Research Article
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Simulation analysis of blood flow and selective drug particles delivery to the targeted tumors in cerebral artery-tissue regions

Abstract

Brain is the most intricate organ of human body. The development of new therapeutic techniques for Brain tumor diseases is a difficult task, yet these treatments are not effective for all the brain diseases. Presence of Blood Brain Barrier (BBB) is the main challenge in development of drugs to treat brain diseases in most of the cases. Among several brain diseases, brain tumors often have poor prognosis, which depends on and changes according to the type of the tumor. In this study a three-dimensional computational simulation model for analyzing multifunctional drug distribution through the cerebral artery and adjacent tissue region with tumor is considered. The simulation model includes solution of governing equations of blood flow dynamics based on Navier-Stokes equations and mass species transport based on Lagrangian particle flow dynamics in the artery network and capillaries of the adjacent tissue-tumor regions subjected to a typical cardiac cycle. The main objective is to evaluate the effective delivery of selective drug particles to the targeted tumor region with variation in the selective multifunctional particle types and sizes.

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Introduction

Brain tumors are identified as growth abnormal cells in the brain. Most of the brain tumors are malignant brain tumors and about 650 people are identified with this type of brain tumor every day.[1] Brain tumors effects human health to greater extent due to their quick development and poor prognosis. There are various options like chemotherapy, targeted therapy available for treating brain tumors. Blood brain barrier (BBB) is the one that protects brain, and it separates the circulating blood from brain extracellular fluid and this barrier allows only some kind of antibiotics. The treatment of tumors is obstructed by the presence of blood brain barrier (BBB) and impede most available effective drugs. Nanotechnology is promising approach where different types of nanoparticles are available for biomedical use with different characteristics and applications enabling the delivery of drugs to target region.

Current research is being conducted in developing the multifunctional drug targeting efficiency by changing parameters such as polymer coatings over drug, particle diameter so that it targets the tumor region.

Design of nano particle drug carriers plays a critical role in the effective delivery of drugs to targeted tumor sites by diffusion through the blood vascular tissues and through the tumor cells. Several physiochemical and blood low dynamics conditions plays critical role in the effective deliver of the dugs to the targeted site.

To enhance the efficacy of the drug delivery system, externally induced forces such as ultrasound, magnetic and electrical fields are also considered in guiding and transport nanoparticle drug carriers to the targeted sites.

Sutradhar and Amin[2] discussed use of nanotechnology in Cancer Drug Delivery and Selective Targeting. This article describes specific drug delivery by nanoparticles to effected tumor region by two various methods considering both active targeting and passive targeting.

Bhaskar et al.[3] reviewed issues such functionalization of nano carriers, delivery to targeted region and in vivo imaging of nano-scaled drug delivery system. Multifunctional Nano carriers for diagnostics, drug delivery and targeted treatment across blood-brain barrier: perspectives on tracking and neuroimaging. This article also focuses structural composition of drug such that it passes over BBB (Blood brain barrier).

Soppimath et al.[4] gives a review on the information about the use of biodegradable polymeric nanoparticles in a drug delivery system. Methods of preparation, drug loading and drug release are discussed. Khaled et al.[5] discussed the role of porous media in modeling flow and heat transfer in biological tissues. This article explains and derives various models available for setting porous medium for biological tissues. Transport in porous media is explained using mass diffusion and different convective models.

Ding et al.[6] discussed preparation of multifunctional polymeric drug carrier for tumor-specific uptake and enhanced intracellular delivery using amphiphilic polymer linker. This article discusses about effect pH in the design of carrier linker in the effectiveness of drug delivery, considering difference in the slightly acidic pH value of solid tumors is compared with the physiological pH value.

Masserini[7] discussed the strategy of using multifunctional nanoparticles in the drug delivery system to enhance the effectiveness of the drug delivery across the BBB. This review also discusses the structural and physiological feature of BBB, and consideration of different nanoparticles with different characteristics, enabling the delivery of drugs to target region.

Muller et al.[8] performed hydrodynamic simulation of blood flow to investigation effects of adhesion and migration dynamics of drug particles' size and shape towards the vascular walls. To prevent aggregation and adherence of drug nano particles, Hoshiar et al.[9] considered externally induced magnetic field force in their simulation study of the targeted and guided drug delivery in a blood vascular system.

Ye et al.[10] discussed in their review study the role of such different external forces on the transport and margination of nanoparticle s blood flow and tumor vasculature systems. Ardhale et al.[11] used numerical model to investigate the effect of magnetic field parameters on the velocity and nanoparticle concentration distributions as well

as on magnetic nature of the blood cells. Fullstone et al.[12] used computational fluid dynamics analysis to demonstrate the effect of nanoparticle carriers' size on its distribution in the vascular capillaries and near the targeted tumor tissue regions.

Shafiullah and Majumdar[13] investigated the use and placement of intravascular stent as a common interventional procedure against atherosclerosis, which is a vascular disease that reduces arterial lumen size through plaque deposition and arterial wall thickening, and a leading cause of mortality in the world. In this study, different stent designs are considered and computational fluid dynamics analysis of is performed on the femoral artery by considering blood flow as a pulsating, incompressible and Newtonian flow over a realistic velocity waveform of the femoral artery.

Narmada[14] used a computational simulation model to analyze blood flow distribution in a femoral artery network artery with curvature considered from the CT scan of atherosclerosis patient and subjected to a waveform based on a cardiac cycle. The simulation model is based on Navier-Stokes equation and based on Newtonian and non-Newtonian blood flow by using Carreau-Yasuda model along with an adjacent capillary porous tissue medium.

Moda and Majumdar[15] developed a methodology for developing three- dimensional computational simulation model of the artery capillary network with cerebral part based on reconstructing multiple CT and MRI scan images of a tumor-affected patient. Furthermore, simulation analysis of blood flow dynamics and mass species transport in a healthy and a tumor-affected cerebral artery is performed considering the reconstructed three-dimension model of the artery network and capillaries of the adjacent tissue-tumor regions.

