Mathematical model of effect of drug delivery on blood flow in external magnetic field by Magnetic Nanoparticles

Somna Mishra[*], V. K. Katiyar[**], V. Arora[***] and Gaurav Varshney[****]

[*] Gurukula Kangri Vishwavidyalaya, Haridwar, Uttarakhand, India, mishra_somna@yahoo.com
[**]Department of Mathematics, Indian Institute of Technology Roorkee, India, vktmafma@iitr.ernet.in
[***] Gurukula Kangri Vishwavidyalaya, Haridwar, Uttarakhand, India
[****]Department of Mathematics, Indian Institute of Technology Roorkee, India, gauvadma@iitr.ernet.in

ABSTRACT

A mathematical model is proposed to study the velocity profiles i.e. velocity of magnetic nanoparticles (diameter 20 nm) as drug carrier and blood in the presence of uniform external magnetic field inside the capillary region. The volumetric flow rate and skin friction are also taken into account and the analytic expressions are also developed.
Keywords: magnetic nanoparticles, nano-drug targeting.

1. INTRODUCTION

Magnetic drug targeting is one of the various possibilities of drug targeting, which aims at concentrating magnetic drugs at a target site with the aid of magnetic field, so that the drug concentration is enhanced at the target and reduces the toxicity and side effects in normal tissue [1].

Magnetic and hydrodynamic interactions between magnetic beads in micro-fluidic field gradient filters are compared theoretically and it is found that hydrodynamic interactions are of a longer range and dominate the magnetic ones [2]. An *in vitro* model was developed to study and demonstrate the potential and feasibility of magnetically targeted deposition of aerosols for potential applications in lung cancer treatment [3]. High-pressure liquid chromatography analyses after magnetic drug targeting showed an increasing concentration of the chemotherapeutic agent in tumor region compared to regular systemic chemotherapy [4].

In this paper, we have considered the velocity profiles of magnetic nanoparticles (diameter 20 nm) and blood in the presence of uniform external magnetic field relative to each other inside the capillary region, in cylindrical polar coordinates. The electrical conductivity of blood is not taken into account. The volumetric flow rate and skin friction are also considered and the analytic expressions are also developed.

2. MATHEMATICAL FORMULATION

The magnetic force on the magnetic nanoparticles is [6]

$$\vec{F}_M = \frac{\chi V_M}{\mu_0}\nabla\left(\vec{B}^2\right). \qquad (1)$$

Where μ_0 is the permeability of free space, χ is the magnetic susceptibility of the particle, $V_M\,(=\frac{4}{3}\pi R_M{}^3)$ is the volume of the magnetic nanoparticle and $\vec{B}$ is the magnetic induction. The magnetostatic field equations are

$$\nabla\cdot\vec{B}=0, \quad \nabla\times\vec{H}=0. \qquad (2)$$

where $\vec{H}$ is the magnetic field intensity.

Using the expression $\vec{B}=\mu_0\vec{H}$ and the magnetostatic field equations, equation (1) can be transformed into

$$\vec{F}_M = \mu_0 V_M\left(\vec{M}\cdot\nabla\right)\vec{H}.$$

Where $\vec{M}=\chi\vec{H}$, $\vec{M}$ is the magnetization of the particle.

Assuming that the fluid is non-conducting and that the displacement current is negligible so that $\nabla\times\vec{H}=0$ as defined in [7]. Hence the magnetic force on a nanoparticle (in the form of sphere) can be calculated as

$$\vec{F}_M = \mu_0 V_M M\nabla H. \qquad (3)$$

In this paper, we have considered the magnetite nanoparticles as drug carrier and also the saturation value of magnetization $(=450{,}000\,Am^{-1})$ is taken for these particles [8]. Here we have considered only those portions of blood vessels, which are oriented perpendicularly to the direction of the magnetization. The intensity of the magnetic field in the direction of magnetization for the cylindrical magnet is given by [9]

$$H_y = \frac{C_1 a^2}{y^2}.$$

Where 'a' is the radius of the cylindrical magnet. O_y is the direction of magnetization oriented perpendicular to the direction of blood vessel feeding the tumor (Figure 1). The value of the constant C_1 is defined in TABLE I.

