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Progress in Nano-Drug Delivery Systems and Computational Nano-Pharmacodynamics

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ABSTRACT:

Cardiovascular disease (CVD) is a leading cause of mortality and morbidity in developed countries. CVD is initiated by atherosclerotic lesions that reduce arterial lumen size through plaque formation and decreasing blood flow to the heart and frequently leading to severe complications. To cure these diseases drug delivery technologies modify drug release profile, absorption and distribution for the benefit of improving product efficacy and safety. Nano-medicine is an expeditiously growing science in which nanoscale range materials are used to serve the purpose of therapeutic agents. Among all the other interesting applications of nanomaterials, the nano-drug delivery system has emerged as an outstanding platform to deliver the remedial agents to a diseased site in a more controlled and targeted manner. By site-specificity, lowering toxicity and target-oriented delivery, nanotechnology endeavours many benefits by treating frightful diseases. The current review examines nano-drug delivery systems, nanoparticles and describes recent computational simulations of magnetic targeted nano-pharmacodynamics.

Keywords: *Drug Delivery System; Nanoparticles; Blood Flow; Cardiovascular Diseases; Nano-Magnetic Drug Delivery; Arterial Lumen; Computational nano-pharmacodynamics.*

1. Introduction

In the recent past quite a good number of theoretical and experimental investigations related to blood flow in arteries in the presence of stenosis have been carried out with various perspectives in the area of arterial biomechanics depending upon the objectivity of the problems of the life sciences. Human blood is a heterogeneous multiphase suspension of blood cells (red blood, white blood, platelets) in *plasma*, which constitutes about 55% of total blood volume and is composed of mostly water, dissipated proteins, mineral ions, clotting factors, hormones and blood cells [1]. It has been pointed out that the plasma behaves as a *Newtonian* fluid; however, whole blood exhibits *non-Newtonian* fluid nature [2]. For shear rate larger than 100 s^{-1}, blood exhibits a Newtonian nature, and this arises in for example, large arteries, veins and in large cavities. However, for shear rate less than 100 s^{-1}, blood behaviour is *non-Newtonian* i.e. hemo-rheological. Blood cell and plasma characteristics are presented in **Table 1 and Table 2**. Blood vessels are one of the important components of the circulatory system. Vessels are mainly divided into capillaries, veins and arteries, in which veins are responsible for carrying deoxygenated blood towards the heart whereas arteries carry oxygenated blood

from the heart to various parts of the body. Generally, capillaries are of size about 5-10 mm in diameter and veins ranges between 1 mm to 1-1.5 cm in diameter. In the case of arteries, elastic artery diameter is always greater than 1 cm and for muscular arteries, it is about 0.1-10 mm.

Blood component		**Per microliter**	**Size (μm)**	**Percentage**
Red blood cell		$4.1\text{-}5.1 \times 10^6$	7-8	97
White blood cell ($4\text{-}10 \times 10^3$)	Neutrophils Lymphocytes Eosinophils Monocytes Basophils	62% of WBC 30% of WBC 2.3% of WBC 5.3% of WBC 0.4% of WBC	10-12 6-14 - 15-20 -	2
Platelet		$1.5\text{-}4.5 \times 10^5$	3	1

Table 1: Blood Cell Characteristics [1]

The thermophysical properties of blood, for example, viscosity, density etc are shown in Table 3. It is seen that different parameters such as temperature, age and hematocrit influence the thermophysical properties of blood. The blood vessels bifurcate at frequent intervals and the diameter of the vessels varies with the distance as propounded by Whitmore [**1**] in 1968. The concept of flow in a varying cross-section forms the prime basis of a large class of problems in understanding blood flows as noted by Manton [**3**]. The accurate reason for formulation of stenosis is not known, but its influence over the flow characteristics has been considered theoretically and experimentally by many researchers. Accordingly, numerous investigations have discussed the blood flow characteristics (such as blood velocity, pressure and shear stress) to understand their role in the formation of stenosis and the validity of treatments [**4**]. A large number of studies have been carried out to elaborate the blood flow circulation in arteries.

Plasma Component		**Component**	**Molecular weight**	**Density (g/dl)**
Plasma	Water 91% Protein 7%	 Albumin Fibrinogen Immunoglobulins Prothrombin	 69000 340000 140000 68700	 4.5 0.3 2.5 0.015
Other	Salt includes vitamin, lipid, sugar etc.			

