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Review Article

Nanoparticle based drug delivery system: opportunities, challenges and mathematical modeling approaches in cardiovascular disease

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ABSTRACT

Cardiovascular disease (CVD) is the most common health problem worldwide and remains the leading cause of death and disease burden globally today. In recent years the increasing incidence of heart problems at younger ages has further exacerbated the situation. Furthermore, the rising cost of treatment places a significant financial burden on patients. Conventional treatment methods often face challenges such as non-targeted delivery, immediate release, short half-life and side effects. Considering these challenges nanoparticle-based drug delivery system has emerged as an increasingly effective technology. After successful use in cancer therapy, these techniques are now using their significant benefits in the treatment of CVD. Nanoparticle have the potential to deliver drugs at specific disease sites in a targeted manner, ensure controlled release, reduce side effects and improve drug biodistribution, thereby increasing treatment efficacy. Metal-based, lipid-based and polymer-based nanoparticles are considered suitable option for the therapy of CVD. In this review, we discuss how nanoparticles significantly improve upon conventional drug delivery systems by providing better targeting, controlled drug release, and reduced side effects and also cover mathematical modeling approaches that make nanoparticles more effective such as drug release models, drug diffusion model in heart tissue and non-Newtonian fluid models. These models help predict drug concentration, release rate and target site penetration making treatment more precise and personalized.

Keywords: Nanoparticles, Cardiovascular disease, Drug delivery system, Conventional drug delivery

INTRODUCTION

In recent year, cardiovascular diseases (CVDs) are recognised as one of the most life-threatening challenges of the 21st century. According to world health organization (WHO, 2023) approximately 19.2 million deaths occur each year due to CVDs, which is 32% of all deaths worldwide. Of these 85% are due to heart attack and stroke. This is why CVD has now become not only the leading cause of death but also the leading cause of long-term disability and financial burden worldwide.[1] The term CVD refers to a wide range of disorders that affect the heart and blood vessels, including coronary artery disease, heart attack/myocardial infarction, heart failure, arrhythmia, heart value disease, cardiomyopathy, congenital heart defects, strokes, ischemia and peripheral artery disease. The epidemiology of CVD has seen a dramatic increase in the last few decades.[2,3]

Better diagnostic tool and improved treatment facilities have reduced mortality rate somewhat in high income countries. However, prevalence and mortality rates continue to rise at an alarming rate in low and middle-income countries**.** Moreover, CVDS isn't limited to the elderly only, data analysis shows that a significant proportion of patients are below 50 years of age, which reflects the impact of modern lifestyle, stress, obesity and lack of physical activity.[4] CVD has become the leading cause of death in India, surpassing infectious disease and maternal child health problems. Analysis suggests that

more than 25% of deaths in India due to CVD. Health care costs associated with CVD are very high. It is not only the hospitalization but also associated with medical procedure that are also expensive which puts a financial burden on the family and the patient.[5,6]

The increase in CVDS is linked to multiples risk factors that include both modifiable and non-modifiable. Although a variety of drugs available for the treatment of heart disease, their effectiveness is often reduced due to the limitations of conventional drug delivery method**.** Traditional dosage forms such as oral tablets, capsules, syrup, and injection are widely prescribed due to their ease of administration and established clinical use.[7] Many heart related drugs such as beta-blockers, calcium channel blockers and nitrates first undergo metabolism in the kidney.[8,9]

CVD are often chronically progressive and life-threatening including serious illness such as heart attack, stroke, arrhythmia and heart failure which required long-term medication to prevent them, but unfortunately fail to achieve consistent therapeutic results. Nanoparticles have emerged as one of the most promising method in the field of drug delivery.[10,11]

In this paper we discuss the importance of nanoparticle-based drug delivery carriers on the treatment of CVD.