Since the magnetic field varies over a length scale, typically $O(10^{-2}-10^{-1}m)$. The diameter of the capillary in which targeting takes place is much smaller than the above mentioned scale. So the magnetic force across a capillary diameter is assumed constant.

The force that counteracts the magnetic force on the particle in blood stream is due to the blood flow and can be calculated as using the Stokes' expression for drag force on a sphere as [5]

$$F_D = 6\pi\mu R_M(u-\upsilon). \qquad (4)$$

Where μ is the viscosity of blood, R_M is the radius of the magnetic nanoparticle, u is the velocity of blood and υ is the velocity of magnetic nanoparticles.

For the present problem, the blood flow has been considered as laminar axi-symmetric flow of a viscous, homogeneous, incompressible Newtonian fluid in cylindrical blood vessel (capillary). The flow in capillary is assumed to

follow Hagen-Poiseuille flow. The electrical conductivity of blood is not taken into account.

The equations of continuity and motion for the flow of magnetic nanoparticles and blood are

$$m\frac{\partial \upsilon}{\partial t} = \mu_0 V_M (M\nabla H)_y + 6\pi\mu R_M (u-\upsilon). \quad (5)$$

$$\rho\frac{\partial u}{\partial t} = -\frac{\partial p}{\partial z} + \mu\left(\frac{\partial^2 u}{\partial r^2} + \frac{1}{r}\frac{\partial u}{\partial r}\right) + \frac{NA}{\rho}(\upsilon - u). \quad (6)$$

where υ is the velocity of magnetic nanoparticles, ρ is the density of blood, p is pressure, N is number density of suspended nanoparticles, $A(=6\pi\mu R_M)$ is Stokes' coefficient, m is the mass of the magnetic nanoparticle ($=\rho_P V_M$, ρ_P is the density of the material of nanoparticle) and t is the time parameter. The initial and boundary conditions are

$$\text{at } t=0,\ u=\upsilon=\frac{\partial u}{\partial t}=0. \text{ and } \quad \text{at } r=R,\ u=0. \quad (7)$$

Where R is the radius of capillary.

3. NON-DIMENSIONALIZATION

We rescale our mathematical model in the following manner, denoting non-dimensional variables with bar:

$$\bar{r}=\frac{r}{R}, \bar{z}=\frac{z}{R}, \bar{y}=\frac{y}{R}, \bar{t}=\frac{t\mu}{\rho R^2}, \bar{u}=\frac{uR}{v}, \bar{\upsilon}=\frac{\upsilon R}{v}, \bar{p}=\frac{pR^2}{\rho v^2}, \bar{H}=\frac{H}{H_0}. \quad (8)$$

Where $v=\frac{\mu}{\rho}$ is the kinematic viscosity and H_0 is the intensity of magnetic field at the surface of the magnet.

After dropping the bars, the governing equations transform to give

$$\frac{\partial \upsilon}{\partial t} = (\omega_1 \nabla H)_y + \omega_2(u-\upsilon). \quad (9)$$

$$\frac{\partial u}{\partial t} = -\frac{\partial p}{\partial z} + \left(\frac{\partial^2 u}{\partial r^2} + \frac{1}{r}\frac{\partial u}{\partial r}\right) + \phi_1(\upsilon - u). \quad (10)$$

Where $\omega_1=\frac{\mu_0 V_M M H_0 R^2}{m v^2}$, $\omega_2=\frac{6\pi\mu R_M R^2}{mv}$ and $\phi_1=\frac{NAR^2}{\rho v}$.

and the initial and boundary conditions are

$$\text{at } t=0,\ u=\upsilon=\frac{\partial u}{\partial t}=0. \text{ and at } r=1,\ u=0., \frac{\partial p}{\partial z}=P_z=\text{constant.} \quad (11)$$

Let $\eta_1=(\omega_1\nabla H)_y$.