Table 2: Plasma characteristics [**1**]

2. Cardiovascular Diseases

Hemodynamics has an integral role in the formation and evolution of cardiovascular diseases. Accumulation of macrophage white blood cells, low-density lipoproteins (LDL) and deposition of cholesterol to the arterial wall of blood vessels results in a hardening of the arteries and reduction in the cross-sectional area of the blood vessel thereby leading to cardiovascular diseases. Many diseases affect the circulatory system. These include a number of cardiovascular diseases such as *Atherosclerosis*, *Aneurysms*, *Stroke*, *Angina* etc. affecting the cardiovascular system, and lymphatic diseases affecting the lymphatic system. Many of these diseases are called "lifestyle diseases" because they develop over time and are related to

a person's exercise habits, diet, whether they smoke, and other lifestyle choices a person makes.

Across a wide range of cardiovascular diseases, the best outcome depends on the ability to successfully direct drugs towards a specific diseased zone. Despite intense research and developments in drug delivery, present-day pharmacological formulations still leave the drug incapable of precisely localizing *en mass* at sites of interest. The drug molecules diffuse and spread in many cases *randomly* throughout the body, resulting in undesirable side effects and a reduction in the active response of proper doses. In recent years a new branch of fluid dynamics, focused on engineering fluids at the nanoscale, has emerged - *nanofluid dynamics*. Nanofluids have had a significant impact in improving miscellaneous applications in energy systems, industrial processes, transport, environmental and biomedical sciences.

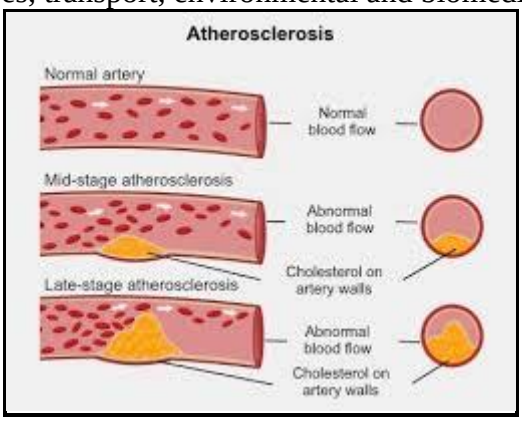


Figure 1: A normal artery versus diseased artery [5]

3. Clinical Importance

According to World Health Organization (WHO) report 2019 [6], CVDs are the number 1 cause of death globally: more people die annually from CVDs than from any other cause. An estimated 17.9 million people died from CVDs in 2016, representing 31% of all global deaths. Of these deaths, 85% are due to heart attack and stroke. Over three quarters of CVD deaths take place in low- and middle-income countries. Out of the 17 million premature deaths (under the age of 70) due to non-communicable diseases in 2015, 82% are in low- and middle-income countries, and 37% are caused by CVDs. Most cardiovascular diseases can be prevented by addressing behavioural risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol using population-wide strategies. In 2016, cardiovascular diseases contributed 28.1% of the total deaths in India. For CVDs, the dominating risk factors include *high systolic blood pressure, air pollution, high cholesterol, dietary risks, tobacco use and high body mass index*.

4. Nanofluids and Applications

Conventional fluids (air, water, oils etc) in industrial applications exhibit excellent lubrication properties; however, they have poor thermal characteristics which severely restrain their use. Nowadays, many researchers have been focused on developing techniques to increase *heat transfer rates* of conventional fluids. Experimentally it was found that the addition of small-sized solid particles in the base fluid can greatly enhance the thermo-physical properties.