The use of nanoparticle-based drug delivery system in cardiovascular therapy offers several clear advantages over conventional dosage forms. The future of novel drug delivery system (NDDS) and nanotechnology-based platforms in CVDs appears highly promising. To enhance the effectiveness and efficacy of therapeutic agent, drug delivery system is used. Additionally, the Nanoparticle based drug delivery systems are dispersed into the blood, which plays a vital role in the transport and distribution of drug in the human body.[12]

CONVENTIONAL DRUG DELIVERY AND ITS LIMITATIONS

The conventional drug delivery system refers to traditional drug administration methods that include oral tablet or intravascular infection. These systems are responsible for distribution of drug systematically through the blood circulation. In this way, only a small portion of the active drug ingredient reaches the affective organs**.** Sometimes the drug also affects the other part of the body, resulting in adverse effect.[13,14]

The evolution of new drug molecule is very costly and time taking process while conventional drug delivery system is simple, low cost as well as the widely used system.[15]

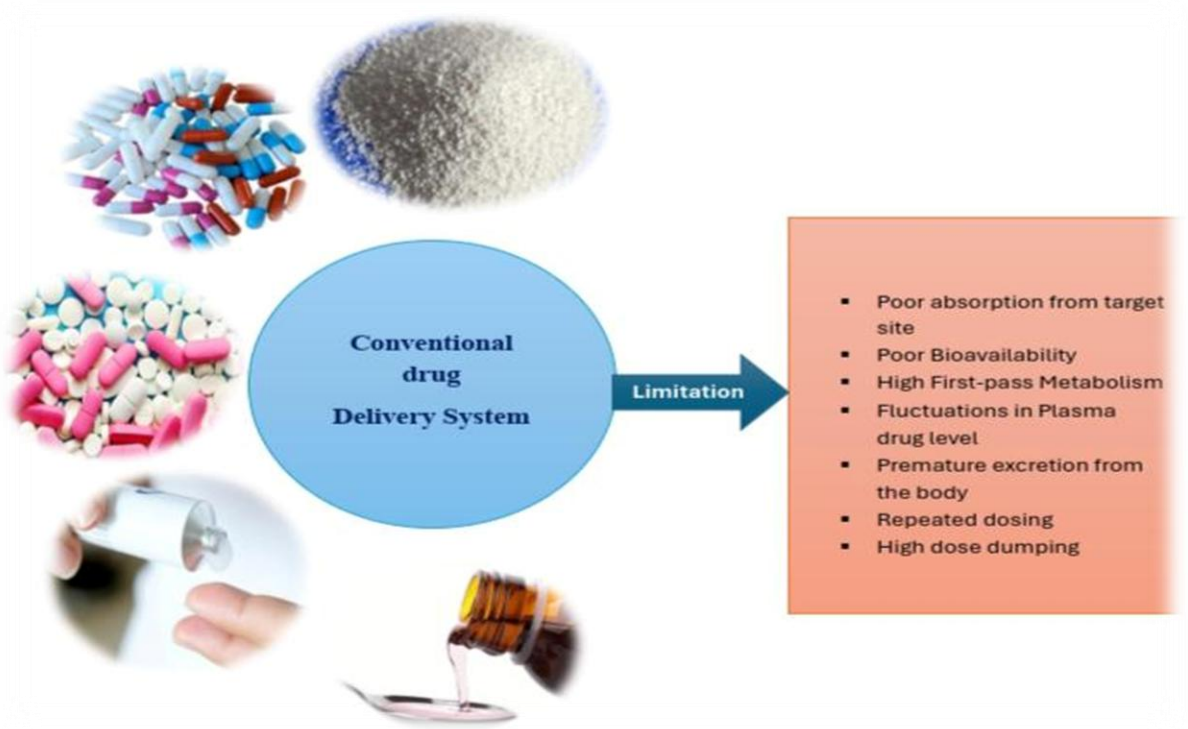

Figure 1: Conventional drug delivery system.