On solving equations (9) and (10) using the initial and boundary conditions in (11), we get,

$$u(r,t)=\left[\frac{e^{\left(\frac{-\psi^2+\sqrt{\psi^4-4\zeta}}{2}\right)t}\left[\phi_1\eta_1 - P_z\left(\frac{-\psi^2+\sqrt{\psi^4-4\zeta}}{2}+\omega_2\right)\right]}{\frac{3}{4}(\psi^4-4\zeta)-\frac{\psi^2}{4}-\frac{\psi^2\sqrt{\psi^4-4\zeta}}{2}+\zeta} + \frac{e^{-\left(\frac{\psi^2+\sqrt{\psi^4-4\zeta}}{2}\right)t}\left[\phi_1\eta_1 - P_z\left(\frac{-\psi^2-\sqrt{\psi^4-4\zeta}}{2}+\omega_2\right)\right]}{\frac{3}{4}(\psi^4-4\zeta)+\frac{\psi^2\sqrt{\psi^4-4\zeta}}{2}+\zeta} - \frac{P_z\omega_2}{\zeta}\right](1-r^2)$$

$$\upsilon(r,t)=\frac{\eta_1}{\omega_2}(1-e^{-\omega_2 t})+$$

$$\left[\frac{\phi_1\eta_1 e^{-\omega_2 t}}{-\omega_2^3+\psi^2\omega_2^2-\omega_2\zeta} + e^{\left(\frac{-\psi^2+\sqrt{\psi^4-4\zeta}}{2}\right)t}\left[\frac{\phi_1\eta_1}{\left\{4\left(\frac{-\psi^2+\sqrt{\psi^4-4\zeta}}{2}\right)^3+3(\psi^2+\omega_2)\left(\frac{-\psi^2+\sqrt{\psi^4-4\zeta}}{2}\right)^2+2\omega_2\psi^2\left(\frac{-\psi^2+\sqrt{\psi^4-4\zeta}}{2}\right)+\left(-\psi^2+\sqrt{\psi^4-4\zeta}+\omega_2\right)\zeta\right\}} - \frac{P_z}{\frac{3}{4}(\psi^4-4\zeta)-\frac{\psi^2}{4}-\frac{\psi^2\sqrt{\psi^4-4\zeta}}{2}+\zeta}\right] + e^{-\left(\frac{\psi^2+\sqrt{\psi^4-4\zeta}}{2}\right)t}\left[\frac{\phi_1\eta_1}{\left\{4\left(\frac{-\psi^2-\sqrt{\psi^4-4\zeta}}{2}\right)^3+3(\psi^2+\omega_2)\left(\frac{\psi^2+\sqrt{\psi^4-4\zeta}}{2}\right)^2-2\omega_2\psi^2\left(\frac{\psi^2+\sqrt{\psi^4-4\zeta}}{2}\right)+\left(-\psi^2-\sqrt{\psi^4-4\zeta}+\omega_2\right)\zeta\right\}} - \frac{P_z}{\frac{3}{4}(\psi^4-4\zeta)+\frac{\psi^2\sqrt{\psi^4-4\zeta}}{2}+\zeta}\right]\right](1-r^2)$$

The volumetric flow rate or the total flux across any section i.e. the total volume of the fluid crossing any section per unit time is given by

$$F=\int_0^1 2\pi r u dr = \left[\frac{e^{\left(\frac{-\psi^2+\sqrt{\psi^4-4\zeta}}{2}\right)t}\left[\phi_1\eta_1 - P_z\left(\frac{-\psi^2+\sqrt{\psi^4-4\zeta}}{2}+\omega_2\right)\right]}{\frac{3}{4}(\psi^4-4\zeta)-\frac{\psi^2}{4}-\frac{\psi^2\sqrt{\psi^4-4\zeta}}{2}+\zeta} + \frac{e^{-\left(\frac{\psi^2+\sqrt{\psi^4-4\zeta}}{2}\right)t}\left[\phi_1\eta_1 - P_z\left(\frac{-\psi^2-\sqrt{\psi^4-4\zeta}}{2}+\omega_2\right)\right]}{\frac{3}{4}(\psi^4-4\zeta)+\frac{\psi^2\sqrt{\psi^4-4\zeta}}{2}+\zeta} - \frac{P_z\omega_2}{\zeta}\right]\frac{\pi}{2}.$$