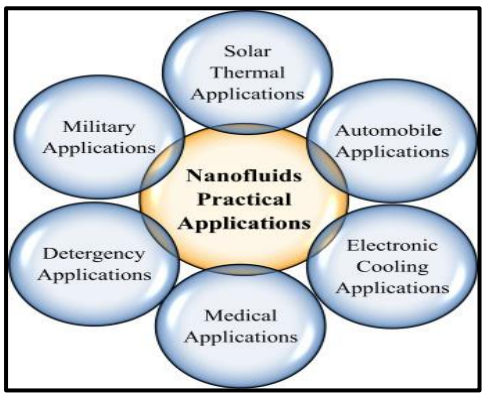


Figure 2: Applications of Nanofluids

In 1995, Choi [7] coined a new term "nanofluid", which is defined as a colloidal suspension of nanometer-sized particles (1-100nm) in a base fluid. These nanoparticles can be oxide, carbide, metallic, non-metallic, carbonic, hybrid and even more liquid droplets. The base fluid includes water, mineral oil, ethylene glycol or refrigerants. Both theoretical and experimental studies, largely based on the Buongiorno model [8] which is a two-component nanoscale formulation emphasizing Brownian motion and thermophoretic body force effects (originating in nuclear engineering at MIT) or the Tiwari-Das model [9] which is a volume-fraction-based doping model. It has been shown that the inclusion of nanoparticles (termed "doping") in base fluids increases the thermal conductivity remarkably and this contributes principally to the improved thermal performance of nanofluids [10]. The nanoparticles employed in biomedicine are also synthetic due to their unique interaction with biological matter [11, 12]. Generally, the rate of heat exchange in thermal systems is enhanced by using a nanofluid, due to the superior thermal conductivity over the conventional fluid. Therefore, by using nanofluids to enhance the heat transfer rate, the size of a thermal system can be optimized by transferring a specific value of heat which makes the system more compact. Relative to microfluids, nanofluids possess a higher stability and better potential to increase the heat conduction. In many heating and cooling applications, nanofluids are superseding conventional fluids. Nanofluids can be used in car radiators, boilers, cooling of electronic equipment, solar collector systems, refrigerators, pharmacological drug delivery, sterilization, fuel cells, lubrication of components, aerospace coatings and fuels, enhanced oil recovery techniques and liquid based heat exchangers. **Figure** 2 gives an overview of different applications of nanofluids.

5. Drug Delivery Systems

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. Drug delivery [13] technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance. Despite numerous research and development for drug delivery, present-day formulations still leave the drugs incompetent in localizing en mass at sites of interest. These drug molecules diffuse and spread randomly throughout the body, resulting in undesirable side effects and this reduces the active response of proper doses. In recent years a new branch of fluid dynamics has appeared, namely as nanofluid dynamics, which finds miscellaneous applications in energetics, medical science and biology. A very different application of nanofluids could be in modern medicine, where for example, nanodrugs are mixed in microchannels for controlled delivery with bio-MEMS (micro electro-mechanical system). For this purpose, nanoparticle- based drug delivery has immense potential for therapeutics having minimal side effects and optimizing specific targeted delivery. In spite of the potential of increasing a drug's propensity to accumulate at a targeted sited, the platform also faces a complex series of biological barriers that limit site-specific bioavailability, preventing achievement of proper therapeutic outcomes. The nanoparticles (especially copper) have been widely used for treatment, diagnosis, medical device coating and in drug delivery areas. Types of nanoparticles used for clinical research are shown in **figure 3**. Mechanisms of clearing blot clots with nanoparticles are shown in **fig. 4**. Among the most attractive and powerful strategies

for pharmacological drug delivery in affected site is the magnetic targeted drug delivery system (MTDDS). In comparison with conventional methods, MTDDS are fast-acting and highly efficient and owing to their capacity in reducing toxicity and other adverse side effects, they are becoming more popular in biomedicine [14]. Biomedical applications of magnetic nano particles (MNPs) are classified according to their application: *in vivo* or *in vitro*. In vivo applications involve therapeutics and diagnostics while in vitro applications relate to diagnostic usage (seperation/selection). MNPs are widely used in cell and macromolecule seperation, targeted drug delivery, electromagnetic hyperthermia, magnetic resonance imaging (MRI) and gene therapy. However the targeting properties of MNPs make them particularly appropriate for drug delivery systems [15].

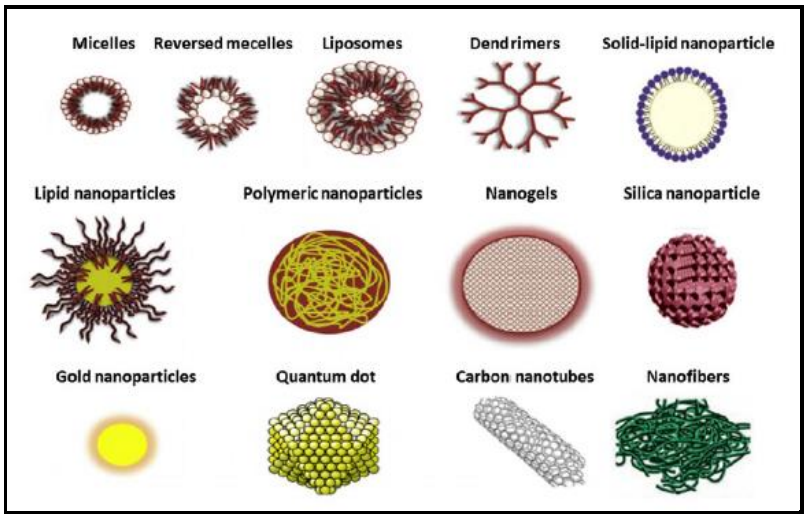


Figure 3 : Types of nanoparticles [15]