EVOLUTION OF NDDS

The evolution of NDDS has revolutionized the field of pharmacology and therapeutics, driven by the need to overcome the limitation of conventional dosage forms. Traditional or conventional drug delivery methods such as tablets, capsules and injections often suffer from limitations such as poor bioavailability, rapid excretion,

short half-life and lack of target specificity and fluctuating plasma drug concentration.[7,16] These drawbacks often result in insufficient concentration of the drug at the target site, requiring repeated doses, and undesirable or harmful side effects due to the drug's spread throughout the body (systematic exposure).[17,18] The growing need to overcome these issues has encouraged researchers to develop innovative delivery strategies capable of improving therapeutic efficiency, while minimizing side effects.[19,20]

In the 21st century NDDS have entered a new era marked by the integration of targeted drug delivery system and smart delivery technologies. These systems employ ligands antibodies or magnetic and pH-sensitive material to ensure that the drug act site-specifically in the body and its release is controlled.[21,22]

Overall, the evolution of NDDS and nanoparticle-based drug delivery system signifies a paradigm shift from conventional formulations towards more effective, safer and patient-centric treatment approaches. This evolution not only enhances the therapeutic outcomes but also opens new opportunities for designing therapies for complex diseases and bridges, the gap between pharmacology, nanotechnology add biomedical engineering in the modern era of CVD, where controlled and targeted drug action is of utmost importance.[3,17]

IMPORTANCE OF NDDS

Effectiveness is increased by delivering the drug to the right place, at the right time, and in the right amount. Blood levels remain in the therapeutic range for a long period, eliminating the need for repeated doses. Patches inhalers, sustained release tablets make treatment easier and increase patient convenience. Provides better and personalised therapy include cancer, cardiovascular, CNS disorders, these are the importance of NDDS.

Table 1: NDDS studied for the efficient treatment of CVDs.

Types of NDDS	Disease targeted	Drugs used in treatment of CVDs	Model organism used	Biological functions
Liposomal NDDS	Atherosclerosis, myocardial necrosis	Atorvastatin, urokinase	Mice	Targeting inflamed endothelium and surface ligands enable active targeting to injured myocardium
Nanoparticle based NDDS	MI	Statins, atrial	Rat, rabbit	Reducing inflammation, inhibiting plaque formation
Injectable hydrogels/ nanogels	Post-MI ventricular remodeling	Exosome cargo and protac peptides	Rat, pig	Mechanical support and microenvironment modulation
Bioparticle NDDS	Atherosclerosis, restenosis	Antioxidants, peptides	Rabbit and rat vascular model	Active targeting of vascular receptors
Micelles	Pulmonary hypertension	Bosentan	Mouse pH model	Improves solubility

NANOPARTICLES

Nanoparticles are microscopic carriers that deliver drugs to the target area with dimensions typically, ranging from 1-100 nm, which allows them to interact closely with biological molecules and cross various physiological barriers that conventional drug formulation fail to overcome.[23] Nanoparticles are advanced drug carriers system that possesses unique physicochemical properties such as large surface area-to-volume ratio, tunable surface charge and control release behaviour, which make them highly effective for drug delivery application. Nanoparticles also improve the solubility and stability of drugs, which is difficult in traditional formulation. It can be used as adjuvant in vaccine or drug carrier.[10,24]

Nanoparticles have opened new possibilities in medicine, offering new hope for both treatment and patient care. Nanoparticle based drug delivery has gained tremendous attention in various systems due its potential to revolutionized therapy, especially in complex and chronic diseases such as CVD.[25,26] In cardiovascular medicine, nanoparticle has proven valuable in targeting atherosclerotic plaque, ischemia tissue and damage myocardium. Depending on their composition and structure, several types of nanoparticles are being explored for CVD.[27,28]

Types of nanoparticles

Nanoparticles have gained significant attention in cardiovascular drug delivery due to their unique properties and versatile behaviour. Thus, nanoparticle-based drug delivery provides a secure and active platform for the controlled and targeted drug delivery. The types of nanoparticles used in cardiovascular therapy can be broadly classified into lipid-based nanoparticles, micelle-based nanoparticles and dendrimers-based nanoparticle, each with its distinct advantages and application.[9]