Skin friction on the surface of the capillary due to fluid is given by

$$S_F=\mu\left(\frac{\partial u}{\partial r}\right)_{r=1} = -2\mu\left[\frac{e^{\left(\frac{-\psi^2+\sqrt{\psi^4-4\zeta}}{2}\right)t}\left[\phi_1\eta_1 - P_z\left(\frac{-\psi^2+\sqrt{\psi^4-4\zeta}}{2}+\omega_2\right)\right]}{\frac{3}{4}(\psi^4-4\zeta)-\frac{\psi^2}{4}-\frac{\psi^2\sqrt{\psi^4-4\zeta}}{2}+\zeta} + \frac{e^{-\left(\frac{\psi^2+\sqrt{\psi^4-4\zeta}}{2}\right)t}\left[\phi_1\eta_1 - P_z\left(\frac{-\psi^2-\sqrt{\psi^4-4\zeta}}{2}+\omega_2\right)\right]}{\frac{3}{4}(\psi^4-4\zeta)+\frac{\psi^2\sqrt{\psi^4-4\zeta}}{2}+\zeta} - \frac{P_z\omega_2}{\zeta}\right].$$

Where $\psi^2=\omega_2+\phi_1+4$, $\zeta=4\omega_2$.

4. RESULTS AND DISCUSSION

The fluid (blood) velocity is maximum at the center of the capillary i.e. at $r=0$ and decreases as the radial distance increases and zero at the capillary wall. Also it is found that the velocity distribution of blood flow is parabolic and same at all the times (figure 2).

The flow behavior of magnetic nanoparticles is shown in figures 3, 4 and 5 with different distances (y) between the magnet and the capillary. Initially at time $t=0$, this profile is same in nature as of blood (i.e. maximum at $r=0$ and zero at the capillary wall). Also it is clear that the parabolic nature of nanoparticles flow gradually decreases with increasing time. Figures 6 and 7 show the velocity distribution of magnetic nanoparticles at time 0.1and 0.12 sec. for different distances (y) between the magnet and the capillary. These figures show that as the time increases, velocity increases in negative direction. The negative sign

indicates that there exists a back-flow towards the magnetic region and also this negative speed increases as the radial distance increases. After a small time they attain a maximum (constant) negative speed depending upon the distance between the magnet and the capillary (figure 8). Also from figures 6, 7 and 8, it is clear that lesser the distance between the magnet and the capillary, greater the velocity of magnetic nanoparticles by which they move back towards the magnetic region. Figure 9 and 10 represents the changes in volumetric flow (F) and shear stress (S_F) against time. Since initially, the magnetic nanoparticles move in the direction of blood flow. With increases in time, the nanoparticles move back towards the magnetic region and therefore the total flux across any section reduces (figure 9). Also, the nanoparticles experience a force (skin friction) against in the direction of their flow. So it is initially negative but as the time increases, the particles start to flow in reverse direction, thus skin friction takes the positive value (figure 10). The parameter values are given in TABLE I.

5. CONCLUSIONS

We have formulated a model of blood and magnetic nanoparticles transport in the very small sized vessels (i.e. capillary). Based on the velocity profiles of magnetic nanoparticles, it is clear that a high magnetic field strength and gradient is desirable for magnetic nano-drug targeting. In the model presented in this paper, it can be achieved by decreasing the distance of the magnet from the vessel. This study also showed that the magnetic saturation, fluid (blood) speed, particle size and amount of solid content have large significance related to how well the magnetic nanoparticles geometrically localized by the applied magnetic field. However, the best value for the particle size and the number density of nanoparticles has yet to be investigated.

Since the drug targeting is effected by pulling magnetic particles to the edge of the vessels (capillary) and as in our model the magnetic field strength and gradient depends upon the distance between the magnet and vessel wall, so the magnetically targeted drug delivery by external magnetic field is more effective for the targets close to the surface of the body in comparison to the interior regions of the body. The drug delivery using the magnetic nanoparticles under a magnetic field is better than other drug delivery devices because the particles (drug coated) move back to the diseased area where the magnetic field is applied without affecting the flow behavior of blood in the capillary.