The objective of this study is to analyze effectiveness of using multi-functional and selective drug particle delivery to a targeted tissue-tumor region. In this study a three-dimensional computational simulation model along with a reconstructed three-dimension model of the artery network and capillaries of the adjacent tissue-tumor regions is used for analyzing multifunctional drug distribution through the cerebral artery and adjacent tissue-tumor region. The simulation model includes solution of governing equations of blood flow dynamics based on Navier-Stokes equations and mass species transport based on Lagrangian particle flow dynamics in the artery network and capillaries of the adjacent tissue-tumor regions subjected to typical cardiac cycle. The simulation analysis is performed to evaluate and analyze the drug particle distributions and consumptions around the targeted region with varying particle sizes and concentrations. The main objective of this study is to evaluate and optimize the effectiveness of the drug delivery to the targeted tumor region with variation in the selective multifunctional particle types, size, and dose concentrations.

Physical description of the model

In this chapter, brief description of the model i.e., geometry, governing equations including boundary conditions, drug and polymer used are discussed.

Artery – capillary network

This network is a part of the circulatory system consisting of the arteries, capillaries and veins which are connected to the heart. According to the blood circulatory system, the blood for the heart is pumped through the arteries, which carry the blood to the capillary. At the capillary, the gas exchange occurs, and the used blood is then pumped back to the heart with the help of veins (Figure 1).

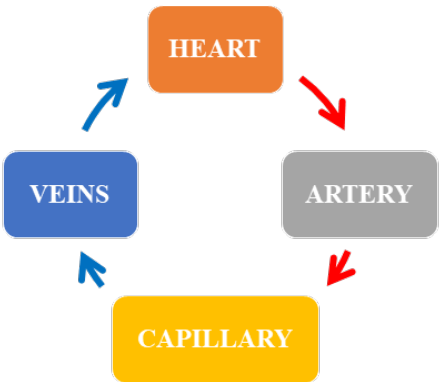

Figure 1 Schematic diagram of circulatory system.

Arteries carry oxygenated blood from heart to all the body parts. During the circulation of the blood high pressure is exerted on its walls, to withstand this high pressure, artery walls are elastic, thicker and muscular. Muscular nature offers smoothness to the arteries which allows it for expansion and contraction, accordingly, resulting in regulating the blood flow.

Capillaries are the smallest blood vessels in the body which connects to various organs of the entire body. It has a thin permeable layer called endothelium, which acts as the barrier between the tissues and the blood in capillaries. This permeable layer helps in the exchange of the nutrients and oxygen as energy to the tissues. Also, the waste gases are in turn taken out from the tissue and carried away by the blood through this layer in capillaries. The exhaust derived from the tissues is carried to veins from capillaries.

Veins

Deoxygenated blood from the capillaries is carried back to heart by veins. Veins are thinner and less elastic in nature. The mechanism employed in pumping the blood back to the heart depends on the inertia, gravity, and the muscle contraction force. This contraction force helps in forcing blood to the heart.

Geometry

A three-dimensional artery with capillary and the tissue tumor region of brain, using the CT and MRI scan images of tumor affected patient is designed using space claim.[15] Artery of length 11 mm and diameter 5mm, capillaries of length 5mm and diameter 1.5mm, an area of 340mm^2 and 120mm^2 for tissue and tumor region were considered as shown in Figure 2.

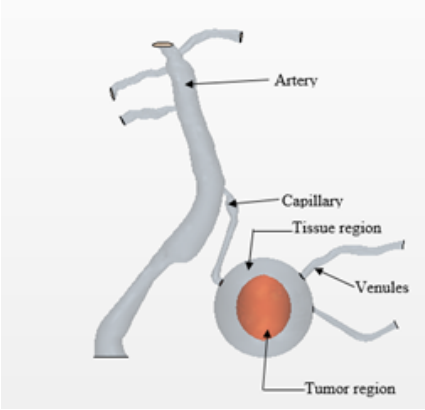

Figure 2 Three-dimensional design model.

The cerebral artery was modeled considering a CT scan image of a 62-year-old human. Although, the CT scan image shows large number of capillaries connected in the brain, only a partial image is considered to simplify the modelling. The initial step in design process is to import the image into the design window and splines are created to selected partial image. Then the splines are linked to form a 2-D planar image. Space claim is used for designing which has the distinctive feature of prompting the 3-D plane to the complex curvature. Using the 3-D plane and the sweep options the 3-D model is designed as shown in the Figure 2. A circular tissue and tumor are designed to the artery capillary unit using Hyper Mesh.

Cardiac cycle

Cardiac cycle explains the mechanism of heart employed during the circulation of the blood. The cardiac cycle has two phases, diastole, and a systole. Systole phase begins with the contraction of the ventricles, causing the blood to be ejected with a high pressure. The velocity in this phase reaches a peak velocity due to high pressure exerted during contraction. As relaxation of ventricles starts there is sudden drop in velocity. Diastole phase starts when the ventricles relax after the ejection of blood. The blood starts to fill after sufficient relaxation as the heart expands in this phase (Figure 3).

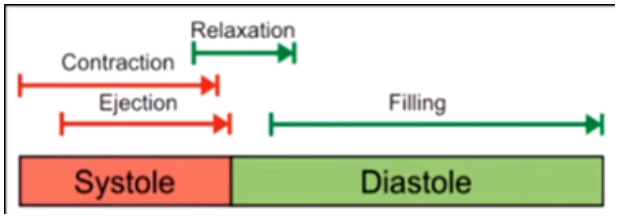

Figure 3 Block diagram of cardiac cycle.

The flow velocity with respect to time is as shown in Figure 4 where V_F indicates systolic forward peak velocity, V_R represents reverse peak velocity, V_{F2} is diastolic forward peak velocity, V_M indicates time-averaged mean velocity and V_D is end diastolic velocity (Table 1).[16]

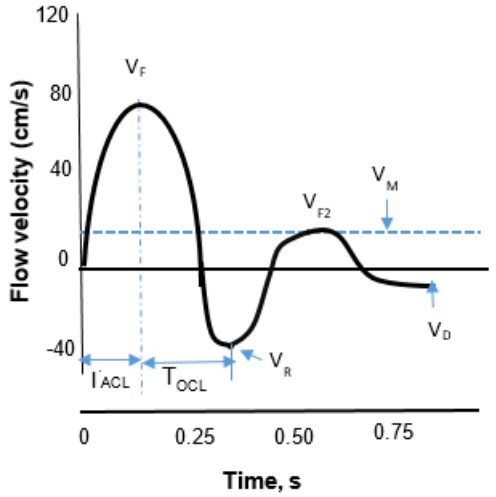

Figure 4 Inlet flow Velocity vs Time.