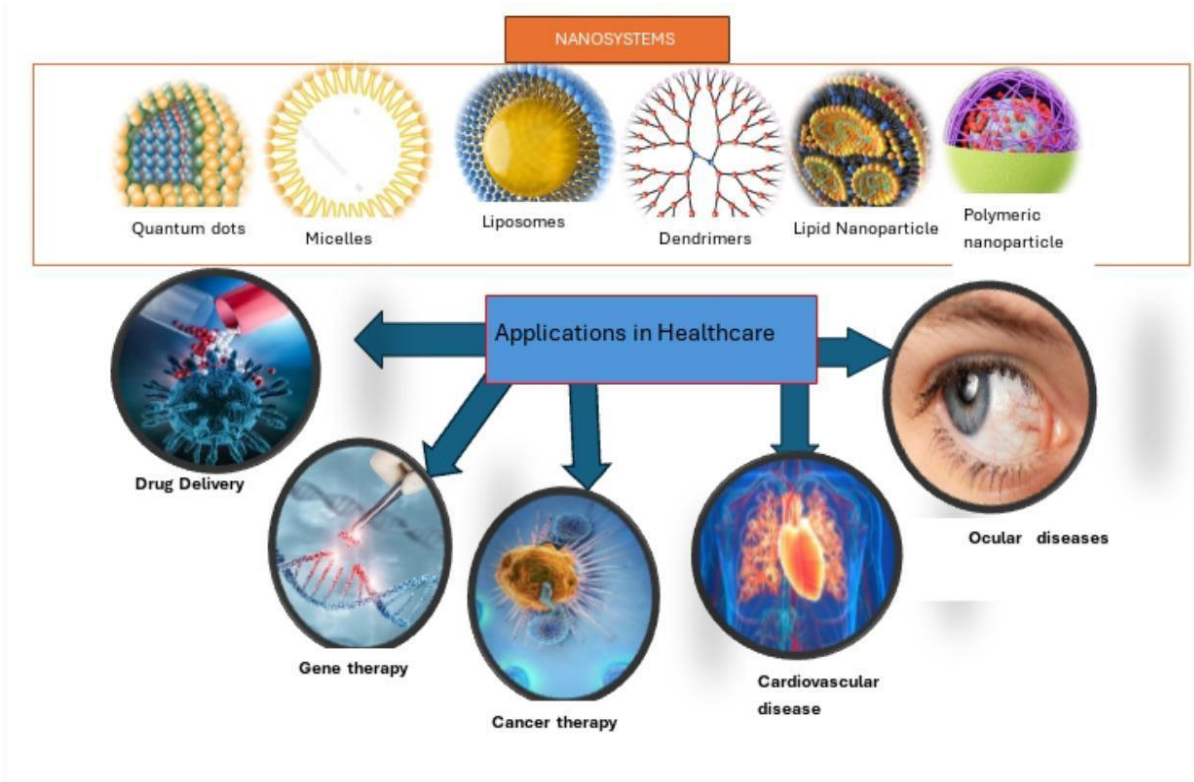

Figure 2: Different types of nanoparticles and their applications.

Lipid-based nanoparticles

Lipid-based nanoparticles, such as liposomes, solid lipid nanoparticles, and nanostructured lipid carriers, use mono-layered or multi-layered vesicles synthesized from phospholipids and other lipid materials through complex processes. In lipid-based nanoparticle, liposomes are most widely used. Liposomes are spherical vesicles made from lipid bilayer membrane structure and amphiphilic lipid molecules that can encapsulate drugs in their aqueous core or within the lipid bilayer itself. For example, pegylated liposomes, which are coated with polyethylene glycol (PEG), are protected from attack by the immune system. Normally, the immune system destroys them as "foreign particles", but the PEG coating prevents them from being destroy. [29,30]

