricor®. The results showed that the drug reached its effects faster while showing improved absorption abilities which resulted in better cholesterol reduction and atherosclerosis prevention. Researchers have used polyvinylpyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC) as alternative polymers to create fenofibrate NCs which improve solubility and stability of the drug. (Jia et al., 2023).

4. SOLID LIPID PARTICLES IN CVD

Lipid Nano Particles (LNP) are described as an emerging concept for drug delivery consisting of liposomes. Liposomes can have one or multiple bi layers, and can range from 20 to 1000 nm in size. Being made up of lipid particles they can be used for delivering hydrophilic drug, by enclosing them in aqueous interior of liposomes, as well as the hydrophobic drugs by trapping them in the lipid bilayer. Making them an effective and efficient medium for drug delivery. Their structure an deficiency is determined by how they are prepared. Their size while being designed plays a key role in influencing it's half life, or how long will it's encapsulation persist in the body (Tenchov et al., 2021). SLNs are capsule like carriers that are composed of a solid lipid core having high melting point, for making it hydrophilic it is also coated with aqueous surfactant layer. They are usually designed to carry hydrophobic drugs that don't dissolve in the water properly or doesn't get absorbed well in the body, Examples include plant based compounds. To put simply the liquid lipid particle is replaced by a solid lipid core in the Lipid based nanoparticle (Hanumanthappa et al., 2025). SLNs compiles the advantages of other nanomaterials like liposomes and polymeric particles. Since they are physiological lipids they have remarkable biocompatibility, biodegradability, and limited toxicity. They are also highly accurate, stable in various physiological conditions, control over release by modifying design and ease in mass production have made them one of the leading nanocarriers or medium for diagnostic and imaging purpose (Satapathy et al., 2021).

Synthesis SLNs are directly influenced by the particle size, visualizing agents to be carried, mechanism of release and it's effectiveness at diagnostic imaging. These factors controls the in vivo behaviour, specificity, and contrast enhancing capacity. Hence choice of preparation plays a key role in the mechanism of SLNs (Tiwary et al., 2026) One of the most commonly used method is High pressure

homogenization (HPH) for the preparation of nano emulsions. In this method we reduce a droplet or a particle size under extreme pressure which is a proven way to prepare SLNs for massive production. It starts with the production of coarse lipid particle pushed down through a narrow gap of microns through homogenizer under high pressure conditions (100-2000 bar) because of the pressure the mixture reaches a high velocity, as the shear stress and shock waves act upon the droplet they turn into nano dimensions. Process is repeated as per the requirement (Duong et al., 2020a) . Another method employed is High speed stirring (high shear homogenization) and ultra sonication, it consists of melted lipids with drugs dissolved within them and homogenized. Then surfactants are added to this mixture in aqueous state, this mixture is then put through a high shear mixer. The resultant formulation is an emulsion and SLNs are obtained after cooling these emulsions and ultra sonication to break release the droplets , this method is easily employable and cost effective (Xie et al., 2011).

Microemulsion method initially developed in 1990s usually starts with the dilution of a microemulsion in cold aqueous solution for the formation of nanoemulsion eventually forming SLNs. Therapeutic substance is usually dissolved in molten lipids with higher temperature than that of the lipid's melting point. After which the mixture of aqueous phase and pre heated surfactant is added and this mixture is gradually mixed to become a transparent microemulsion, Once this microemulsion is poured in a cold aqueous solution with mild mixing mechanism making lipids crystalize to form SLN particles (Duong et al., 2020b).

