Numerical Simulation of Fluid Flow over a Ceramic Nanoparticle in Drug Delivery System

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ABSTRACT

In this work, for better understanding of drug delivery systems, blood flow over a ceramic nanoparticle is investigated through microvessels. Drug is considered as a nanoparticle coated with the rigid ceramic. Due to the low characteristic size in the microvessel, the fluid flow is not continuum and the no-slip boundary condition cannot be applied. To solve this problem lattice Boltzmann method is used with the slip boundary condition on the particle surface. Furthermore, the effects of Reynolds number, Knudsen number and stiffness (which depends on the kind of material) on drag coefficient are investigated in this paper. The present results show that lattice Boltzmann method can be used accurately to simulate the effects of different parameters on drug delivery. Moreover, the results show that the accuracy of lattice Boltzmann method is the same as second slip boundary condition. Also, the effect of nanoparticle stiffness as the important parameter on the period of time to deliver drugs in system is demonstrated.

1. Introduction

Although nanoparticles are generally considered an invention of modern science, they actually have a very long history. In according to the numerical progress in the world, micro and nanoscale particles have an increasing interest in engineering and scientific researches. These particles are very important and they have different environmental, drug delivery, mass transfer and industrial applications [1].

There is increasing optimism that nanotechnology, as applied to medicine, will bring significant advances in the diagnosis and treatment of disease. Nanoparticles offer advantages of protecting the drugs within the particles for reduced effects of plasma or body fluid induced deactivation or degradation [2]. So, engineered nanoparticles are an important tool to realize a number of these applications. It has to be recognized that the particle physical properties have effect on particle transport in drug delivery systems. One of the most important properties is material stiffness. Hence, the journey of particles in blood flow is determined by a combination of physical, chemical, and mechanical factors. Many of these factors are influenced by particle geometry, morphology and stiffness. Recent researches have focused on the role of particle physical properties in influencing particle transport in the flow [2].

Kulkarni and Feng [3] investigated the effects of the particle size and surface coating on the polymeric nanoparticles for drug delivery. Their results showed that the nanoparticles of smaller size (<200nm) can escape from recognition so they can stay in the body for a long time. Kumar and Graham [4] studied the effects of variety of parameters including the capillary number,

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rigidity ratio, volume fraction, confinement ratio and number fraction in drug delivery systems. They showed that the stiff particle experiences much larger cross stream displacement than the floppy particle. Shukla et al. [5] investigated the effects of nanocarrier aspect ratio on bio distribution in the setting of drug delivery. They used tobacco mosaic virus components to derive the rigid, soft matter nanoassemblies. They showed the effect of aspect ratio in vivo and in vitro. Huang et al. [6] analyzed the effect of nanoparticle stiffness on cellular uptake. They found that a stiffer substrate results in a higher total cellular uptake on a per cell basis, but a lower uptake per unit membrane area.

There have been very few investigations for modeling nanoparticle in microvessels to show the effect of material and shape on drag coefficient. So, the aim of this paper is simulating the flow over a ceramic nanoparticle to show the effect of stiffness. This numerical simulation can be useful to predict the kind of material and shape for nanoparticle as the drug coating. In fact Understanding how the shape of the particles influences their lateral migration within pressure driven flows could help enhancing the design of more effective drugs.

It should be mentioned that in micro and nanoscale particles, the characteristic size decreases down and it becomes a value comparable to the mean free path of the molecules. In this situation the fluid flow is not continuum and the Navier-Stokes equations with no-slip boundary condition cannot be applied. Because the rarefaction effect becomes important and slip on the solid surface could affect the force. There are some methods to analyze the flow over nanoparticles. The numerical method which is not based on continuity of flow should be used to solve the flow over these particles. Lattice Boltzmann method (LBM) is an effective computational tool for the simulation of complex flows which continuity of flow does not impose on it.

In this paper, the flow over the ceramic nanoparticle is simulated and the effects of Reynolds number, Knudsen number and stiffness on the dragcoefficient are studied as the important parameters in drug delivery systems by LBM.

