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Effect of non-Newtonian characteristics of blood on magnetic particle capture in occluded blood vessel

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ABSTRACT

Magnetic nanoparticles drug carriers continue to attract considerable interest for drug targeting in the treatment of cancer and other pathological conditions. Magnetic carrier particles with surface-bound drug molecules are injected into the vascular system upstream from the desired target site, and are captured at the target site via a local applied magnetic field. Herein, a numerical investigation of steady magnetic drug targeting (MDT) using functionalized magnetic micro-spheres in partly occluded blood vessel having a 90° bent is presented considering the effects of non-Newtonian characteristics of blood. An Eulerian–Lagrangian technique is adopted to resolve the hemodynamic flow and the motion of the magnetic particles in the flow using ANSYS FLUENT. An implantable infinitely long cylindrical current carrying conductor is used to create the requisite magnetic field. Targeted transport of the magnetic particles in a partly occluded vessel differs distinctly from the same in a regular unblocked vessel. Parametric investigation is conducted and the influence of the insert configuration and its position from the central plane of the artery (z_{offset}), particle size (d_p) and its magnetic property (χ) and the magnitude of current (I) on the "capture efficiency" (CE) is reported. Analysis shows that there exists an optimum regime of operating parameters for which deposition of the drug carrying magnetic particles in a target zone on the partly occluded vessel wall can be maximized. The results provide useful design bases for in vitro set up for the investigation of MDT in stenosed blood vessels.

1. Introduction

In conventional drug delivery the drug is administered by intravenous injection; it then travels to the heart from where it is pumped to all regions of the body. For the small target region that the drug is aimed at, this method is extremely inefficient and leads to much larger doses (often of toxic drugs) than necessary. To overcome this problem, a number of targeted drug delivery methods have been developed [1–3]. Among them, the magnetic targeted drug delivery system (MDT) is one of the most attractive strategies because of its non-invasiveness, high targeting efficiency and its ability to minimize the toxic side effects on healthy cells and tissues [4,5]. MDT is a therapeutic technique that uses an external magnetic field to retain magnetic drug carrier particles (MDCPs) at a specific site in the body. Häfeli et al. [6], Jurgons [7] among many others provides sufficient introductory and background information on MDT. MDT therapy is a promising technique for the treatment of various diseases, especially cancer, arteriosclerosis, like stenosis, thrombosis and aneurysm, what is important is to keep the therapeutic drug in the targeting site, which is located along the inner wall of the blood vessel [8,4,5,9,10]. Some in vitro [9,10] and in vivo [8,11,12,7] experiments have been performed in this direction.

The newer magnetic particles are composed of a magnetic core material (usually iron or iron oxide) that has been treated to retain drugs on its surface or internally. The particles are small enough ($< 5\ \mu m$) to navigate the artery and capillary systems of the body, but larger particles can lodge into certain tissues. By configuring magnets externally (outside the body), the particles can be stopped in the bloodstream or pulled in a direction of flow until the particles are positioned at the disease site. For tumors, the particles are drawn into the blood supply arteries of the tumor and lodged in the tissue. Radioisotopes or chemotherapeutic drugs attached to the particles can irradiate the tumor cells or desorb from the particles and attack the tumor cells. Indeed, given the intricate network of blood vessels and capillaries in the human body, precise guidance of particles to capillary beds is prohibitive. A sophisticated and powerful magnet system capable of operating in parallel with an imaging scheme (e.g., magnetic resonance imaging or computed tomography) may be needed to target or concentrate the magnetic particles in all but the most accessible (e.g., a superficial target or an organ that displays other conditions such as enhanced blood flow, natural filters, or sheer mass that naturally accumulates the particles) sites in the body. Crude bar

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magnets have been determined to work well for superficial tumor sites and for targeting liver tumors, and offer a relatively inexpensive capital investment compared with superconducting magnet designs. The most advanced superconducting magnet system has been developed by Stereotaxis, Inc. [13], for guiding catheters within the human vasculature.

Typically, this compound in which drugs are bound with nanoparticles is injected through a blood vessel supplying the targeting tissue in the presence of an external magnetic field with sufficient field strength and gradient to retain the carrier at the target site. Recent development on carriers has largely focused on new polymeric or inorganic coatings on magnetite/maghemite nanoparticles [14], such as ferrofluids. Ferrofluids are colloidal solutions of ferro or ferromagnetic nanoparticles in a carrier fluid, which are widely used in technical applications. Because of a high magnetic moment of nanoparticles in ferrofluids, ferrofluids are gaining increasing interest to be utilized as drug carriers in magnetic targeting for biological and medical applications [15]. When they are used in medicine, ferrofluids must be biocompatible and bio-degradable [7]. Recently, some theoretical studies of magnetically targeted drug delivery considered tracking individual particles under the influence of Stokes drag and a magnetic force alone [16], and formulated a two-dimensional (2D) model, suitable for studying the deposition of magnetic particles within a network of blood vessels [17]. Other theoretical studies investigated the basic interaction between magnetic and fluid shear forces in a blood vessel [18] or utilized high gradient magnetic separation principles to study a magnetic drug targeting system [19].