Another such method to formulate SLNs are Solvent emulsification evaporation method where organic solvents like chloroform, toluene etc are used. Drug and lipid are dissolved in a solvent and then emulsified in aqueous phase, the organic solvent is later evaporated with the help of a rotor like mechanism after stirring. The Lipid precipitates as the solvet gets evaporated and tat is how the SLN are obtained. Other Polymeric nanoparticles go with the mechanism of burst release of the enclosed drug substance and can't be used for drugs that work with the principle of prolonged release. SLNs on the other hand have a special function of controlled release for drug substances as the design of the SLN particle can be modified with multiple layering depending on the drug used. Unlike other carriers that use liquid fats, SLNs use solid fats (which don't melt easily), making them stable and good for controlled drug release. Another advantage of using SLNs are reduced toxicity due to them being composed of natural lipid molecules that does not trigger or make unnecessary alterations in the extracellular or intracellular environment after degradation (Tapeinos et al., 2017). Phytocompounds that are substances derived from plant source like like resveratrol, curcumin, quercetin, and diosgenins are often used in CVD treatment as they offer protection to heart by providing antioxidants, preventing blood clots, seen in conditions like atherosclerosis and thrombosis etc. and reducing excess levels of lipids in blood. Since these compounds have less effectiveness due to low absorption when taken orally, SLNs can offer more effective and reliable delivery. Studies show that SLNs are proven to show improvement in the absorption of these substances. For instance peuranin is an effective protecting compound, displayed better delivery to the heart and brain after using SLNs for it's delivery. Another example is Flavonoid from Dracocephalum moldavica that helps heart conditions when facing reduced blood flow,

Hydrocitric acid that has a tendency of getting degraded in a short span of time once orally administered. It showed improved absorption rate when delivered via SLN encapsulation. Commonly used compound like heparin also showed better absorption rates when encapsulated in SLNs despite having low molecular weight (Couto et al., 2017; *Full Article: Recent Developments in Solid Lipid Nanoparticle and Surface-Modified Solid Lipid Nanoparticle Delivery Systems for Oral Delivery of Phyto-Bioactive Compounds in Various Chronic Diseases*, n.d.-a; Ganesan et al., 2018) (Fig.8.3).

5. POLYMERIC NANO PARTICLES IN CVD

Polymeric nanoparticles are the solid particles composed of macromolecular polymers, with particle size in the range of 10 to 1000 nm. Polymer nanoparticles can protect the encapsulated macromolecules from enzymatic degradation and change the dynamic behavior and tissue distribution of the encapsulated drugs in vivo. The drugs can not only be dissolved or encapsulated in the nanoparticles but also be bound or adsorbed on the surface of the polymer nanoparticles (Jiang et al., 2017).

Polymers are widely used because they have lesser toxicity than metals and chemically active sites are available to functionalize the target. There are synthetic and natural polymers. Natural polymers can be starches, cellulose, latex, chitosan, gelatin, alginate, and proteins. Synthetic polymers include polylactic acid (PLA), polyglycolic acid, poly lactic-co-glycolic acid (PLGA), polyvinyl imine, polycaprolactone, and polyvinyl alcohol, they are manufactured on a large scale and are extensively used for the production of polymeric biodegradable nano-drug delivery systems. Polymeric nanoparticles are commonly nanocapsules or nanospheres. In nanocapsules, within a polymeric capsule shell, the therapeutic component is encapsulated compared to the nanosphere, drugs, or other solid particles inserted into a polymeric matrix. In general, they are very economical and more accessible for production. These nanoparticles transport the medicine to a specific site and provide the medicine at a specific level, which is beneficial in treating diseases such as cancer, neurodegenerative diseases, cardiovascular disorders, etc. Nanosystems for the treatment of atherosclerosis have been developed based on polymer nanoparticles as drug carriers. For diagnosing atherosclerosis, novel and improved substitutes of therapy are required for minimizing the chance of serious cardiovascular complications in patients after standard treatment (Sreenivasan Soumya & Gopalan Raghu, 2023).

Food and Drug Administration have approved some polymers for the production of nano particles such as polylactic acid (PLA), polyglycolic acid (PGA), and poly lactic-co-glycolic acid (PLGA), are widely used for the synthesis of polymeric biodegradable nano particles, because they are eliminated from the body in the form of water and carbon dioxide. PLGA is a copolymer of PLA and PGA, the most frequently used constitution among these polymers, and is being tested for a drug delivery systems (DDS) for intractable diseases, including cardiovascular disease. PLA is more hydrophobic, whereas PGA is more hydrophilic; the degradation speed of PLGA can be adjusted by the PLA:PGA ratio and their molecular weights, which

achieves controlled release of incorporated drugs. PLGA polymers incorporate hydrophilic and hydrophobic therapeutic agents, including chemicals and nucleotides by emulsion solvent diffusion methods. The diameter of polymeric nanoparticles widely ranges from 20 to 1,000 nm. FDA-approved PLGA nanoparticle utilizing these advantages is leuprolide acetate (a testosterone inhibitor)-incorporated nanoparticle for prostate cancer (Eligard®). PLGA achieves slow and sustained leuprolide acetate release after subcutaneous injection (Katsuki et al., 2017).