Key characteristics of magnetic nanoparticles are that they can be: (a) projected in place by using of magnetic field (b) visualized (c) heated in the presence of magnetic field to generate drug release. The Food and Drug Administration (FDA) have approved the use of iron oxides (or particular, magnetite) and confirmed that they are totally safe for humans [16]. Nano-based drug delivery systems have great potential in the field of health care. They provide better penetration of drugs through the body as their size allows delivery via injection or other routes. The application of nanoscience in medicine aims to improve the existing treatment regarding these diseases. Nanotechnology provides an effective and safe platform in controlled drug delivery systems for a range of active ingredients, which are directed to lipid disorders, angiogenesis within atherosclerosis and inflammation and avoidance of thrombosis among other diseases. Iron oxide super-paramagnetic nanoparticles are a major development in the magnetic drug targeting [17]. The *magnetic drug targeted system* provides appropriate

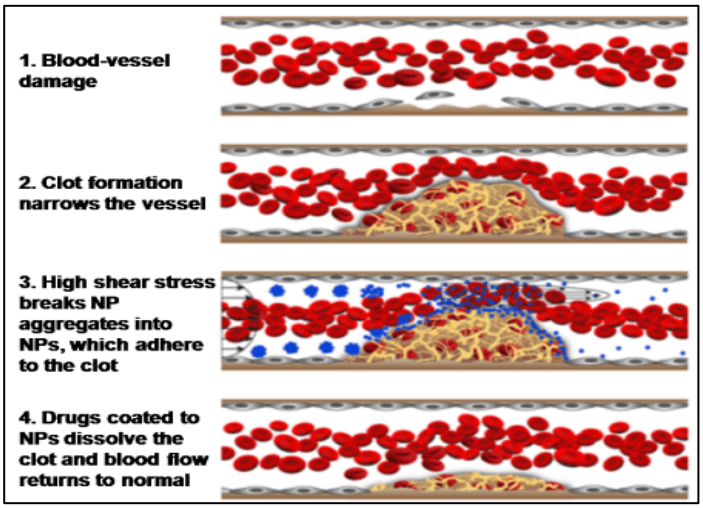


Figure 4: How nanoparticles clear the blood clot

magnetic gradients, which further increase the concentration of nanoparticles at the affected site [18].

6. Computational Nano-Pharmacodynamics/Nano-Hemodynamics

Many theoretical studies have been explored to illustrate the effect of various nanoparticles (drugs) in blood flows and this area of study is known as *nano-pharmacodynamics* or *nano-hemodynamics*. In particular, *stenotic nano-hemodynamics* has witnessed considerable interest in the engineering sciences and applied mathematics communities owing to its significance in combatting diseased arteries. The many studies reported have also featured numerous computational methods which are required to tackle the nonlinearity of the mathematical models. Nadeem *et al.* [19] studied the steady blood flow through tapered stenosed arteries using nanoparticles with a Prandtl blood flow mode and a homotopy perturbation method. Ahmed *et al.* [20] investigated the influence of different nanoparticles (Cu, TiO^2, Al_2O_3) on Newtonian blood flow in a single stenosed vessel, noting that flow acceleration in the core region is greater for Al_2O_3 nanoparticles than either Cu or TiO_2 nanoparticles. Ali *et al.* [21] performed a numerical simulation of time-dependent non-Newtonian (Sisko fluid) nano-pharmacodynamic transport phenomenon in an overlapping tapered artery using Buongiorno's model and a forward time central space (FTCS) method. Results were validated with finite element method (FEM) and it was found that flow rate at stenotic throat decreases with an increase in the Brownian motion parameter. Very recently, Vasu *et al.* [22] have developed a robust model of non-Newtonian nanofluid hemodynamics with heat and mass diffusion in a stenosed coronary artery in the presence of a radial magnetic field. We briefly describe some of the details of that simulation here to provide a deeper understanding of nano-drug diffusion in the treatment of cardiovascular disease (stenotic arteries). Buongiorno's nanoscale model and the Reiner-Rivlin second order differential model are employed in the formulation. The geometry considered is reproduced in **Fig. 5**.