2. Lattice Boltzmann method

In this study, LBM is used as the mesoscopic computational methods to simulate fluid flow. Although the lattice Boltzmann method has been derived from the lattice gas, but He and Lue [7] showed that this method could be gained from Boltzmann equation. In this method the fluid is considered as number of particles which collide and stream on specific links. In 2D geometry, D_2Q_9 model usually has been used as a lattice to discrete the fluid. By using Bhatnagar-Gross-Krook (BGK) approximation, the related equation can be derived as [8]:

$$f_k(\vec{x}_i+\vec{e}_k,t+1)-f_k(\vec{x}_i,t)=-\frac{1}{2}\left[f_k(\vec{x}_i,t)-f_k^{eq}(\vec{x}_i,t)\right] \qquad (1)$$

Where τ is the relaxation time, f_k is distribution functions and f^{eq} is equilibrium distribution function expressed as [8]:

$$f_k^{eq}=\rho\omega_k\left[1+\frac{3(\vec{e}_k.\vec{u})}{c^2}+\frac{9(\vec{e}_k.\vec{u})^2}{2c^4}-\frac{3|\vec{u}|^2}{2c^2}\right],\begin{cases}\omega_0=4/9,\omega_1=\omega_2=\omega_3=\omega_4=1/9\\ \omega_5=\omega_6=\omega_7=\omega_8=1/36\end{cases} \qquad (2)$$

Where $c=c_s\sqrt{\square}$, c_s is the speed of sound and $\vec{e}_k$ vectors are [8]:

$$\begin{array}{ll}\vec{e}_0=(0,0) & \vec{e}_1=\vec{e}_3=(c,0)\\ \vec{e}_2=\vec{e}_4=(0,c) & \vec{e}_5=\vec{e}_6=\vec{e}_7=\vec{e}_8=(c\sqrt{2},c\sqrt{2})\end{array} \qquad (3)$$

The flow quantities can be evaluated as [8]:

$$\rho=\sum_{i=0}^{8}f_i \qquad \vec{u}=\frac{1}{\rho}\sum_{i=0}^{8}f_i\vec{e}_i \qquad (4)$$

The kinematic viscosity in the Navier-Stokes equation is related to the relaxation time by the following equation [8]:

$$\nu=\frac{1}{3}\left(\tau-\frac{1}{2}\right) \qquad (5)$$

When geometry of body and computational domain is axisymmetric, Eq.1 should be modified. In fact two terms should be added in the right hand side of Eq.1, these terms are [9]:

$$h_i^{(1)} = \frac{-\omega_i \rho_0 u_r}{r}$$
$$h_i^{(2)} = \omega_i \frac{3\nu}{r}[\partial_r P + \rho_0 \partial_x u_x u_r + \rho_0 \partial_r u_r u_r + \rho_0 (\partial_r u_x - \partial_x u_r) e_{ix}] \quad (6)$$

where r is radial distance from center of sphere, and u_r and ∂_r are radial component velocity and derivative, respectively. Horizontal component velocity and derivative was shown by u_x and ∂_x, respectively.

3. Boundary conditions

We use constant velocity and pressure respectively for inlet and outlet of microvessels lumen which is employed by Zou-He method [10].For the curved surface (nanoparticle) the method proposed by Bouzidi [11] is implemented in macro scale.

When the characteristic length of flow is comparable to the mean free path of fluid, the rarefaction affect must be considered. For this situation, the no-slip boundary condition cannot be applied for wall boundaries. The Knudsen number (Kn) are used to identify the rarefied phenomena. The Kn number is the ratio of the mean free path (λ) to the characteristic length (L) of the flow. In flow over the sphere characteristic length is diameter of sphere (D).