Table 1 Wave form range values

Variable	Velocity range (cm/sec)
Systolic forward peak velocity (VF)	69±19
Diastolic reverse peak velocity	-19±6
End diastolic velocity (VD)	8±4
Time-averaged mean velocity (Vm)	1±3

Blood flow governing equations

Governing equations are the equations that describe the behavior of a system in terms of its motion as a function of time. These equations specifically describe the behavior of a system as a set of functions in terms of dynamic variables like, spatial coordinates, time, momentum components and many others. The fundamental governing equations for blood and drug flow are discussed in this section.

Navier–Stokes equations are useful as they define the physics of several phenomena of scientific and engineering importance. Some assumptions are made such as Continuous media, viscous constant, incompressible fluid, implicit unsteady, constant density, laminar, and segregated flow.

The Navier-Stokes equation for incompressible flow is used to govern the motion of the fluid. The following is the Navier-Stokes equation used for the analysis of blood flow for Newtonian model

$$\rho\left(\frac{\partial u}{\partial t}+\left(ui\nabla\right)u\right)=-\nabla p+\quad\nabla^2u+g \tag{1}$$

Where u is the fluid velocity, p is the fluid pressure, ρ is the fluid density, g is gravity and u is the fluid dynamic viscosity. And $\frac{\partial u}{\partial t}$ is variation, $\left(u.\nabla\right)u$ and $i.\nabla^2u$ are convection and diffusion terms, $-\nabla p$ is internal source and g is external source term, $\frac{\partial u}{\partial t}+\left(u.\nabla\right)u$ is Inertia term.

For non-Newtonian fluid with varying viscosity, the following is the Navier-Stokes equation used for the analysis of blood flow

$$\rho\left(\frac{\partial u}{\partial t}+\left(u.\nabla\right)u\right)=-\nabla p+\nabla(\eta(\nabla u+(\nabla u)^T) \tag{2}$$

Boundary conditions

The subject of appropriate and precise boundary conditions or the initial conditions in computational fluid dynamics is especially important. These conditions describe the detailed solutions to be gotten from the governing equations.

Velocity Inlet: All inlets in model are velocity inlets and a set of tabulated values are given as velocity input which follows the cardiac cycle as shown in Figure 4 that was calculated by Hashimoto and Ito.[16]

Pressure outlet: All the outlets for the artery and venule are considered as pressure outlets and set to zero pressure conditions.

Tissue region porous media model

Porosity is the physical property of a material having pores on its structure, which allows liquids to flow through it. Tissues are porous as it is composed of cells that are separated by voids, which allow for exchange of nutrients, minerals to all the cells.

The flow and transport of mass species in porous biological tissue region is primarily dominated by transport model involving pressure, viscous, and inertial forces. One of the simplest models for flow transport in porous media is the Darcy model given as

$$v=-\frac{K}{\mu}\nabla P \tag{3}$$

v=Velocity

P =Pressure Gradient

μ =(Tex translation failed)

K = Permeability Coefficient

The model in Darcy drags resistance and neglects convective term and work well for unbounded regions, neglecting boundary effects on the flow.

Brinkman's flow model is a generalized Darcy model that considers of the boundary effect and has been used in many biological porous regions.[5] In this study, the blood flow and drug transport in the porous regions for both the tissue and tumor regions is model by the Brinkman's model given as

$$\nabla P = -\frac{\mu}{K} v + \tilde{\mu} \nabla^2 v \tag{4}$$

Where $\tilde{\mu}$ is effective dynamic viscosity, u is dynamic viscosity of the fluid i.e., blood in this case, v is the velocity of the fluid, ∇P is pressure gradient vector and K is permeability of the porous medium. The first term on the right-hand side is the Darcy's viscous term and the second term represents the viscous diffusion term like that in Navier-Stokes equation. This model also neglects the convective terms.

Lagrangian flow model

In Lagrangian flow model, the flow of particles is considered as the dispersed phase and the particle tracking with respect to its path is considered individually.[15] This flow model is good for this study and is used for the flow of drug particles. The Lagrangian governing equation used is shown below

$$\frac{\mathrm{d}U_P}{\mathrm{dT}} = \mathrm{F}\left(\mathrm{u} - U_P\right) + \frac{g\left(\rho_P - \rho\right)}{\rho_P} \tag{5}$$

Were U_P is particle velocity vector, ρ_P is particle density, F_l is additional forces, F is Inverse of relaxation time, g is gravity and u is fluid velocity. The shape of the particle considered for this study is spherical with varying diameters. The first term on left side inertial force per unit mass and the first term on right side is drag term, second term represents gravity, buoyancy.

Coupling is a phenomenon used when there are different types of materials which need to be combined for obtaining an accurate solution. In this case, there are two mediums like the blood which is a liquid and drug particles that are immersed in the fluid. To obtain the combined behavior of this, the Navier Stokes equation is coupled with the Lagrangian equation.

Mass species transport for drug concentration

$$\frac{\partial(\rho\phi_d)}{\partial t} + div(\rho\phi_d u) = div(\Gamma \,\mathrm{grad}(\phi_d)) + \mathrm{S}_{\phi_d} \tag{6}$$

Were

ϕ_d is drug species concentration

u is velocity vector and

$\tilde{\mathrm{A}}$ is diffusivity term.

S_{ϕ_d} is source and consumption of drug

$S_{\phi_d} = \dot{m}''' \phi_d$

Source term is manipulated to explain the drug consumption.

Role of polymers in drug delivery

This section describes the role of polymers used in drug delivery of therapeutic agents. The polymers are used to deliver the drug to the target region. Biodegradable polymers are used to deliver the drugs to a specific region of the body as they degrade with a constant rate of drug release. The process used for the release of drug from the polymers is either by degradation or diffusion. They are used as binders, as film coating over the drug, to improve the stability and alter the release characteristics of the drug at the targeted site.[17]

There are few drugs used for treating brain tumors. Among them Temozolomide is the drug used for this study. The molecular formula is $C_6H_6N_6O_2$ with a density of 1970 kg/m^3. Polyethylene Glycol (PEG) with a density of 1260 kg/m^3 is used for the drug coating such that it penetrates the blood brain barrier. According to the structural organization, nanoparticles are of two types' nanocapsule and nanoshpere as shown in Figure 5.[18] In nanocapsule the drug particles are with in a closed polymeric membrane whereas in nanoshpere the drug particles are distributed in the polymeric matrix. For this we considered nanocapsule where the drug Temozolomide is coated with PEG layer with varying particle diameter and increasing coating over the particle.