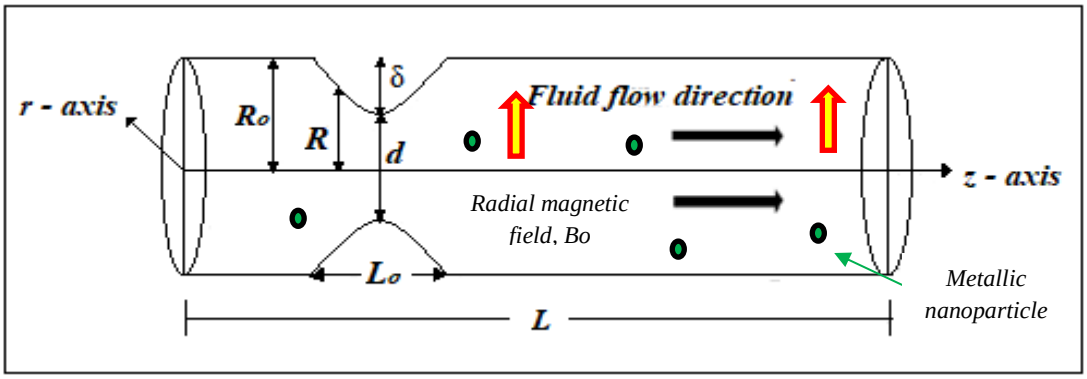


Figure 5. Schematic illustration of stenosed coronary arterial model [22]

The FreeFEM++ finite element code [62] was used to compute hemodynamic characteristics in this study. The finite element mesh was designed with 5928 unstructured fixed triangular elements with 12177 nodes as presented in **Figure 6**. The mesh generation was accomplished with the automatic FreeFEM++ mesh generator based on the Delaunay-Voronoi algorithm.

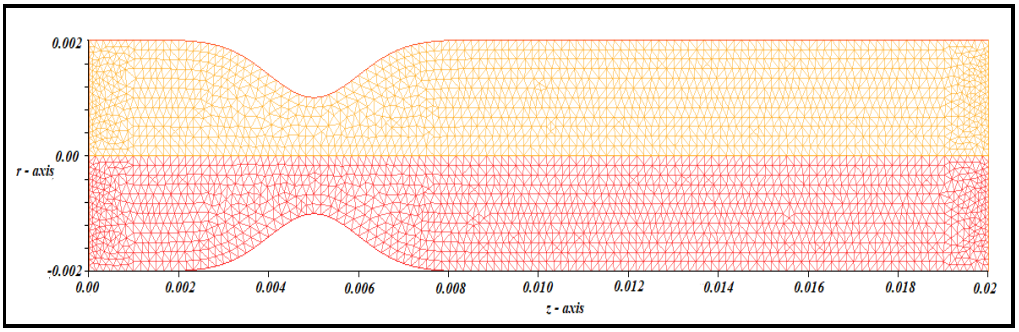


Figure 6. Unstructured triangular fixed finite element mesh [22]

Some selected simulations are shown in **Figs. 7** (a) to (d) which depict the streamlines of blood flow for specific values of *M and* N_t *when* $N_b = 0.3, \lambda_1 = 0.5, A = B = 5$ *and* $c = 0.3$. In Fig 7(a), the presence of a circulating bolus of blood enclosed by the streamlines in the stenotic region of the artery represents that if the size of the bolus will be decreased, the flow acceleration will also be decreased at the stenotic part of the artery. The bigger the bolus the higher the acceleration at that point. It can be seen from the two figures 7(a) and 7(b), by applied magnetic field the strength of the circulating region reduced. However, comparing the 7(a) with 7(c), even with alteration in magnetic parameter (*M*) there seems no significant deviation in size and circulation of this bolus of blood. This indicates that the circulating bolus of blood is relatively insensitive to magnetic field. However, inspection of Figs. 7(b), 7(d), shows that there is some deviation in the characteristics (magnitude and structure) of the bolus of blood with a change in thermophoresis parameter.