Polymeric-based nanoparticle

Polymeric nanoparticle can be coupled to another substance or freely flowing throughout the body. Polymer nanoparticles can be synthesized using various natural or synthetic macromolecular substances with different structures and surface charge and size of particle of the nanoparticles vary with the polymer type.[31] Drugs are commonly integrated into polymer nanoparticles using different methods, such as encapsulation, dissolution embedding or covalent attachment variations in the methods and patterns of combining drugs with the nanoparticles result in different type of drug delivery capabilities for polymer nanoparticle.[32,33]

Micelle-based nanoparticles

Micelles are a type of nanosized particle used to deliver drugs to the target site. Micelle-based nanoparticles can be made in a variety of structures, with spherical structures being the most common. Micelles are very useful for delivering drugs into the body that do not dissolve easily in water.[34] These are very small particles whose outer layer is hydrophobic because of this, drug can be safely contained inside, and the outer layer helps it to dissolve and circulate in the body. However, their drug loading capacity is slightly lower than that of liposomes. Because of this, ischemic myocardium allows micelles to enter more easily-means these tissues are more “permeable” to micelles.[35,36]

CHARACTERIZATION OF NANOPARTICLES

Nanoparticles are designed in such a way that they can evade the body’s immune system, they possess certain beneficial properties that can be used to effectiveness of the medication, ensuring safety and reducing side effects. The size, shape and charge of nanoparticles determine their behavior. The average size of nanoparticles, their size distribution and surface charge all significantly impact their physical stability and *in vivo* distribution. These properties determine how stable the drug will be in the body and where it goes.[37,38]

Particle size

The size of nanoparticles is most important characteristic for drug delivery as it determines whether they can travel in the bloodstream and where they will accumulate in the body. Nanoparticles can control the amount of drug to load, when and how to release it and how long it remains stable. Smaller nanoparticles are more likely to enter leaky or damaged blood vessels-such vessels are found in cancer and CVD, where angiogenesis occurs such small nanoparticles can also easily leak into the normal tissues.[39,40]

Smaller nanoparticles (<10 nanometers) are excreted through the kidneys, meaning they are excreted in the urine. Large nanoparticles (>10 nm) are removed by thermonuclear phagocytesystem. These systems mainly occur in the liver, spleen and lymph nodes, which remove waste and foreign particles from the body.[12,41]

Particle shape

The shape of nanoparticles determines how long they will circulate in the blood and how much adheres to blood vessel walls.[41] Non-spherical nanoparticles penetrate blood vessel wall more easily than spherical nanoparticle and adhere more strongly to the wall**.** Studies show that disc-shaped and hemispherical nanoparticle performs better than their spherical counterparts. Experiments have shown that gold nano rods have a higher margination propensity than gold nanospheres, meaning, the nanorods are more easily drawn to the vessel wall. Following these researchers Vahidkhah and Bagchi conducted computational studies to investigate how the shape of nanoparticle affects, the behaviour of drug carrier at different stages of the margination adhesion cascade.[42,43]

Surface charge

Nanoparticles have an electrical charge on their surface and it plays a very important role in biological systems as it determines many of their interactions. This charge depends on either composition of their surface and the liquid or medium in which they are dissolved. Nanoparticles can have a positive, negative or neutral surface. This charge determines how they react with cells, proteins and membranes, whether the body will accept or reject them and their drug delivery, toxicity and distribution. Positively charged nanoparticle adheres easily to cell membrane and negatively charged nanoparticle interact less, so their toxicity may be lower.[40] Zeta potential is used to measure this charge and value that indicates the electric potential around a particle, higher the zeta potential more stable the particle are, and if zeta potential is lower, the particle aggregate, more easily. Nanoparticle with a zeta potential of ±30 mv or greater are repel from each other and dispersed well in the mixture, preventing particle sticking or the aggregation.[41]