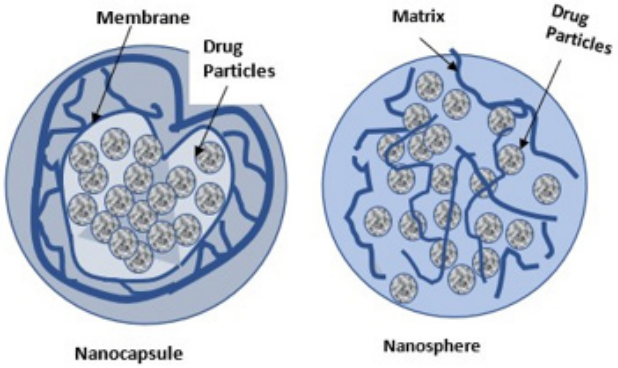

Figure 5 Schematic representation of Nanocapsule and Nanosphere.[18]

Effect of pH

The final goal of drug delivery is to attain a desired therapeutic concentration at the targeting tumor while the drug concentrations at other tissue regions are at safe levels. Therefore, multifunctional drug carriers with the ability to interact with different biological membranes with the change of environmental conditions during the entire delivery procedure.[6] Surface charge conversion of a drug carrier in response to the change of external pH around 6.8-7.4 would also help to deliver the drug to targeting tumor region, since the solid tumors is slightly acidic with pH of 6.8 when compared with the physiological pH of 7.4 and multifunctional antitumor drug delivery systems have a pH range of 5.0 – 6.5.[6]

Design and formulation of multifunctional drug particles

Over the recent years, the polymer-based drugs have been emerging as a promising therapeutic method to treat various diseases. Various polymer drug delivery systems are presently approved in treating cancer effectively compared to conventional drugs. Studies have proved that integrating low molecular mass drugs into polymers increases drug solubility and stability, accumulates drugs in solid tumors, thus reducing the side effects. Multifunctional particle composed of drugs encapsulated with a layer of polymer. Polymer coating makes the particle as a carrier and prevents it to dissolve in

blood stream. Keeps the drug concentrations at other tissue regions are at safe levels.

Combined density and size

Combined density is calculated using following formulation (Figure 6).

$$m_s = m_{sd} + m_{sp}\ m_{sd} = \rho_d\ v_i\ m_{sp} = \rho_p\ v_p \tag{7}$$

$$v_p = v_o - v_i\ v_o = \frac{4}{3}\pi r_o^3\ v_i = \frac{4}{3}\pi r_i^3 \tag{8}$$

$$\varnothing_s = \frac{m_{sd}}{m_s} \tag{9}$$

$$\rho = \varnothing_s \rho_d + \left(1 - \varnothing_s\right)\rho_p \tag{10}$$

Were

m_s is total mass (kg), m_{sd} is mass of the drug (kg), m_{sd} is mass of the polymer (kg), r_o is outer radius (m), r_i is inner radius i.e., radius of drug particle (m), ρ is combined density (kg/m^3).

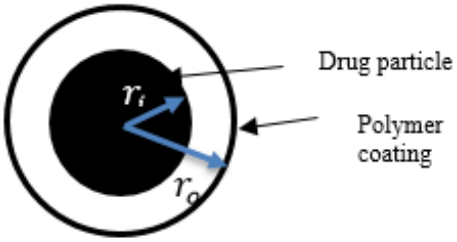

Figure 6 Schematic representation of polymer coating over drug.

Computational model

This section describes about the suitable model of the flow. The flow of the blood is considered as non-Newtonian with varying viscosity input, implicit unsteady, constant density, and laminar, segregated flow. Drug flow is assumed as multi-phase, Lagrangian model, injectors, spherical particles, liquid, density, and particle dimensions.

The geometry model that is designed using space claim is imported into fluent software and assigned all inlets and outlets as shown in Figure 7.

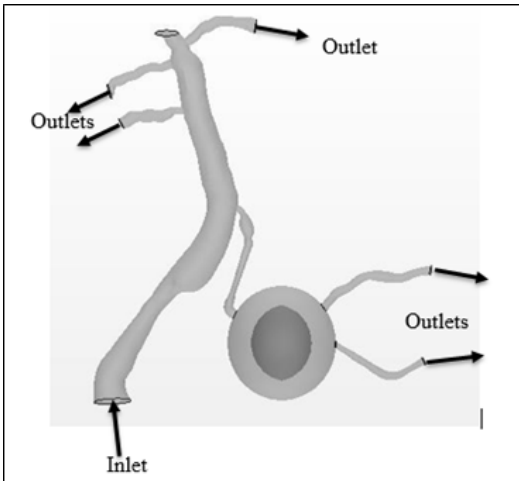

Figure 7 Geometry model showing inlets and outlets.

Mesh

In computational solutions of the governing equations, meshing is a discretization of the geometry into sub domains that participate in the problem over which the equations can be estimated. The accurate solution can be achieved faster with better mesh quality and a greater rate of convergence.

Mesh is generated as shown in Figure 8 with node values of 405257,125087,385455,849953 for arteries, capillaries, tumor, tissue respectively using the surface remesher, prism layer mesher, trimmer models with a base size of 0.3 and three prism layers.

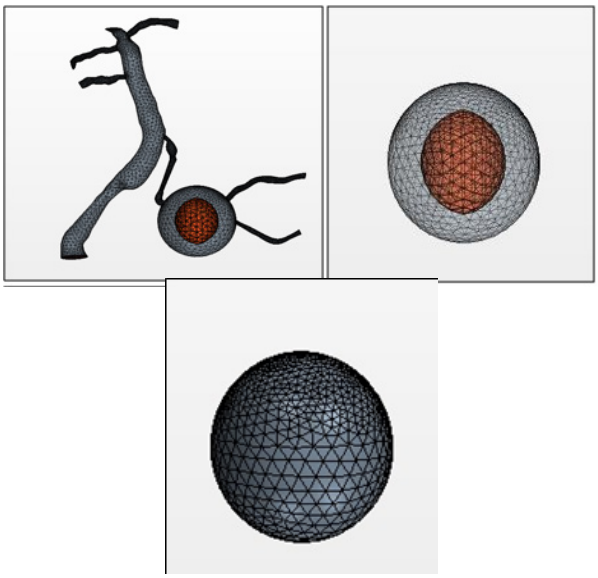

Figure 8 Preview of mesh.