Nanocapsules are composed of an oily core in which the drug is dissolved. It is surrounded by a polymeric shell which controls the release profile of the drug from the core. Polymeric nanoparticles (NPs) have attracted considerable interest over recent years due to their properties resulting from their small size. The use of polymeric NPs as drug carriers provides hospitals with two main benefits. The first benefit allows hospitals to control medication release while the second benefit enables hospitals to keep their drugs and active biological substances safe from environmental threats. The nanoparticles create better drug distribution and stronger therapeutic effects through their ability to improve particular drug elements. The nanoparticles enable engineers to design them for particular cardiovascular system targets which include endothelial cells and macrophages and thrombi control. The nanoparticles enable the delivery of multiple therapeutic substances which include small molecule drugs and proteins and nucleic acids and imaging contrast agents but these substances require special delivery methods that conventional drug formulations cannot provide according to Zielinska et al 2020. In cardiovascular diseases polymeric nanoparticles use their delivery system to transport drugs directly to heart tissues and blood vessel systems. The nanoparticles target damaged heart tissue in myocardial infarction. PLGA nanoparticles loaded with anti-inflammatory drugs reduce swelling and help healing. The body uses leaky blood vessels to create a pathway which allows them to build up within damaged regions. The polymeric nanoparticles enhance blood pressure drug delivery for hypertension treatment because they extend the effects of losartan while decreasing the number of times patients need to take their medication. The nanoparticles deliver statins to arterial plaques in atherosclerosis which stops blockages from developing in arteries. (Fig.8.4).

6. COMPARATIVE ANALYSIS

While both solid lipid nanoparticles (SLNs) and Polymeric nanoparticles (PNPs) are about the same size rage which is about 10nm to 1000nm, they differ in various roles and are widely being explored in the cardiovascular disease treatment. Polymeric nanoparticles can have multiple functions for providing competent absorption and are modifiable based on the requirements like dendrimers, star shaped structure, amphiphilic and other complex geometrical shapes which exhibits features accordingly (*A Review on Comb-Shaped Amphiphilic Polymers for Hydrophobic Drug Solubilization: Therapeutic Delivery: Vol 3 , No 1 - Get Access*, n.d.; Hoskins et al., 2012). Though sometimes they can be toxic, their biodegradable forms are much preferred alternatives like poly lactic co glycolic acid (PLGA), Polyglycolic Acid and Polylactic acid (PLA). PLGA is the commonly studied medium for cardiovascular disease treatments due to its effective drug release and biocompatibility (Jha et al., 2024a).

Solid Lipid nanoparticles are made of lipids that may or may not consist of triglycerides, glycerides blends , that makes them solid at the regular temperature of body. They comprise of surfactants to make them stable. They aren't much toxic and can be designed to have single or multiple layer making them an effective choice of transportation for Drugs that require sustained release. They can also be customized to be target specific and deliver the therapeutic substance with precision. Active compounds can be incorporated into the solid matrix of such nanoparticles to prevent their degradation from environmental factors before delivering the drug. SLNs can easily deliver hydrophilic and lipophilic drugs effectively (Pandey et al., 2021). Even though Both the SLN s and PNPs are type of nanoparticles used with the intention of delivering therapeutic agent into the body, aiding in the treatment, diagnosis and imaging of diseases like CVD, they still vary in their mode of action, bioavailability, stability, structure and formulation. Having awareness about their distinct qualities and limitations can help us select the proper candidate to deliver the therapeutic agent (Dikpati et al., 2024; Floyd et al., 2025; Koroleva et al., 2022; Xiao et al., 2022).