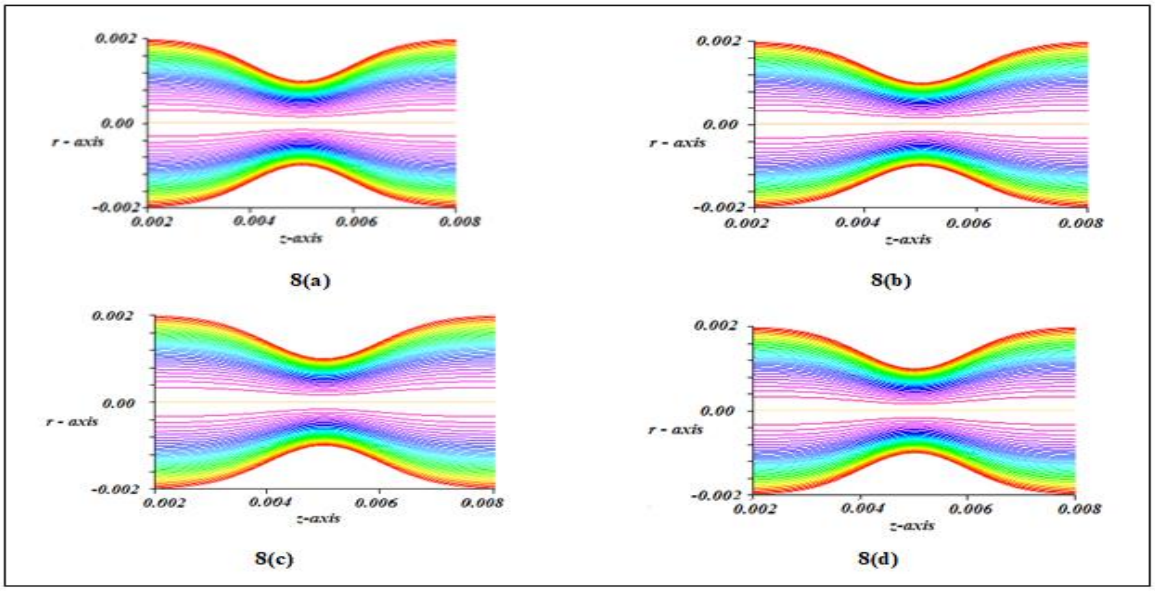
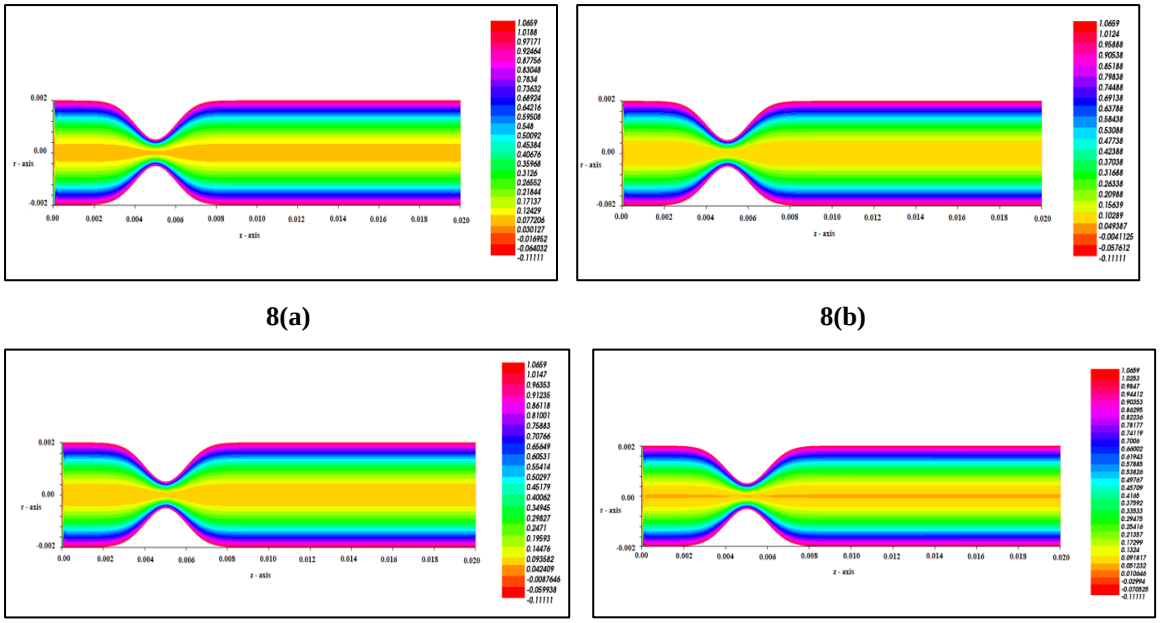