Input value conditions at artery

Velocity inlet with transient velocity data input: The set of tabulated values is given as input velocity table for inlet of artery. This velocity table is observed from the waveform calculated by Hashimoto and Ito.[16]

Drug flow rate as another input: To set the particle flow for analyzing the drug concentration distribution, Lagrangian multiphase flow is considered. A separate physics is set for analyzing the particle flow in the artery- capillary-tissue-tumor network. The flow rate is given an inlet to the artery using Lagrangian injectors. Also, particle specifications such as diameters shape are indicated.

Computational parameters and data

Simulation executes by considering the segregated flow solver which solves the flow equations. First order discretization is used to solve, and results are taken at different time steps with the maximum physical time of 0.25sec, time step of 0.01sec and 50 inner iterations for each time step. Also, under relaxation factor of 0.7 and 0.3 is considered for velocity and pressure respectively.[19]

Computational data

The tissue and tumor regions are considered as porous regions. A porosity of 0.3, 0.2 is taken for tissue and tumor, respectively. A higher porosity value for tissue is because the tissue region is less resistant than tumor region.

By using formulation that is discussed in section 2.6, combined densities are calculated and represented in Table 2.

Mass source is activated at tumor region for reducing the particle count by giving negative mass source term value. Two cases are considered 80% and 50% of total density is converted into kg/m^3-s and is shown in Table 3.

Table 2 Combined density for various drug-polymer coating ratios

Ratio (D:P) (volume)	Density (kg/m^3)	Size before coating (microns)	Size after coating (microns)
1:08	1294.8	0.05	0.1
0.086805556	1148.8	0.05	0.2
0.125	1137.7	0.05	0.25

Table 3 Mass source term values

Density	1970 kg/m^3	32.833 kg/m^3-s
50%	985 kg/m^3	16.41666 kg/m^3-s
80%	1576 kg/m^3	26.266 kg/m^3-s

Results and discussions

The computational simulation model is used to find the velocity and particle volume in the flow of blood with respect to the cardiac cycle. Further particle distribution of drug into the targeted tumor region is observed in terms of velocities and particle volume with which drug reaches the tumor by varying particle size and polymer coating. Mass source is activated at tumor region to reduce the particle flow at tumor region to explain uptake of the drug at target region.

Velocity distribution in brain tissue region

Three-line probes are drawn at different positions such as bottom, top, and center of the tumor as shown in Figure 9 and velocity along these line probes is observed.

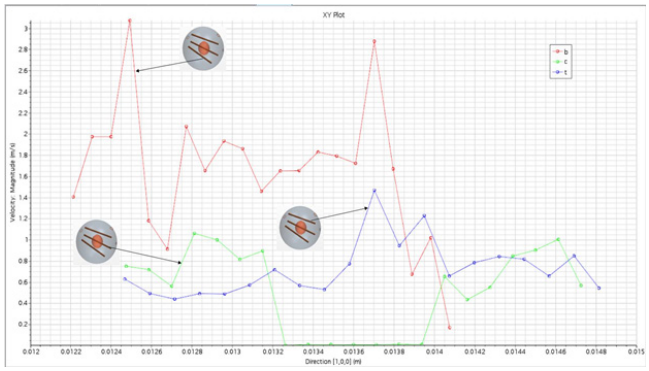

Figure 9 Velocity distribution plot in brain tissue region.

The blood flow is unevenly distributed due to the highly heterogeneous and anisotropic nature of the region. The flow is further complicated due to presence of the tumor. The results show a dominant blood flow through the bottom region compared to top region around the tumor. Flow is significantly reduced and slow in the tumor region because of high resistance. Flow is also highly modulating before and after the tumor region due to cyclic nature of the inlet cardiac flow condition.

Drug flow distribution in cerebral artery and tissue region for 50nm size

The Figure 10 shows the flow of drug particle at increasing time steps i.e., at 0.072sec, 0.076sec, 0.081sec and 0.095sec.

The drug particle reaches the tumor at 0.081sec and dosage of drug increases continuously following cardiac cycle. However, the flow velocity of blood tissue and tumor regions is less compared to artery region because there is obstruction for the flow of the blood at the tissue-tumor region.

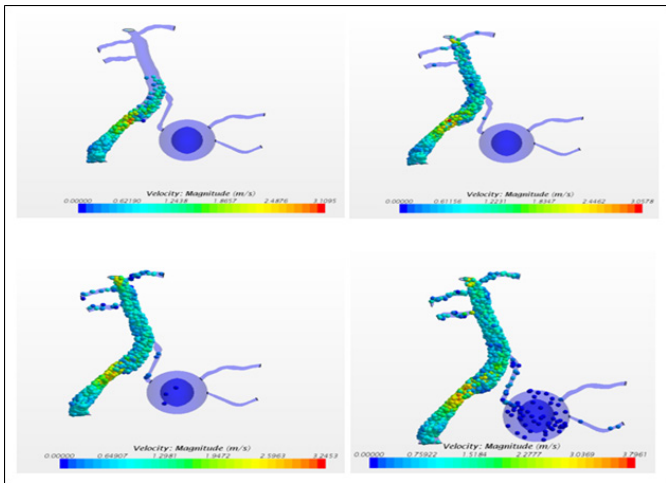

Figure 10 Drug particle flow at various times.

Drug flow distribution in cerebral artery and tissue region at differ time and with varying sizes

In this section, velocity distribution is discussed by varying particle diameter. This variation can be seen for particle size of 20nm, 30nm and 50nm.