In micro and nanoscale flow, the continuum assumption fails and the Navier-Stokes equations with no-slip boundary conditions cannot be applied. In such situations intermolecular collisions play a prominent role and the flow properties will be affected by the Knudsen number. There are some slip boundary conditions for the slip flow regime. The first order slip boundary condition is [12]:

$$(u_\theta)_{slip} \equiv (u_\theta)_{fluid} - (u_\theta)_{wall} = \frac{2-\sigma}{\sigma}\frac{Kn.R}{\mu}\tau_t \quad (7)$$

In this formula 2_t is tangential stress, R is sphere radius and σ is accommodation coefficient [12], μ is viscosity and u_- is the tangential velocity.

Two applicable types of the second order slip boundary conditions are [12]:

$$(u_\theta)_{slip} = \frac{2-\sigma}{\sigma}\frac{R}{\mu}[Kn.\tau_t + \frac{1}{2}Kn^2.R\frac{\partial \tau_t}{\partial r}] \quad (8)$$

$$(u_\theta)_{slip} = \frac{2-\sigma}{\sigma}\frac{Kn}{1-b.Kn}\frac{R}{\mu}\tau_t \qquad b = \frac{1}{2}R\frac{\partial \tau_{t,o}/\partial r}{\tau_{t,o}} \quad (9)$$

where $\tau_{t,0}$ is the tangential stress in no slip regime. In micro and nanoscale problem by LBM the relaxation time should be computed by Knudsen number instead of viscosity as follows [8]:

$$\tau = Kn.N + 0.5 \quad (10)$$

N refers to a number of nodes along the characteristic length. For a constant Mach number (Ma=v/c_s), the Kn and Re ($Re = \rho VD/\mu$) numbers are inversely proportional. For general flow the relation of Kn number, Re number and Ma number is according to [12]:

$$Kn = \sqrt{\frac{\pi\gamma}{2}}\frac{Ma}{Re} \quad (11)$$

Thus Re number cannot change arbitrary for a given Ma number in the slip flow regime stands. For incompressible flow, Ma number must be less than 0.2, thus in selection of Kn and Re value should be noted that Ma is less than 0.2.

In the slip flow regime the boundary conditions should be changed. The DMBC method (discrete Maxwell boundary condition) which is a straight forward discretization of Maxwell's diffuse reflection boundary condition in kinetic theory was used for slip boundary condition.

The slip correction factor is a very important parameter which considers the slip effects on the drag force of acting on spherical nanoparticle. The slip correction factor which is called Cunningham correction factor can be defined as [13]:

$$C_c = \frac{C_{D_0}}{C_{D_s}} \quad (12)$$

where C_{D_0} is the no-slip drag coefficient and C_{D_s} is the slip drag coefficient. One of the most important equations to compute Cunningham correction factor is [14]:

$$C_c = 1 + 2Kn\left[1.257 + 0.4\exp\left(\frac{-0.55}{Kn}\right)\right] \quad (13)$$

In the present study, the immersed boundary method (IBM) is used to simulate the RBC deformations.

To understand the effects of elastic force on the behavior of nanoparticle, the following dimensionless parameter is defined as [15]:

$$G = \frac{\mu U_m}{E_s} \tag{14}$$

where U_m is the mean velocity of plasma, E_s is the membrane elastic modulus and. G shows the competition between the viscous force in the plasma flow and the elastic resistance force of the membrane.

The hydrodynamic force induced by a fluid flowing over a wall surface can be defined by the momentum exchange method. The total force acting on a solid body is obtained as [16]:

$$F = \sum_{all x_s} \sum_{\alpha \neq 0} e_\alpha \left[\tilde{f}_\alpha(x_s,t) + \tilde{f}_{\bar{\alpha}}(x_f,t)\right] \times \left[1-\omega(x_f)\right] \times \frac{\delta\forall}{\delta t}$$
$$\omega(x_f) = \begin{cases} 0 & \text{in solid body} \\ 1 & \text{out of body} \end{cases} \tag{15}$$