MECHANISM OF CVD

CVDs are the leading cause of disability and the number one cause of death worldwide. In 2015, approximately 17.7 million people died from CVDs, and this number is expected to rise of approximately 23.6 million by 2030, according to the world health organization. CVDs account for 45% of all deaths in Europe, equivalent to approximately 3.9 million deaths each year.[9,20]

Application of nanoparticles in the treatment of atherosclerosis

In the treatment of atherosclerosis, nanotechnology is a very promising and useful technique in which nanoparticles act as small carriers that deliver the medicine directly to the blood vessel wall. This helps in reducing important steps of atherogenesis, such as intimal hyperplasia.[44] Non-stimuli-responsive nanoparticles used in the treatment of atherosclerosis are mostly made of polymeric materials, such as PLGA, cyclodextrin, and chitosan. Katsuki and his team reported that delivering pitavastatin via PLGA nanoparticles was more effective than delivering the pitavastatin drug and significantly controlled plaque rupture. Kim et al created core-shell nanoparticles prepared by self-assembly of 2-hydroxypropyl-β-cyclodextrin and statins. In this nanoparticle system: 2-hydroxypropyl-β-cyclodextrin accelerates removal of cholesterol from plaque area.[45,46]

Application of nanoparticles in the treatment of hypertension

Nanoparticles are a promising tool for improving the efficacy, bioavailability, and safety of antihypertensive treatments. Due to their small size, high surface area, and ability to be functionalized, nanoparticles can deliver drugs in a controlled and targeted manner, helping to overcome the limitations of conventional antihypertensive drugs. Nanoparticles can be designed to target vascular smooth muscle cells, endothelial cells, or components of the renin-angiotensin system. The blood pressure-lowering effect was enhanced the drug's effect lasted longer and the required dose of Olmesartan was reduced by almost three times. In a new study, scientists have created a new platform based on hydrogel/glass hybrid nanoparticles, which allows for the controlled release of nitric oxide (NO).[47]

MATHEMATICAL MODELING OF NANOPARTICLE IN CVD

Mathematical models play a crucial role in understanding and predicting the behaviour, transport, distribution and therapeutic performance of nanoparticle-based drug delivery in CVDs. These models estimate future outcomes such as the motion of nanoparticles in the bloodstream, their interaction with arterial walls, and drug release and diffusion.

