Drug delivery and adhesion of magnetic nanoparticles coated nanoliposomes and microbubbles to atherosclerotic plaques under magnetic and ultrasound fields

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ABSTRACT

The use of external fields such as magnet and ultrasound to enhance the targeted drug delivery (TDD) by nano-microcarriers could be a potential method. In this research, the drug delivery of magnetic nanoparticles (NPs) coated nanoliposomes and microbubbles (MBs) to the atherosclerosis plaque was investigated under magnetic and ultrasound fields in terms of their adhesion to the plaque through ligand–receptor binding. The Halbach arrangement enhanced the surface density of nanoliposomes and MBs adhered to the plaque by ∼121% and ∼94%, respectively. A focused transducer at the power of 60 W led to better drug delivery performance and caused ∼67% and ∼58% enhancement in the surface density of nanoliposomes and MBs adhered to the plaque, respectively. Better drug delivery efficiency was achieved upon using a magnetic field as compared with the ultrasound field. The simultaneous employment of magnetic and ultrasound fields can increase the delivery of nanoliposomes and MBs by ∼148% and ∼121%, respectively. The results of this study can broaden our insight on the effects of a magnet (its size, location, and arrangement) and the type of ultrasound transducer on TDD to the carotid artery disease using nanoliposomes and MBs.

ARTICLE HISTORY

Received 1 June 2021
Accepted 26 September 2021

KEYWORDS

Targeted drug delivery; microbubble; nanoliposome; magnetic targeting; ultrasound targeting

1. Introduction

Atherosclerosis refers to the accumulation of fibrofatty lesions at the coronary and carotid vessels and is responsible for many heart diseases and strokes. Statistics have shown that in 2019, 6.6 million deaths globally attribute to stroke (Virani et al., 2021). In the case of the intensification of atherosclerosis and the emergence of threatening complications, in-time diagnosis and angioplasty are vital. Bypass graft surgery, carotid endarterectomy (CEA), balloon angioplasty, and stenting are among the conventional methods used to resolve atherosclerosis (Chang et al., 2018; De Vries et al., 2016; Kim et al., 2018; Rajamani & Chaturvedi, 2007). In addition to minimizing the use of invasive methods, the development of medications can reduce or stop the local growth of lesions (Wang, Chen, et al., 2018). Targeted drug delivery (TDD) has shown high potential in treating this type of disease (Dai et al., 2020; Gao et al., 2020). TDD prevents the deviation of the free drugs from the target site (disease site) by using appropriate drug carrier. In this regard, designing a suitable carrier to improve the delivery process is crucial (Ebrahim et al., 2021; Forouzandehmehr & Shamloo, 2018).

Previous studies have addressed the role of drug carriers in TDD. All these studies are aimed to improve the performance of guided drugs (Gao et al., 2020; Shen et al., 2016). In a TDD approach, the drug is attached to a carrier through a targeting ligand. Then the drug-coated carrier will be transferred to the target site by the blood flow and release the drug there. This simple process requires several fundamental conditions such as nonspecific interactions, reaching and then releasing the drug to the target site, and drug compatibility (Petrak, 2005). TDD is often achieved by lipid nanocarriers, polymeric nano and microcarriers, nonorganic nanocarriers, polymeric micelles, and lipoproteins (Cui et al., 2016; Zugic et al., 2020). The performance of various carriers has been evaluated in recent years. It has been revealed that nanoliposomes are the most successful carriers in the TDD process (Natarajan et al., 2014). Nanoliposomes
are spherical vesicles from phospholipids. Amphiphilic molecules have a hydrophilic head and a hydrophobic tail. When placed in an aqueous medium, they will form an addition or double spherical layer of molecules, which can be a proper place for hydrophobic drugs (Sercombe et al., 2015). Microbubbles (MBs) are an instance of microcarriers. In addition to their diagnostic role, MBs have shown potentials in TDD; hence they can be an innovative choice in the field of carriers (Unger et al., 2014; Wang, Searle, et al., 2018). MBs are gas-filled microbubbles whose core includes perfluorocarbons, and their stabilizer membrane is made from various materials such as polymers, phospholipids, and proteins. Based on the type of the species, the diameter of the MBs may vary in \( \sim 1 - 5 \mu m \). Drugs are loaded on the external surface or inside of the MBs, providing TDD opportunity (Shamloo et al., 2020). Thanks to the development of nano-microcarriers, it is possible to increase the sensitivity of nano-microcarriers to enhance their targeting ability by designing a TDD system under the manipulation of external factors such as magnetic or ultrasound forces (Liu et al., 2017; Nieminen et al., 2015).