where $\omega(x_f = x_s + e_{\bar{\alpha}})$ is an indicator, which is zero at x_f (fluid node) and one at x_s (solid node). The analytical drag coefficient ($C_D = F/1/2\rho U^2 A$) for creeping flow over a sphere in macro scale is [17]:

$$C_D = \frac{24}{Re} \tag{16}$$

There are experimental results for the flow over a sphere in macro scale which was used to check the LBM results [17]:

$$C_D = \frac{24}{Re} + \frac{6}{1+\sqrt{Re}} + 0.4 \tag{17}$$

4. Results and discussion

4.1 analytical analysis for creeping flow over a sphere

In micro and nanoscale, there are different analytical solutions which were used as a reference to check the numerical results. By using the first order slip boundary condition (Eq.7) for Re<<1, one of the analytical solutions can be derived.

In fact after solving the Biharmonic equation ($\nabla^4\psi = 0$) for creeping flow, the drag coefficient was derived as [18]: (It should me mentioned that σ=1)

$$\frac{C_D Re}{24} = \frac{2Kn+1}{3Kn+1} \tag{18}$$

Other analytical solutions could be derived by using two second order slip boundary conditions (Eqs.8, 9). The drag coefficients which were derived as follows respectively:

$$\frac{C_D Re}{24} = \frac{1+Kn(1+2Kn)}{1+3Kn(1+2Kn)} \tag{19}$$

$$\frac{C_D Re}{24} = \frac{1-2Kn+2Kn}{1-2Kn+3Kn} \tag{20}$$

Figure 1 shows that the drag coefficient which was computed by using the second order slip boundary condition has more accuracy and it is in good agreement with direct numerical simulation (Monte Carlo).

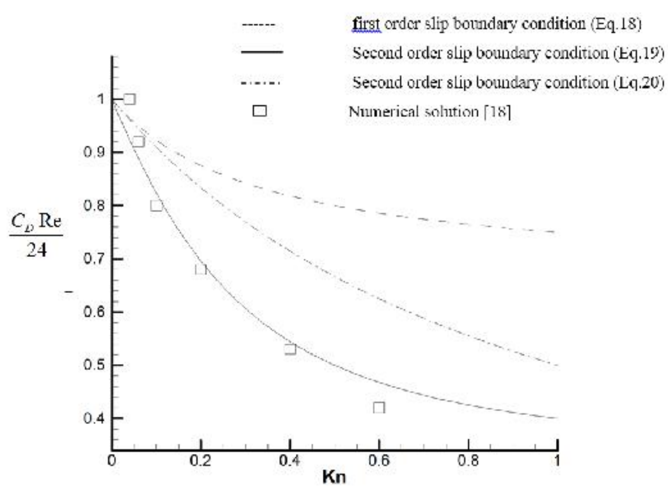

Fig 1. drag coefficient distribution for various Knudsen number in creeping flow over sphere

4.2 Numerical results

In the present study, the laminar, Newtonian and incompressible flow is considered in the microvessels over a ceramic nanoparticle as illustrated in Fig. 2. The density and viscosity of the blood plasma is set to be $\rho = 1025\,kg/m^3$ and $\nu = 1.17\times10^{-6}\,m^2/s$.

Computational grids were considered as 360×700. These solution domain and computational grids were the best grids which were derived after using different computational grids and solution domains. For the left and right boundary condition, the velocity inlet and pressure outlet was considered respectively. Upper and lower boundary conditions were supposed respectively as far distance boundary and symmetrical boundary. On the upper boundary u_x is equal to the velocity inlet and u_y is zero. All these boundary conditions were treated by Zou and He method [10]. DMBC has been considered to impose the curved and slip boundary conditions over the sphere.