Figure 7 Streamlines of blood flow in the arterial segment when **a)** $M = 0.3, N_t = 0.3$ **b)** $M = 0.3, N_t = 0.6$ **c)** $M = 0.6, N_t = 0.3$ **d)** $M = 0.6, N_t = 0.6$



8(a) **8(b)**

8(c) **8(d)**

Figure 8 Nanoparticle Concentration for **(a)** $\lambda_1 = -0.5,\ M = 0.3, N_b = 0.3\ and\ N_t = 0.3$ **, (b)** $\lambda_1 = -0.5,\ M = 0.3, N_b = 0.3\ and\ N_t = 0.6$ **, (c)** $\lambda_1 = -0.5,\ M = 0.6, N_b = 0.3\ and\ N_t = 0.3$ **(d)** $\lambda_1 = -0.5,\ M = 0.6, N_b = 0.3\ and\ N_t = 0.6$.

Figures 8(a) - (d) visualize the nanoparticle concentration contours for various magnetic body force parameters (*M*) and thermophoresis parameters (N_t) with fixed values of Brownian motion parameter (N_b =0.3) and viscoelastic parameter (λ_1= -0.5). Comparing fig. 8a with 8d the thermophoresis parameter is increased from 0.3 to 0.6 with all other parameters constrained, there is an expansion in the orange (lower magnitude contour) zone is expanded and the engulfing yellow zone (higher magnitude contour) is contracted. The values for nano-particle concentration are therefore reduced along the axial direction and radial direction in the vicinity of the stenotic region. Species diffusion of nanoparticles into the core region is therefore decreased with greater thermophoretic effect. Comparing fig. 8a with fig. 8c, the magnetic parameter is increased from *M* = 0.3 to 0.6, with all other parameters fixed. A similar response to the thermophoretic effect is observed i.e. the orange zone is expanded and the yellow zone is diminished Stronger magnetic field therefore also inhibits nano-particle diffusion into the core zone and results in decreasing magnitudes of nano-particle concentration along the entire arterial section i.e. with all axial coordinate locations. Comparing fig. 8c and 8d this trend is further amplified with the emergence of a thin brown zone along the arterial mid-line indicating an even greater depletion in nano-particle concentration values. The combination of maximum magnetic parameter value and maximum thermophoresis parameter value therefore serves to strongly diminish nano-particle concentration values. The opposite effect i.e. *elevation in nano-particle diffusion* may therefore be induced by utilizing a weaker magnetic field and lower thermophoresis in nano-particle deployment in stenotic blood flows. *Computational nano-hemodynamics* clearly is a powerful tool for visualization in modern nano-biomedicine and drug delivery systems and provides an excellent methodology for optimizing the impact of different nano-drugs in clinical treatments. Other numerical methodologies are also very promising in this regard and include Lattice Boltzmann [23], molecular dynamics [24], smoothed particle hydrodynamics [25] and boundary element methods [26].

Conclusions

In the present review, recent advances in nanomedicine have been considered in addition to progress in the delivery of old drugs with new therapeutic methods. Initially, to enhance the solubility, bioavailability, absorption and targeted and controlled release of drugs is the main motivation for implementing nanotechnology in biomedicine. The use of nano- carriers formulated with dendrimers, liposomes, micelles, solid lipid nanoparticles, gold, silver, titanium oxide and cadmium sulphide polymeric nanoparticles together with superparamagnetic iron oxide nanoparticles has been shown to substantially improve the efficacy of conventional pharmacological agents. Magnetic drug delivery systems also offer excellent potential due to their unique properties which are ideal for targeted and controlled delivery. This review has also described significant progress in the use of mathematical and computational hemodynamic models for simulating nanoparticle drug delivery effects in cardiovascular diseases (stenotic arteries, aneurysms etc). Computational nano-pharmaco/hemo-dynamics offers great advantages in providing deeper insight into the inherent mechanisms involved in nano-drug delivery. Many methods have been developed in this regard and warrant further investigation and corroboration with clinical findings. The advancement in nano-biomedicine along with improved safety and reduced toxicity will be greatly accelerated with computational modelling techniques.

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