The hydrodynamic drag on the magnetic particles in the arteries is very large. Therefore, establishing sufficiently strong magnetic field and gradients (by permanent magnets or electromagnets) for the guided transport of MDCPs and their localized aggregation in an arterial system remains to be major challenge. For superficial arteries magnetic bandages employing buttons or Halbach array arrangements can provide strong holding force [6]. However, for blood vessels embedded deep into the body, magnetizable inserts, e.g., stents [20,21], wires [22], and mesh [23] have been proposed. Although these studies have successfully demonstrated the feasibility of targeting MDCPs in regular blood vessels, to the knowledge of the authors, such studies in occluded vessels have not been well-reported. Since the hydrodynamics of occluded blood vessels differ considerably from that of regular ones [24], targeted localization of magnetic drug careers in a stenosed arterial geometry can provide useful information for magnetically targeted anti-angiogenic drug therapy, or for thrombolytic treatment in a partly occluded blood vessel. A recent numerical study by Haverkort et al. [25] has demonstrated feasibility of using superconducting magnets and magnetic particles of 250 nm–4 μm diameters for targeted delivery in mildly stenosed coronary and carotid arteries.

The magnetic force on a particle is strongly dependent on the size of the particle (i.e., the force is proportional to d^3, where d is the diameter of the particle) and many studies have consequently focused on micron-sized magnetic particles. In a recent simulation study on the retention of magnetic particles in small arteries exposed to a magnetic field generated by a Maxwell coil pair electromagnet it was concluded that particles should be significantly larger than 10 μm to be captured efficiently. Such large particles are not suitable for in vivo applications since they will obstruct the blood capillaries [26].

Although there have been a number of theoretical studies for magnetic drug targeting, very few researchers have addressed the hydrodynamic models of magnetic fluids in magnetic drug targeting delivery. Thus, the transport issues related to magnetic drug targeting delivery are yet poorly understood and it retards the extensive application of the magnetic drug targeting delivery. Therefore, it is very necessary to study the flow of the ferrofluids in the blood vessel under the action of the external magnetic field.

The Blood being a suspension of cells in plasma, it exhibits a non-Newtonian behavior at the low shear stress mainly when it flows through small arteries and micro-vessels [27]. The biophysical aspects of blood flow in the micro-vessel has been analyzed by Prier et al. [28], gives intricate interaction between the mechanical behavior of blood and its cellular constituents, and also its effect in the complex and irregular geometries of microvessels. Bugliarello and Sevilla [29] and Cokelet [30] have shown experimentally that when blood flows through a narrow blood vessel there is a peripheral layer of plasma and a core region of suspension of all the erythrocytes. They also suggested that Casson model and Herschel–Bulkley model are more suitable for the study of blood flow through narrow arteries. It has been established by Merrill et al. [31] that Casson model holds satisfactory for blood flowing in tubes of diameter 130–1300 mm, where as Herschel–Bulkley fluid model could be used in micro-tubes of diameter 20–100 mm.

Recently Shaw and coworkers [32–38] has been doing a considerable work in the field of MDT, both theoretical as well as experimental to find out the trajectories of the drug dosed magnetic carrier particle in a micro vessel, which is subjected to the external magnetic field using different rheological model of blood.

Here we have numerically investigated the targeting of micron-size magnetic beads in the partly occluded region of a blood vessel having a 90° bend using a magnetic insert as proposed by Haverkort et al. [25] considering the non-Newtonian characteristics of blood. This technique can offer strong local magnetic field gradient, causing the desired magnetic capture of the drug carrying magnetic beads even for vessels that are located deep inside the body. A mathematical model presented in this article describes the hydrodynamics of ferrofluids in a blood vessel under the action of the magnetic field. Numerical simulations are performed to obtain better insight into the theoretical analysis. Furthermore, the ferrofluids flow is analyzed numerically with computational fluid dynamics (CFD) in a model of an idealized 3D blood vessel containing an occlusion to understand the clinical application of ferrofluids. Distribution of particle capture along the endothelial wall of the occluded region of the vessel, and the particle targeting efficiencies are investigated as functions of the hemodynamic, geometric and magnetic parameters for four different rheological models. Results of the analysis provided important information leading to adequate drug delivery to the target site and can suggest strategies for improving delivery in favour of the clinical application.

2. Model equations

2.1. Blood flow

Three dimensional continuity and Navier–Stokes (NS) equations are used as the governing equations of blood flow.

$$\nabla \times \mathbf{u} = 0 \tag{1}$$

$$\rho\left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \times \nabla \mathbf{u}\right) = -\nabla p + \mu \nabla^2 \mathbf{u} \tag{2}$$

where, $\mathbf{u}$ is three dimensional velocity vector, ρ is density of the blood, t is time, p is pressure, μ is viscosity of blood (flow).

The fully developed velocity profile is used for the inlet, while the outlet is set to be of zero gauge pressure and the no slip velocity boundary condition is used for the artery wall.