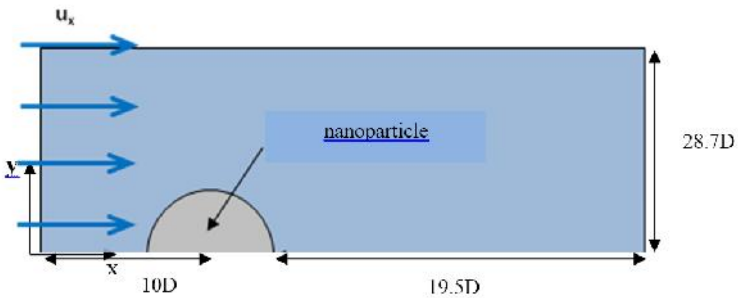

Fig 2. computational domain

To validate the presented results at first the flow over a sphere was simulated in macro scale. In Table.1 the drag coefficient for different Re numbers was computed in compare with analytical solution and implement correlation. It is clear for Re<1 the result has a good agreement with analytical solution and for Re>1 there are good agreement between computational and correlation results.

Table 1. drag coefficient for macro scale for various Reynolds number

method / Re	LBM	Eq.16	Eq.17
Re=0.125	192.05	192	196.84
Re=0.8	30.35	30	33.57
Re=20	2.6613	----	2.6969
Re=30	2.08	----	2.1259

It should be mentioned that in microvessel, the flow velocity for transporting the material between plasma and cells is low [19] and the Reynolds number is less than 1.

In Table.2 the drag coefficient in nanoscale is shown in comparison with the result in macro scale and analytical result for the creeping flow over a sphere. In according to the result, slip could decrease drag coefficient in every Re number.

In according to Eq.19, the drag coefficient for Re=0.125 is 173.87. It is clear that the result which is derived by DMBC has a good agreement with analytical solution which was derived by second order slip boundary condition in Re<<1. As mentioned before, the second order slip boundary condition is more accurate than the first order one, so it is clear that the accuracy of DMBC method is similar to the second order slip boundary condition. In fact the present results show that the accuracy is more than the first order boundary condition so LBM is the suitable numerical method to simulate the drug through microvessels.

Table 2. drag coefficient for nano and macro scale

Re (Kn) / Boundary condition	No slip	DMBC
0.125 (0.05)	192.05	178.3
0.8 (0.09)	30.35	24.5

In Fig.3 the influence of Re number and Kn number on drag coefficient is shown. This figure shows that Re and Kn numbers could decrease drag coefficient. It is obvious that Re number has more effect on drag coefficient in comparison with Kn number. In fact the small changes in Re number could have a big influence on the drag coefficient, although the small changes in Kn number have a small influence on drag coefficient. Drag coefficient is a dimensionless parameter which is shown the resistance of a ceramic nanoparticle in the blood. Low drag coefficient for drug delivery systems means, low period of time to travel through microvessels. Reduce the Re number, shows the fluid flow in the narrower microvessels, so the drag coefficient increases through the small vessels.

In Table 3 the slip correction factor is shown in compare with Cunningham factor. As it is shown the present results are in good agreement with the results presented by Moshfegh et al. [20] so, LBM can be used as an efficient numerical method to simulate nanoparticle transfer in microvessels. As it is shown Eq. 13, although Re number is an important parameter to affect the slip correction factor, but it was not considered in Cunningham factor. Moreover, as it is shown in Table 3 the accuracy of the Cunningham factor decreases by increasing Re number.