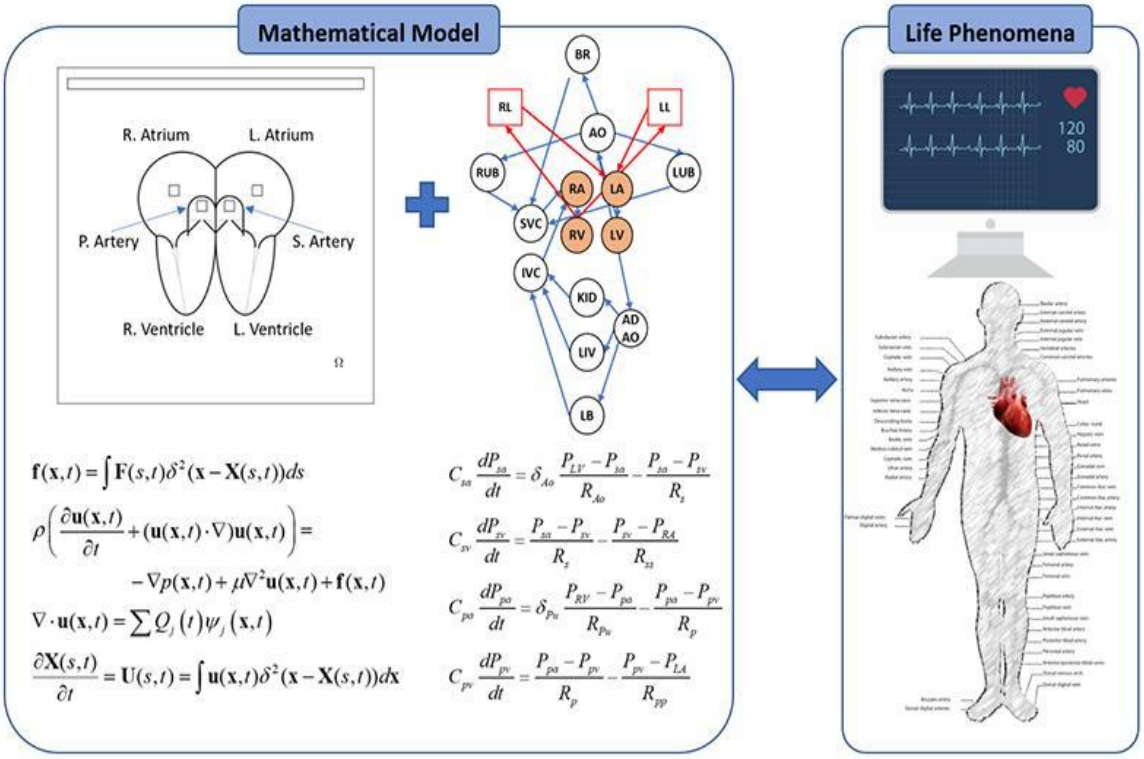

Figure 3: Schematic representation of mathematical modeling of CVDs.

Nanoparticle transport in blood flow

The movement of nanoparticles is primarily modelled using the Navier-Stokes equation. It is assumed that the flow of blood and nanoparticle dispersion in artery, governed by Navier-Stokes equation:

$$\rho\left(\frac{\partial v}{\partial t} + v.\nabla v\right) = -\nabla.\tau - \nabla P \quad (1)$$

And the continuity equation for an incompressible fluid

$$\nabla.v = 0 \quad (2)$$

where v is the velocity, t is the time, P is pressure, ρ is density, $\partial v/\partial t$ is time derivative of velocity and ∇P is pressure gradient.

Blood is a non-Newtonian shear-thinning fluid, so different viscosity models are used in the mathematical modelling of cardiovascular diseases using nanoparticle. Some non-Newtonian models are described below:

Power-law model

Many fluids (such as blood, slurry, etc.) are not Newtonian that is, their viscosity is not constant. There are several models to mathematically describe the behaviour of such non-Newtonian fluids. The most commonly used model is the Power-Law Model.

$$\eta = m\dot{\gamma}^{n-1} \quad (3)$$

Where η is a non-Newtonian effective viscosity of blood, $\dot{\gamma}$is the shear rate, m is the consistency index and n is the flow behaviour index. If n<1, a shear-thinning fluid is obtained. As the shear rate (speed or deformation of flow) increases, the relative viscosity of the fluid decreases. If n>1, a shear-thickening fluid is obtained. As the shear rate increases, the relative viscosity of fluid also increases. When n=1, a newtonian fluid is obtained.

Tripathi et al reviewed computational simulations of blood flow in stenosed arteries using hybrid nanoparticles, where blood is modelled as non-Newtonian fluid using power-law model. Power-law formulation is used to analyze velocity distribution, wall shear stress and flow resistance in nanoparticle drug delivery systems.[48]

Mahmoud studied how slip velocity affects flow of non-Newtonian power-law fluid moving over continuously moving surface, when heat is generated inside the fluid.[49]

Casson model

The primarily equation for Casson model is

$$\sqrt{\tau} = \sqrt{\tau_y} + \sqrt{k_c}\sqrt{\dot{\gamma}} \quad (4)$$

Where $\tau$is the shear stress, $\tau_y$is the yield stress, k_c is the Casson consistency coefficient and$\dot{\gamma}$isthe shear rate. For shear stress values less than the yield stress ($|\tau|<|\tau_y|$), the fluid behaves as a rigid solid with no flow ($|\dot{\gamma}|=0$). The

equation shows that blood, considered a Casson fluid, has a yield stress, and above this stress, the relationship between stress and shear rate is non-linear.