PNPs have multiple application in the treatment of cardiovascular diseases, examples are mentioned below. Polylactic-co-glycolic acid (PLGA) encapsulating antiproliferative agents like paclitaxel have shown notable efficacy for decreasing restenosis rates (continuous narrowing of arteries) via angioplasty as it prevents the proliferation of SMCs (smooth muscle cell) helping the intima and endothelial cells to regrow. PLGA are also used to deliver siRNA or shRNA for gene therapy in mouse model, targeting prolyl hydroxylase domain protein 2 (PHD2) resulting in it's inhibition. Resulting in the stabilization of HIF-1α pathway enhancing angiogenesis and significant reduction in infract size (Jha et al., 2024b). SLNs are underexplored but still diverse in their application in the drug delivery for the cardiovascular disease treatment. Clinical examples mentioned below serves as evidences.
Gelan Xinning Ruanjiaonang is a traditional Chinese medicine used for treating coronary heart disease, it was noted that the clinical impact of the drug improved significantly when delivered encapsulated by solid lipid nanoparticle (Fan et al., 2020). In another experiment involving Total flavonoid extract from *Dracocephalum moldavica* L. (TFDM), the use of SLNs were observed. For a little background TFDM consist of *D. moldavica* L. which is proven to be a myocardial protectant, challenge arises in the solubility of TFDM reducing it's cardio protecting function. Hence TFDM were loaded into the solid lipid nanoparticles and TFDM-SLNs was designed. It was demonstrated that the cardioprotecting effect of TFDM-SLNs were much better than just TFDM, and it was proven to be a reliable and effective carrier mechanism for oral delivery (Tan et al., 2017).

7. MOLECULAR PATHWAYS AND CLINICAL APPLICATIONS

The key requirement for using nanomaterial for any clinical application is to protect the intended drug from degradation and accuracy in delivery. Both hydrophobic and hydrophilic drugs can be delivered by choosing the right nanocarrier. Distribution of these nanostructures are influenced by size, shape, charge etc. The nanoparticle of size more than 1000nm generally gets accumulated in the liver and lung region. If the size is smaller than 8nm, they are tend to get filtered, nanomaterials between the size range 10 ti 300nm

accumulate in organs with high density of macrophages (Spleen, lymph, bone marrow, and liver (Das et al., 2025a). As there particles approach the body they interacts with the immune system and immune cells tends to remove them. Hence they require synthetic coating like PEG polyethylene glycol prolonging the half life in blood (Gonciar et al., 2022a).

Majority of nanoparticles can be segregated into these categories: Polymeric, lipid based and inorganic or a combination of these. They are currently being explored for the treatment of cardiovascular disorders. Liposomes are beneficial for both drug delivery as well as the visualisation for diagnostic purpose and can be used to seal the damaged endothelium though they might sometimes trigger immune response (Gonciar et al., 2022b)

Development of nanoparticles made from yeast based particles that encapsulate bindrait blocks protein MCP-1/CCL-2, that plays a key role in inflammatory mechanism. These nanoparticles can be administered orally, they directly reach towards the effected arteries. These particles are absorbed by intestinal cells, and later on carried by Ly 6C+ monocytes through the blood towards the plaque thereby reducing inflammation and prevent plaque buildup (*Biomimetic Oral Targeted Delivery of Bindarit for Immunotherapy of Atherosclerosis - Biomaterials Science (RSC Publishing)*, n.d.; Yin et al., 2020). Seijkens along with his team built nanoparticles using artificially derived high density Lipid nanoparticles encapsulating TRAF6 inhibitors, lowering the activity CD40 and integrins (adhesive for immune cells) reducing inflammation and plaque (Seijkens et al., 2018).
Nanoparticles encapsulating curcumin, lignin, tannic acid, and a reduce key inflammation signals like NF-κB, TGF-β1, IL-6, IL-1β in blood vessel cells triggered bacterial toxin. Shi et al. incorporated iron oxide nanoparticles coated with PtdSer and 9-CCN to deliver curcumin directly to macrophages converting them to anti-inflammatory molecules type (M2) (Shi et al., 2024). Anti- inflammatory compound like andrographolide works by blocking the NF-κB pathway, the challenge lies in it's insolubility hence reducing it's effectiveness. PNPs micelles made from hydrophilic and hydrophobic copolymer (PEG-PPS) that responds to oxidative conditions, can encapsulate andrographolide to restrict inflammatory molecules (IL-6 and MCP-1) and relive oxidative stress in macrophages with least amount of side effects . These nanoparticles also reduces oxidative stress in the arteries by neutralizing damaging ROS (reactive oxygen species) (Wu et al., 2018).
Skin based delivery using polycrylic acid (PAA)-coated with molybdenum disulfide nanoparticles (PAA-MoS2 NPs) to treat high blood pressure (hypertension). These nanoparticles encapsulate atenolol which is a drug that blocks β1-adrenergic receptors aids in reducing blood pressure. PAA is a non harmful hydrophilic substance that acts as a aqueous layer mean while MoS2 NPs responds to nearby infrared laser light resulting in the generation of heat boosting atenolol release and enhance its absorption through skin (*Full Article: Poly(Acrylic Acid)-Modified MoS2 Nanoparticle-Based Transdermal Delivery of Atenolol*, n.d.).