The Figure 11 shows the flow of drug particle of 20nm at increasing time steps i.e., at 0.1sec, 0.125sec, 0.2sec and 0.25sec. Initially at 0.1 sec, velocity in artery region is 4.47m/sec which increases to 4.7m/sec at 0.125sec. later again its starts decreasing. The drug particle reaches the tumor and dosage of drug increases continuously following cardiac cycle. However, the flow velocity of blood tissue and tumor regions is less compared to artery region because there is obstruction for the flow of the blood at the tissue-tumor region.

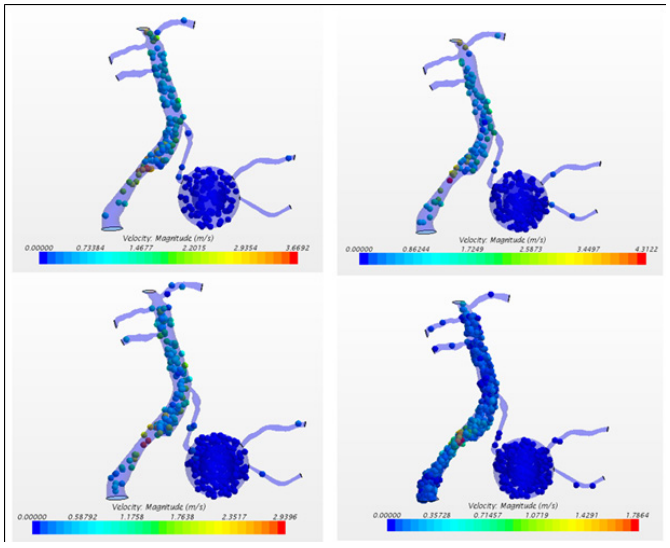

Figure 11 Velocity distribution for particle size of 20nm.

The Figure 12 shows the flow of drug particle of 30nm at increasing time steps i.e., at 0.1sec, 0.125sec, 0.2sec and 0.25sec. Initially at 0.1sec, velocity in artery region is 3.99m/sec which increases to 4.7m/sec at 0.125sec. later again its starts decreasing.

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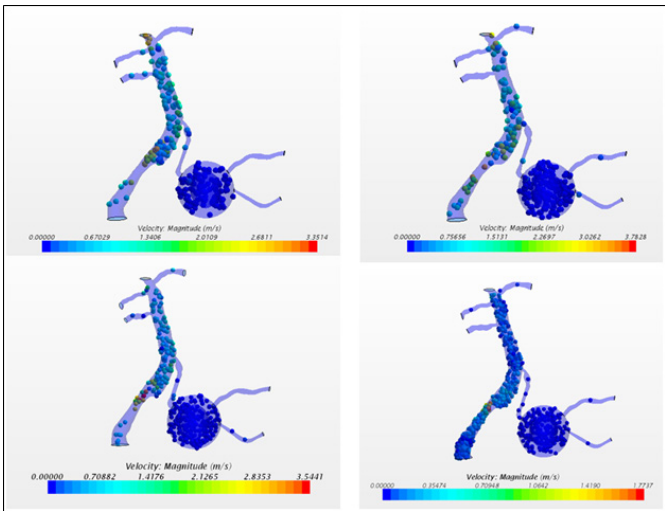

Figure 12 Velocity distribution for particle size of 30nm.

The drug particle reaches the tumor and dosage of drug increases continuously following cardiac cycle. However, the flow velocity of blood tissue and tumor regions is less compared to artery region because there is obstruction for the flow of the blood at the tissue-tumor region. As size of the drug particle increases the velocity decreases.

The Figure 13 shows the flow of drug particle of 50 nm at increasing time steps i.e., at 0.1 sec, 0.125sec, 0.2 sec and 0.25sec. Initially at 0.1sec, velocity in artery region is 3.99 m/sec which increases to 4.7 m/sec at 0.125sec. later again its starts decreasing.

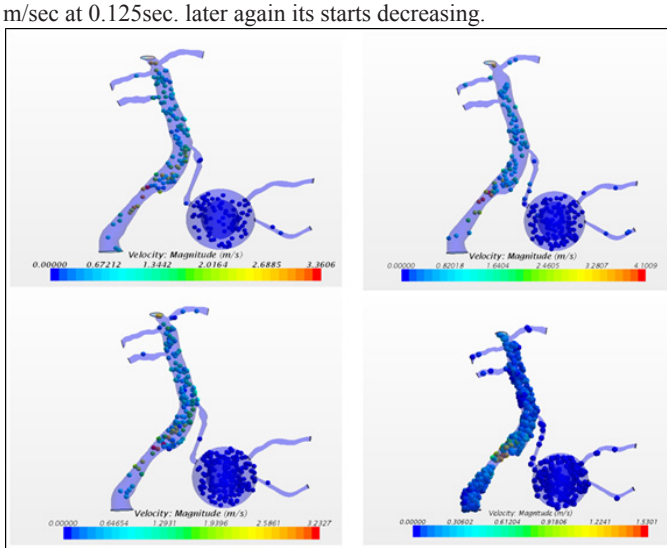

Figure 13 Velocity distribution for particle size of 50nm.

The drug particle reaches the tumor and dosage of drug increases continuously following cardiac cycle. However, the flow velocity of blood tissue and tumor regions is less compared to artery region because there is obstruction for the flow of the blood at the tissue-tumor region. As size of the drug particle increases the velocity decreases. This variation can be seen for particle size of 20nm, 30nm and 50nm.

Effect of particle size on velocity magnitude (Centre of the tumor)

To observe velocity at the center of the tumor for varying particle sizes, a point probe is considered at the center of the tumor as shown in Figure 14. A point is considered at center of the tumor as shown in Figure 14 and velocity at the center of the tumor region is compared with varying sizes of particle diameter as plotted in Figure 15. Velocity at the center of the tumor region is compared with varying sizes of particle diameter as plotted in Figure 15 (Table 4).

Table 4 Data showing velocity distribution

Size(nm)/Time(sec)	20	30	50
0.1	0.042	0.042	0.042
0.125	0.075	0.075	0.075
0.2	0.033	0.032	0.032
0.25	0.00052	0.00052	0.00052

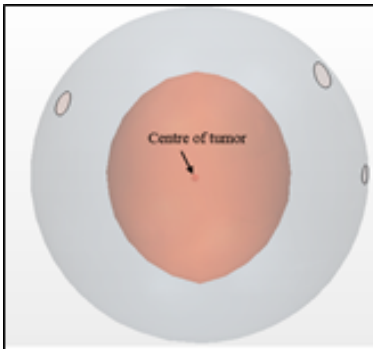

Figure 14 Point probe at the center of the tumor.