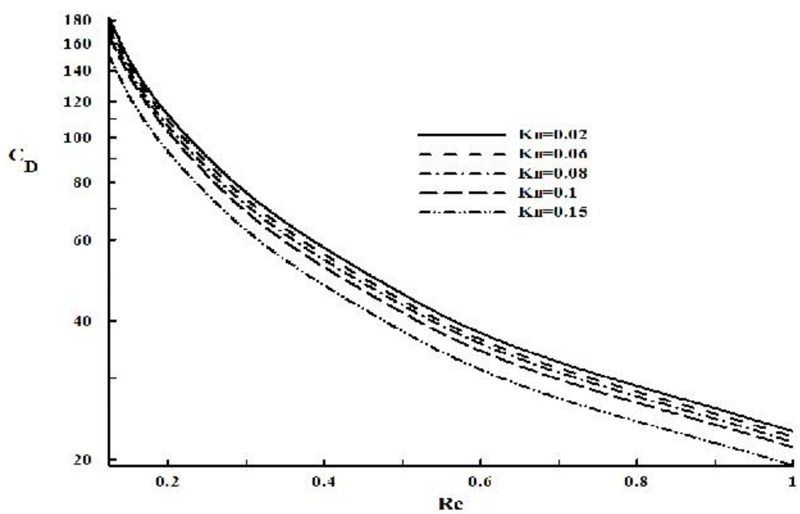

Fig 3. the effect of Kn and Re numbers on drag coefficient of sphere

Table 3. the effect of Re numbers on slip correction factor

$Kn = \frac{\lambda}{D}$	$Re = \frac{\rho v D}{\mu}$	FVM [20]	Present study LBM	Cunningham factor(Eq.13)
0.025	0.125	-----	1.0625	1.0628
	0.25	1.1	1.09	
	0.5	1.118	1.135	
	0.75	1.16	1.18	
	1	1.2	1.23	
0.05	0.125	------	1.108	1.1257
	0.25	1.175	1.125	
	0.5	1.2	1.175	
	0.75	1.24	1.225	
	1	1.275	1.27	

In the following, the effect of stiffness on drag coefficient is studied by changing the nanoparticle coating. As mentioned before, presented results are considered the nanoparticle coated with the rigid ceramic in the blood flow. Ceramic nanoparticles are rigid and they are not able to suffer deformation in order to navigate into tiny vessels. Table 4 shows the effect of stiffness on drag coefficient and consequently on drug delivery in microvessels. In order to investigate the effect of stiffness on nanoparticle transfer, we considered a polymer nanoparticle as the drug coat in drug delivery systems. As shown in Table 4, the drag coefficient decreases by increasing flexibility. The more flexible drug, shows low resistance in the blood flow so, it can travel through microvessel sooner than the ceramic nanoparticle and also, it can stay in the vessels longer than ceramic nanoparticle. It should be mentioned that the filo micelle research in the lab of Discher et al. [21] has shown that the flexibility of high aspect ratio worm-like filo micelles causes them to stay in circulation for a long period of time, possibly by avoiding interaction and uptake by the macrophages. In fact the present numerical results are in good agreement with the previous experimental result.

Table 4. the effect of stiffness on drag coefficient (G=0.9)

Re (Kn)	No slip	DMBC (rigid)	DMBC (flexible)
Re=0.5 (0.06)	48.02	44.3	41.82
Re=0.75 (0.06)	31.91	29.7	27.05

5. Conclusions

The lattice Boltzmann method is utilized to study the fluid flow over a ceramic nanoparticle in drug delivery systems. The effects of Reynolds, Knudsen number and stiffness are analyzed in the microvessels. At first by presenting the analytical solution, we showed that the second order slip boundary condition is more accurate than the first one and LBM can provide solution of the same accuracy as the analytical results derived by using boundary the second order slip boundary condition.

The present results demonstrate that Kn and Re numbers affect the drag coefficient and consequently the slip correction factor. In fact they increase the slip correction factor. It should be mentioned that the effect of Re number is more than Kn number. Furthermore, the effect of stiffness is studied by changing the material of nanoparticle coat in the flow. Ceramic is considered as the rigid material and polymer as the elastic one. The results show that the flexible nanoparticle can travel through microvessel sooner than the rigid material, because the rigidity increases the drag coefficient and consequently the resistance of the flow.

References

[1] Z. Wilczewska, K. Niemirowics, K. H. Markiewicz, H. Car, " Nanoparticles as drug delivery systems", Pharmacol. Rep., Vol. 64, 2012, pp. 1020-1037.

[2] S. R. Mudshinge, A. B. Deore, S. Patil, Ch. M. Bhalgat, "Nanoparticles: Emerging carriers for drug delivery", Sau. Pharm., Vol. 19, 2011, pp. 129-141.