8. CHALLENGES AND FUTURE

The use of nanoparticles in treating heart diseases shows good results in early lab tests, but many problems stop them from being used in real patients. The study found that a inorganic nanoparticle combination shows three risk factors through its ability to produce long-term toxic effects while spreading through the body and needing specific testing to track its distribution and elimination from the body. The study showed that their biological performance requires two tests because their long-term safety remains uncertain and there is a risk of their accumulation in non-target organs and their potential to trigger immune system responses. It is important to improve how they spread and clear from the body, because the size, shape, and surface of nanoparticles affect their actions inside living things. Getting them to target correctly in the complicated heart system is still difficult, even if lab tests look promising. Technical problems involve making large amounts under good manufacturing practice (GMP) rules, keeping the formula stable when stored, and controlling how the drug releases. Also, there are no standard ways to test nanoparticle safety and effectiveness, so current research is focused on development of new testing methods (Jha et al., 2024c).

Researchers have conducted extensive research on polymeric nanoparticles (NPs) during the past 50 years to study their ability to encapsulate and deliver imaging agents and therapeutic molecules into diseased tissues. The nanoparticles use EPR-based passive targeting for their accumulation in inflamed regions which show broken blood vessels similar to tumors and heart tissue that has been damaged from myocardial infarction (MI).The small size of polymeric NPs helps this EPR effect, but their making must be controlled carefully. Particles smaller than 10 nm clear quickly through kidneys, reducing effectiveness. To increase circulation time and reduce early clearance, NPs are coated with biocompatible polymers or proteins, which make them larger and heavier. Still, the small size can lead to uptake by wrong cells or long circulation without proper targeting.

To improve placement and staying, other delivery ways like releasing NPs from bigger carriers such as hydrogels or scaffolds are being explored. These may help margination and sticking to endothelial walls, increasing targeted delivery chances. Adding targeting ligands to NPs allows active targeting, useful in heart applications. For MI, finding surface markers like proteins, receptors, or glycosaminoglycans on damaged heart cells enables precise targeting. This improves NP buildup at the infarct site, longer stay, and better imaging and treatment results. For diagnosis, polymeric NPs with contrast agents having optical or magnetic properties can improve imaging like CT and cardiac magnetic resonance (CMR), helping assess heart injury and infarct size after ECG and troponin tests (Liu et al., 2025). Recent progress has extended polymeric nanomaterials to cardiovascular stents, solving issues of biocompatibility, drug release control, and degradability. New functionalized coatings like stimuli-responsive layers, gene or protein coatings, and bio-inspired molecules have opened ways for precise stent therapies. In the future, multifunctional coatings that combine drug delivery, real-time imaging, and biological signal control are important research areas. Improving radiopacity and mechanical strength of biodegradable stents is needed for structure and imaging visibility. Using artificial intelligence in stent design and personalized stents for precision medicine will drive

progress. These strategies in polymeric nanotechnology promise much for heart diagnostics and therapies. This comes from the papers on polymeric NPs and cardiovascular stents (Karam et al., 2022).