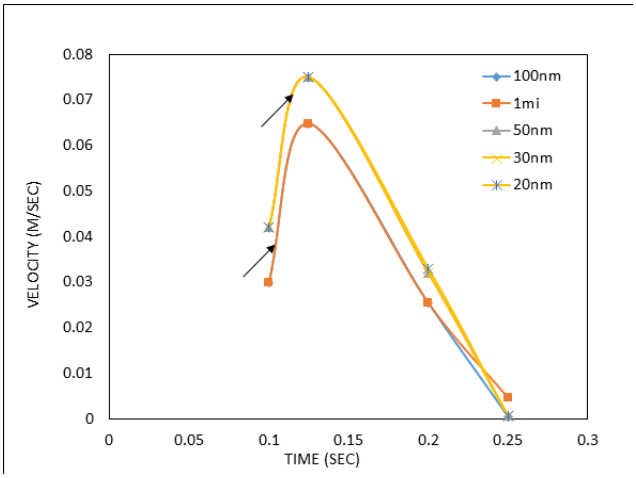

Figure 15 Velocity plot at the centre of the tumor.

The flow velocity of blood tissue and tumor regions is less compared to artery region. Velocity magnitude is following the cardiac cycle. Velocity changed when particle diameter changed from 100nm to 50nm and remained same for 20nm, 30nm and 50nm. No further changes are notice for sizes higher than 100 nm and smaller than 50nm.

Effect of drug particle density

From Figure 16 it is observed that lower the density higher is the velocity. Decrease in particle diameter and density as a combination could prompt us with better penetration effect of the drug to the tumor.

Particle accumulation

Only velocity cannot assure us to find out the effect of drug in the region of tumor. Particle volume distribution at tissue and tumor region analysis gives better idea to explain more about uptake of drug (Table 5).

Table 5 Data showing particle volume

Tissue -tumor region				
Size/Time (sec)	**50nm**	**30nm**	**20nm**	**10nm**
0.1	8452	13038	10551	11012
0.125	17345	22368	22778	32656
0.2	24754	26925	33521	41292
0.25	30024	33876	42042	49532
Tumor region				
0.1	4911.5	4110.4	5642	7977.4
0.125	10175	10281	11667	15408
0.2	22007	16008	22325	26223
0.25	21967	22362	24177	23648

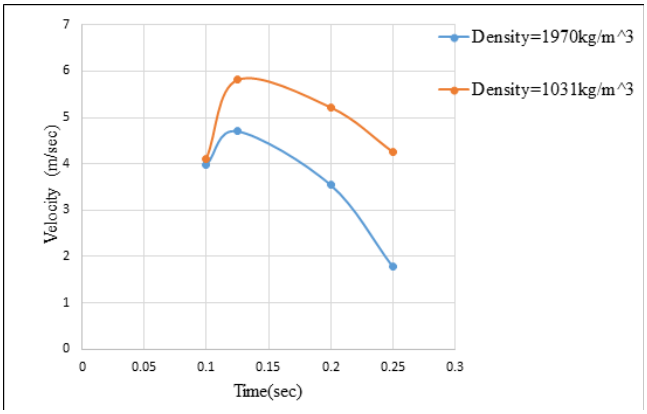

Figure 16 Effect of drug particle density.

Figure 17 shows particle volume variation with respect to time for different sizes of particle. Amount of drug accumulated near tissue-tumor region increases with time. Rate of accumulation is higher with decrease in drug particle size.

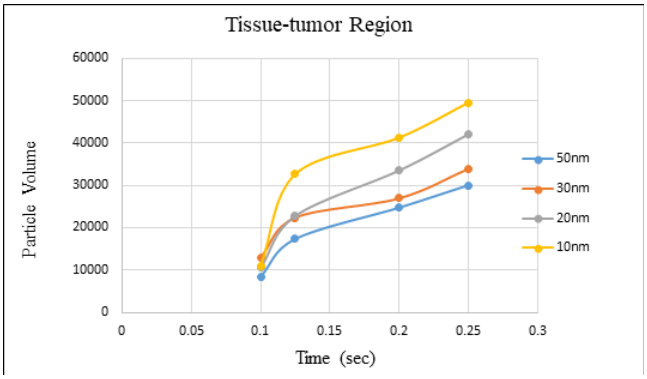

Figure 17 (a) Particle volume vs time for different particle size.

Figure 18 shows particle volume variation at tumor region with respect to time for different sizes of particle. However, Particle accumulation at the tumor region also increases till 0.2sec and later decreases for sizes of 10nm, 20nm and 50nm. There is increase in amount of drug after 0.2sec for a 30nm size particle.

Polymer coating

The polymers are used to deliver the drug to the target region. Biodegradable polymers are used to deliver the drugs to a specific region of the body as they degrade with a constant rate of drug release. Multifunctional particle composed of drugs encapsulated with a layer of polymer. Polymer coating makes the particle as a carrier and prevents it to dissolve in blood stream. The computational data that is discussed under section 3.5 and tabular data from Table 6 is used to discuss the results in this section.

Table 6 Data showing particle volume after polymer coating

	Tissue- Tuirior region		
Ratio(dp)/Time(sec)	1:08	1:65	1:120
0.1	2.35E±O5	2.41E±O5	1.16E±05
0.125	1.89E±05	1.83E±05	1.78E±05
0.2	2.65E±05	2.30E±05	2.14E±05
0.25	4.67E±05	3.81E±05	3.97E±05
	Tumor region		
0.1	13172	10250	12496
0.125	18934	18771	19616
0.2	31910	28936	34440
0.25	28936	32121	30710

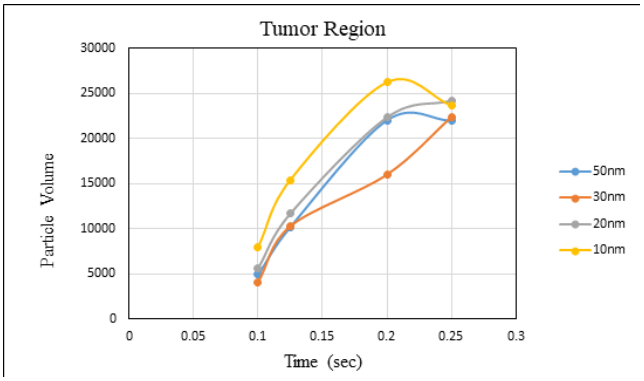

Figure 18 (b) Particle volume vs time for different particle size.