If $|\tau|<|\tau_y|$, then$\dot{\gamma} \doteq 0$and the fluid does not flow. This represents the "solid-like" behaviour of the fluid under low stress. If $|\tau|\geq|\tau_y|$, then the relationship is defined by the equation (4).

Rearranging for shear rate, the equation (4) becomes as

$$\dot{\gamma} = \frac{1}{k_c}(\sqrt{\tau} - \sqrt{\tau_y})^2 \quad (5)$$

Suneetha and Ramasekhar discuss about the magneto hydrodynamic (MHD) non-Newtonian blood flow in a stenosed artery associated with cardiovascular disease, using iron oxide and silver nanoparticles. It reports that increased magnetic field strength reduces blood velocity, while higher flow parameters increase the temperature. This research has significant implications for targeted drug delivery and cardiovascular treatments.[50]

Cross model

The Cross model for viscosity is

$$\mu(\dot{\gamma}) = \mu_\infty + \frac{\mu_o - \mu_\infty}{1+(k\dot{\gamma})^m} \quad (6)$$

Where $\mu(\dot{\gamma})$ is the shear dependent (effective) viscosity, μ_0 is the zero-shear viscosity, μ_∞ is the infinite-shear viscosity, k is constant time, m is cross model exponent and $\dot{\gamma}$ is the shear rate.

It was introduced by Cross in 1965.[51] In contrast, Zaman employs the Cross non-Newtonian fluid model to blood flow under magnetic effects in stenosed arteries, demonstrating its utility for capturing shear-thinning effects in complex arterial geometries.[52]A cross model for NP drug delivery in CVD describes how nanoparticles cross vascular barriers, target specific cardiac or inflamed endothelial cells via surface ligands, and enter cells through endocytosis or paracellular routes.

DISCUSSION

The collective analysis of the studies for this review indicates that nanoparticle-based drug delivery systems hold great potential for enhancing therapeutic efficacy, providing targeted drug delivery, and reducing side effects in cardiovascular diseases. Various types of nanoparticles such as polymeric based nanoparticle, liposomes, solid-lipid nanoparticles showed improve drug bioavailability, site-specificity, and controlled release. Nanoparticles deliver the drug directly to the site of disease, such as damaged heart tissue or a plague region. Traditional drugs are dispersed throughout the body, but nanoparticles are targeted to a specific location, making them more effective. Targeted nanoparticles functionalized with ligands exhibited higher accumulation at diseased sites such as atherosclerotic plaques, ischemic myocardium, and inflamed endothelium. This targeting reduced off-target toxicity and minimized systemic side effects, a major limitation of traditional CVD therapies.

A comparative analysis of the Power-Law, Cross model and Casson model reveals that the Power-Law Model offers simplicity and computational efficiency whereas the Cross and Casson models provide better physiological accuracy. The Cross model is best suited for general cardiovascular flow simulations, while the Casson model is more accurate for pathological conditions involving yield stress. Overall, integrating multiple models provides a more comprehensive understanding of nanoparticle-based drug delivery in cardiovascular disease.

CONCLUSION

Nanoparticle based drug delivery system have emerged as a highly promising and multifaceted technology in the treatment of cardiovascular disease. Nanoparticles high surface area, surface modification capabilities, tunable size and controlled release behaviour make them significantly more effective than traditional drug delivery methods. However, despite these advances, clinical translation remains limited. Challenges such as long-term toxicity, immune clearance, and uncertainty of biodistribution, manufacturing costs, and regulatory complexities remain major barriers in this field. Overall, nanoparticle-based drug delivery offers a highly promising direction for CVD therapy. If experimental findings, advanced modeling techniques, and clinical trials are integrated, personalized, targeted, and safer cardiovascular therapies may be developed in the future. This field has the potential to significantly transform the therapeutic landscape of CVD management in the coming years.

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