Solid lipid nanoparticles (SLNs) serve as modern drug delivery systems that deliver cardiovascular disease treatments through their ability to enhance drug stability and bioavailability and their capacity to deliver drugs to specific targets. The clinical application of the technology faces multiple obstacles which researchers continue to work on to improve its performance in medical settings The use of SLNs to treat cardiovascular diseases encounters various challenges. The delivery of SLN results in low bioavailability for phyto-bioactive compounds such as resveratrol and curcumin because these compounds undergo burst release when they reach the stomach's acidic environment which results in decreased capacity to protect against myocardial ischemic–reperfusion injury. The antihypertensive drugs demonstrate low bioavailability and restricted effectiveness resulting in the requirement for SLNs to solve these challenges to achieve stable drug concentrations needed for hypertension management. The formulation and stability challenges represent major obstacles. The development of a universal SLN system which can handle multiple compounds presents difficulties because storage instability will result in operational failures. The possibility of organ toxicity development represents a critical issue which especially affects cardiovascular applications that require proof of long-term safety. The development of surface-modified SLNs (MSLNs) with chitosan coatings incurs high costs which limit their ability to scale up production (Ishtiaq et al., 2023). Despite these limitations, the future prospects of SLNs in cardiovascular therapy are promising. The ferulic acid-loaded SLNs hold potential for protecting the heart from MI-related inflammation due to their enhanced antioxidant properties, with further studies needed to confirm their clinical efficacy. The SLNs can improve the delivery of phyto-bioactive compounds to the heart and brain, enhancing protection against cardiovascular damage, and calls for research into more phytocompounds for cardioprotective effects. Its Conclusion section further emphasizes that SLNs and MSLNs offer 5–10 times higher bioavailability than native compounds, and surface modifications like chitosan or trimethyl chitosan coatings enable sustained release, which could revolutionize oral delivery for cardiovascular treatments (*Full Article: Recent Developments in Solid Lipid Nanoparticle and Surface-Modified Solid Lipid Nanoparticle Delivery Systems for Oral Delivery of Phyto-Bioactive Compounds in Various Chronic Diseases*, n.d.-b). The SLN has the potential to transform hypertension management by improving drug solubility, sustained release, and stability, which could reduce the global burden of cardiovascular diseases through better blood pressure control (Das et al., 2025b).

CONCLUSION

Cardiovascular diseases (CVDs) are among the biggest health problems in the world today. Every year, millions of people die because of heart attacks, strokes, or other related heart problems. While doctors have found many ways to treat these diseases, such as surgery and medicines, most of these treatments come with certain side effects, poor drug absorption, and short-lasting effects. This makes the search for new and safer treatment methods very important. In this scenqario nano technology emerged as a promising method for the treatment of cardio vascular diseases. Polymeric nanoparticles (PNPs) and solid lipid nanoparticles (SLNs)

are two of the most researched nanoparticles in the treatment of cardio vascular diseases. They help in precise transfer of medicine to the exact site, thus increase the effectiveness of the drug and reduce the side effects. The working of polymeric and solid lipid nanoparticles is based on improving the way medicines move inside the body. Many medicines for the cardio vascular system lacks solubility and quickly removed from blood stream, which reduces the effect of medicine. Nano particles help in this by making the drug stay longer in the blood stream. Nano particles cross the biological barriers and release slowly at the release site. Polymeric nanoparticles is made up of polymers such as PLA,PLGA,PCL etc, which carry hydrophilic and hydrophobic drugs. Due to it's small size, it can move through the blood vessels easily and reach the affected tissues. Solid lipid nanoparticles (SLNs), on the other hand, are made of physiological lipids. These are natural fat molecules that make SLNs very safe and biocompatible. They contain plant-based compounds and natural antioxidants like curcumin, quercetin, and resveratrol. These natural compounds are known to protect the heart by reducing oxidative stress and inflammation, but they have poor bioavailability when taken orally. Both PNPs and SLNs have similar size, but their internal composition, release mechanisms, and degradation rates are different. Polymeric nanoparticles are better suited for drugs that need long-term, controlled release, whereas SLNs are ideal for natural compounds and hydrophobic drugs. The use of both systems can be combined to create hybrid nanocarriers that offer the advantages of both — high stability from solid lipids and precise control from polymers.

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Authors' Contributions

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