Figure 19 shows that initially the amount of drug reaching the tissue tumor region decreased later as time goes on the amount of drug increased except for 1:120 ratio where it increased continuously from initial state.

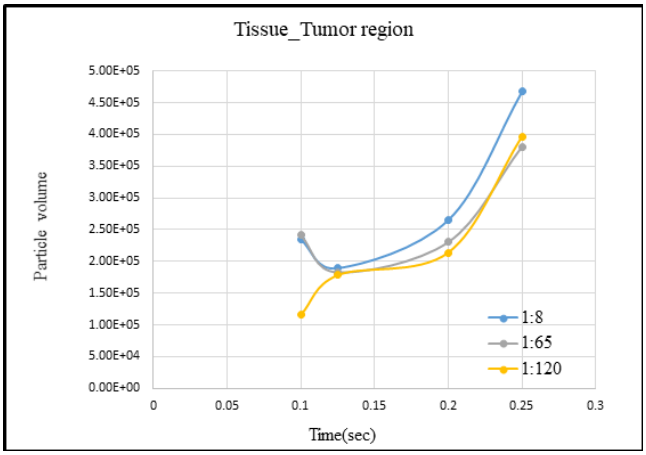

Figure 19 (a) Particle volume vs time for different drug-polymer coating ratios.

Whereas for tumor region the amount of drug near tumor region increased at initial stage only and a sudden drop at 0.25sec as shown in Figure 20.

For a drug- polymer ratio of 1:120 the amount of drug reaching the tumor is much higher than remaining.

Uptake of the drug (Figure 21)

Initially mass source term is deactivated for all the three cases and later it is activated for 80% and 50% cases to observe the uptake of

the drug. In Figure 16, it can be seen that there is decrease in particle count at tumor region for the negative value of mass source term i.e., there is uptake of drug at tumor region (Table 7).

Table 7 Data showing particle count

Mass term/time (sec)	Mass term off	80%	50%
0.1	446.88	446.88	446.88
0.125	2177	1568.2	2037.4
0.2	6508.2	5229.9	5933.6
0.25	8248.1	6344.1	7389.8

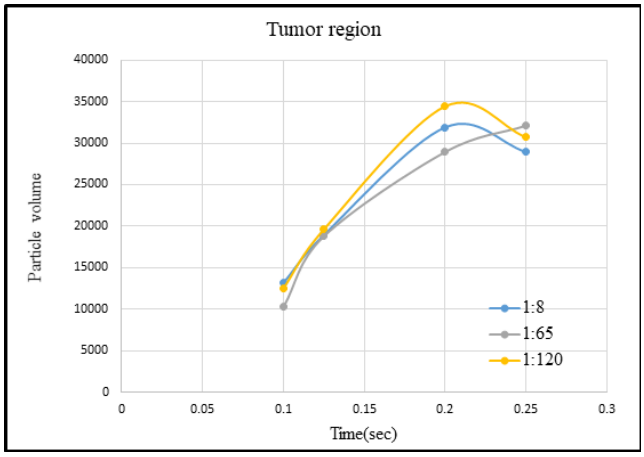

Figure 20 (b) Particle volume vs time for different drug-polymer coating ratios.

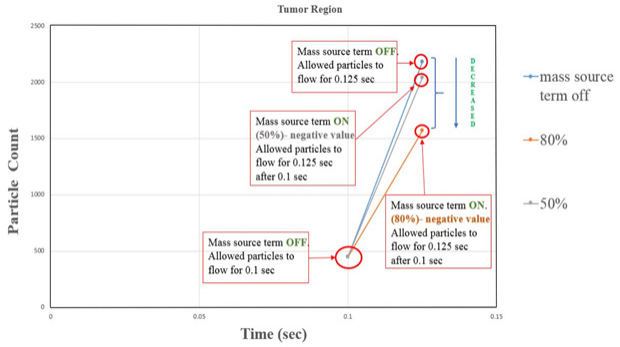

Figure 21 Uptake of the drug.

Figure 22 shows uptake of drug with respect to time. As time increases the amount of drug increases but there is decrease in particle count when mass source term is activated.

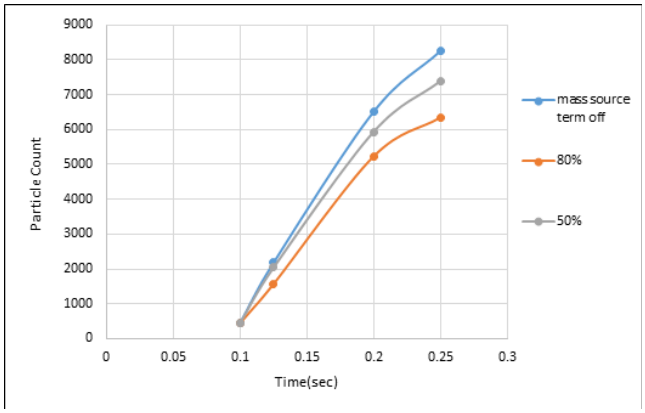

Figure 22 Uptake of drug with respect to time.

Conclusion

A computational simulation model has been developed for analyzing multi-functional and selective drug particle delivery to a targeted tissue-tumor region. The computational analysis is done by solving governing equations of blood flow dynamics based on Navier-Stokes equations and mass species transport based on Lagrangian particle flow equations. The diffusion considered in the capillary-tissue regions is based on brinkman's model. Analysis of blood flow is performed using experimentally derived cardiac input as inflow and considering the blood as non-Newtonian in nature which is closer to reality.

Sensitivity of drug particle types and size on the delivery of the drugs to the target region is analyzed. The simulation analysis results shows that the decrease in particle diameter and density as a combination could prompt us with better penetration effect of the drug to the tumor. Higher the polymer coating over the drug increases the particle volume near the targeted region. Drug uptakes in the tumor region is also analyzed.

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None.

Conflicts of interest

Author declares that there are no conflicts of interest.

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