6. APPENDIX

Pressure:

For the steady axi-symmetric flow of incompressible fluid (i.e. Hagen-Poiseuille flow), the equation of motion in cylindrical coordinates reduce to

$$\mu\left(\frac{\partial^2 u}{\partial r^2}+\frac{1}{r}\frac{\partial u}{\partial r}\right)-\frac{\partial P}{\partial z}=0.$$

Since P is a function of z alone and u is a function of r alone, the above equation may be written as

$$\mu\left(\frac{\partial^2 u}{\partial r^2}+\frac{1}{r}\frac{\partial u}{\partial r}\right)=\frac{dP}{dz}.$$

Differentiating both sides w.r.t. z, we get,

$$\frac{dP}{dz}=P_z=\text{constant.}, \qquad \left(\frac{\partial^2 u}{\partial r^2}+\frac{1}{r}\frac{\partial u}{\partial r}\right)=\frac{P_z}{\mu}.$$

$$u=\frac{-P_z\left(R^2-r^2\right)}{4\mu}. \qquad u_{\max}=\frac{-P_z R^2}{4\mu}. \qquad (\text{at } r=0)$$

The average velocity distribution for the present flow is given by

$$u_{av}=\frac{1}{\pi R^2}\int_0^{2\pi}\int_0^R urdrd\theta=-\frac{P_z R^2}{8\mu}=\frac{u_{\max}}{2}.$$

From [9], the average velocity of blood in the capillary of mouse is $7\times10^{-7}\,ms^{-1}$.

So we get, $$P_z=\frac{\partial P}{\partial z}=-\frac{8\mu u_{av}}{R^2}=-18.66\times10^5\,Kgm^{-2}s^{-2}.$$

In non-dimensional form (on dropping bar),

we get, $P_z=-0.0059$

Number Density of nanoparticles:

The density of magnetite $=5.1\times10^3\,Kgm^{-3}$.

From [9], in mouse the assumed length of the capillary $=6\times10^{-4}\,m$.

So the volume of capillary (cylinder) $=1.697\times10^{-14}\,m^3$.

The volume of a nanoparticle $=\frac{4}{3}\pi R_M^{\,3}=\frac{4}{3}\times\frac{22}{7}\times\left(10\times10^{-9}\right)^3 m^3$.

Again from [9], the dose of $250\,\mu g$ Fe per mouse is injected. So we also assume that $250\,\mu g$ magnetite is injected per mouse.

So the number of nanoparticles (radius $=10nm$) in $250\,\mu g$ magnetite $=11.69\times10^{12}$.

If it is assumed that 11.69×10^{12} nanoparticles remain in $1.697\times10^{-14}\,m^3$ (assumed volume of capillary).

Thus the number density of nanoparticles $=6.88\times10^{26}\ particles/m^3$.

7. REFERENCES

[1] Xu H., Song T., Bao X., Hu L., "Site-directed research of magnetic nanoparticles in magnetic drug targeting", J. Magn. Magn. Mater., **293**, pp. 514-519, 2005.

[2] Mikkelsen C., Hansen M. F., Bruus H., "Theoretical comparison of magnetic and hydrodynamic interactions between magnetically tagged particles in microfluidic

[3] Ally J., Martin B., Khamesee M. B., Roa W., A. Amirfazli, "Magnetic targeting of aerosol particles for cancer therapy", J. Magn. Magn. Mater., **293**, pp. 442-449, 2005.

[4] Alexiou C., Jurgons R., Schmid R., Hilpert A., Bergemann C., Parak F., Iro H., "In vitro and in vivo investigations of targeted chemotherapy with magnetic nanoparticles", J. Magn. Magn. Mater., **293**, pp. 389-393, 2005.

[5] Pankhurst Q. A., Connolly J., Jones S. K., Dobson J., "Application of magnetic nanoparticles in biomedicine", J. Phys. D: Appl. Phys., **36**, pp. pp. R167-R181, 2003.

[6] Tzirtzilakis E. E., "A mathematical model for blood flow", Physics of Fluids, **17**, 077103, 2005.

[7] Neuringer J. L., Rosensweig R. E., "Ferrohydrodynamics", The Physics of Fluids, **7 (12)**, pp. 1927-1937, 1964.

[8] Rotariu O., Strachan N. J. C., "Modelling magnetic carrier particle targeting in the tumor vasculature for cancer treatment", J. Magn. Magn. Mater., **293**, pp. 639-646, 2005.