[3] S. A. Kulkarni, S. S. Feng, "Effects of particle size and surface modification on cellular uptake and biodistribution of polymeric nanoparticles for drug delivery", Pharm. Res., Vol. 30, 2013, pp. 2512-2522.

A. Kumar, M. D. Graham, " Segregation by membrane rigidity in flowing binary suspensions of elastic capsules", Phys. Rev. E. Stat. Nonlin. Soft. Matter. Phys. , Vol. 84, 2011.

[4] S. Shukla, F. J. Eber, A. S. Nagarajan, N. A. Difranco, N. Schmidt, A. M. Wen, S. Eiben, R. M. Twyman, C. Wege, N. F. Steinmetz, " The impact of aspect ratio on the biodistribution and tumor homing of rigid soft-matter nanorods", Adv. Healthc. Mater, Vol. 4, 2015, pp. 874-882.

[5] Huang, P. J. Butler, S. Tong, H. S. Muddana, G. Bao, S. Zhang, " Substrate stiffness regulates cellular uptake of nanoparticles", Nano Lett., Vol. 4, 2013, pp. 1611-1615.

[6] X. He, L. S. Luo, "Theory of the lattice Boltzmann method: from the Boltzmann equation to the lattice Boltzmann equation", Phys. Rev. E, Vol.56, 1997, pp.6811-6817.

[7] S. Succi, The lattice Boltzmann equation for fluid dynamics and beyond, Oxford University press, 2001.

[8] T. S. Lee, H. Huang, Ch. Shu, "An axisymmetric incompressible lattice BGK model for simulation of the pulsatile flow in a circular pipe", Int. J. Numer. Methods Fluids, Vol.49, 2005, pp.99-116.

[9] X. He, Q. Zou, "Analysis and boundary condition of the lattice Boltzmann BGK model with two velocity components", J. Stat. Phys., Vol.87, 1995, pp.115-136.

[10] M. Bouzidi, M. Firdaouss., P. Lallemand, "Momentum transfer of Boltzmann-lattice fluid with boundaries", Phys. Fluids, vol.13, 2001, pp.3452-3459.

[11] G. Karniadakis, A. Beskok, N. Aulru, Microflows and nanoflows fundamentals and simulation, Springer, 2005.

[12] E. Cunningham, On the velocity of steady fall of spherical particles through fluid medium, Proc. R. Soc. Lond. A83, 1910, pp. 357-365.

[13] N. Davies, "Definite equation for the fluid resistance of spheres", Proc. Phys. Soc., Vol. 57, 1945.

[14] KoohyarVahidkhah, Nasser Fatouraee, "Numerical simulation of red blood cell

[15] behavior in astenosed arteriole using the immersed boundary- Lattice Boltzmann method",Int. J. Numer. Meth.Biomed.Eng.., Vol. 28, 2011, pp.239-256.

[16] O. Filippova, D. Hanel, "Grid refinement for lattice- BGK models", J. Comput. Phys, vol. 147, 1998, pp. 219-228.

[17] F. W. White, Viscous fluid flow, McGraw-Hill, New York, 2006.

[18] S. K. Stefanov, R. W. Barber, M. Ota, D. R. Emerson, "Comparison beween Navier-Stokes and DSMC calculations for low Reynolds number slip flow past a confined micro sphere", 24th Symposium of Rarefied Gas Dynamics, American institute of physics,2005.

[19] C.Guyton, J. E. Hall, Textbook of medical physiology, Elsevier Saunders, 2006.

[20] Moshfegh, M. Shams, G. Ahmadi, R. Ebrahimi, "A novel surface-slip correction for microparticles motion", Collids and Surfaces A, Vol. 345, 2009, pp.321-329.

[21] Y. Geng, P. Dalhaimer, S. Cai, R. Tsai, M. Tewari, T. Minko, D.E. Discher, " Shape effects of filaments versus spherical particles in flow and drug delivery", Nat Nanotechnol, Vol. 2, 2007, pp. 249-255.