[9] Mykhaylyk O., Dudchenko N., Dudchenko A., "Doxorubicin magnetic conjugate targeting upon intravenous injection into mice: High gradient magnetic field inhibits the clearance of nanoparticles from the blood". J. Magn. Magn. Mater., **293**, pp. 473-482, 2005.

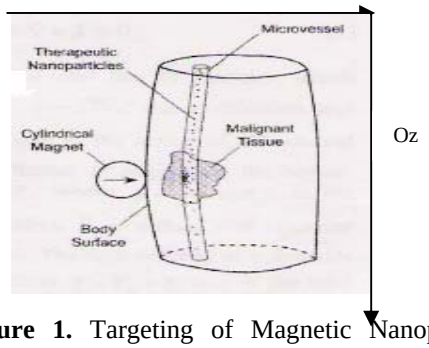

Figure 1. Targeting of Magnetic Nanoparticles at a specific site inside the body using a cylindrical magnet positioned outside the body.

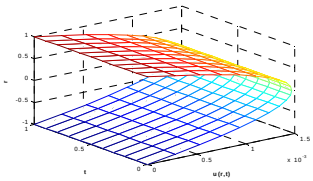

Figure 2. The spatio-temporal dynamics of the blood velocity $u(r,t)$.

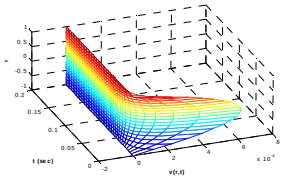

Figure 3. The spatio-temporal dynamics of velocity of nanoparticles $\upsilon(r,t)$. In this simulation, the distance between the magnet and the capillary surface is $y = 2.5cm$.

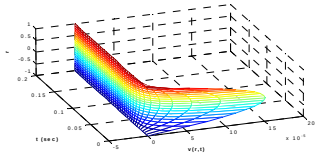

Figure 4. The spatio-temporal dynamics of velocity of nanoparticles $\upsilon(r,t)$. In this simulation, the distance between the magnet and the capillary surface is $y = 4cm$.

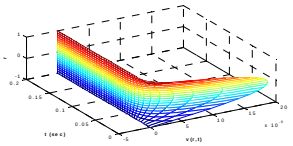

Figure 5. The spatio-temporal dynamics of velocity of nanoparticles $\upsilon(r,t)$. In this simulation, the distance between the magnet and the capillary surface is $y = 8cm$.

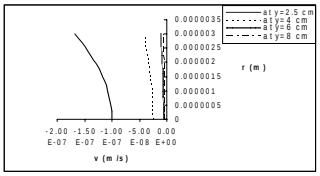

Figure 6. The velocity distribution of magnetic nanoparticles at time t=0.1 sec. for different distances (y) between the magnet and the capillary surface.

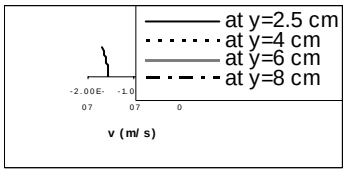

Figure 7. The velocity distribution of magnetic nanoparticles at time t=0.12 sec. for different distances (y) between the magnet and the capillary surface.

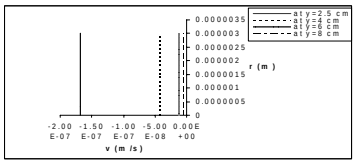

Figure 8. The velocity distribution of magnetic nanoparticles at time t=0.2 sec. for different distances (y) between the magnet and the capillary surface.

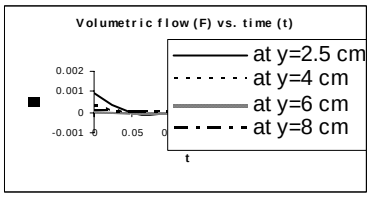

Figure 9. Volumetric flow rate at different distances (y)between the magnet and the capillary surface.

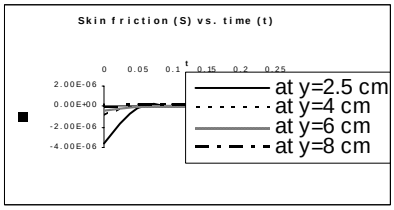

Figure 10. Skin friction on the capillary surface against time when the magnet is placed at different distances $(y)$from the capillary surface.