Designing a proper TDD system requires optimizing the response of the various therapeutic carriers to external fields. Coating magnetic nanoparticles (NPs) on the MBs makes it possible to improve the targeting efficiency (Beguin et al., 2019). Under an external magnetic field, the released magnetic nanocarriers from the magnetic MBs will experience a controlled migration having the opportunity to penetrate and diffuse into the tissues which had not been easily accessible (Beguin et al., 2020; Crake et al., 2016; Gao et al., 2016). Owen et al. (2015) conducted an in vitro study to show that magnetic MBs can be maintained by applying magnetic field under physiologically compatible conditions (i.e. high shear rates in the arterioles and high flow rates in arteries). Dwivedi et al. (2020) investigated the effect of doxorubicin (DOX) loaded magnetoliposome (DOX-ML) MBs (DOX-ML-MBs) in the treatment of pancreas cancer. They showed that the deep penetration of the synthesized drug, even at lower dosages, into the tumor tissue is due to its high magnetic properties, eliminating the cancer cells and significantly decreasing the tumor size. Wu et al. (2011) conducted an in vivo study on vascular cell adhesion molecule-1 (VCAM-1) targeted MBs and observed that using magnetic MBs along with magnetic field in the aorta region can improve the attachment of endothelial VCAM-1 to atherosclerotic aorta. Liu et al. (2017) observed that the use of a magnetic field can significantly influence the preventing of the tumor growth by localization and more effectiveness of treatment mechanism with the help of anethole dithiolethione (ADT)-loaded magnetic nanoliposome (AML).

Studies have shown that it is feasible to handle nano-microcarriers by applying external fields such as ultrasound force (Huang et al., 2004; Karlsen & Bruus, 2015; Muller et al., 2012). Non-invasive local destruction of osteoarthritis drug carriers to the articular cartilage using intensive Hertz ultrasound was investigated by Nieminen et al. (2015). By regulating the frequency and other ultrasound-related factors, they managed to deliver the drug as deep as 53% of articular cartilage thickness. To better understand the effect of ultrasound waves on manipulating the drug carriers, Peng et al. (2019) designed a trapping system using ultrasound waves to increase effective drug delivery and reach real-time positioning. Using finite element models, they analyzed the path of MBs in a fluid under an external ultrasound force to explore the ability of this external force to trap and guide MBs to a specific site. Their results indicated accurate drug localization by this ultrasound-based force, introducing this method as a promising alternative for the invasive clinical methods.

Recently, numerical methods using the computational fluid dynamics (CFD) model have become popular in the prediction of macroscopic and microscopic hydrodynamic parameters (Ghalandari et al., 2019; Mosavi et al., 2019). In our previous research, the path of the nano-microcarriers to the left anterior descending artery was evaluated to assess the particle transfer potential at various sizes considering non-Newtonian properties of the blood (Forouzan dehmesh & Shamloo, 2018). Our results indicated an optimal range for the size of the spherical particles in which the probability of the particle adhesion will be maximal. Then the influence of the magnetic field was numerically investigated on the migration of the magnetic particles to the atherosclerotic plaque (Shamloo et al., 2019). The simulation results demonstrated an optimal range of the particle size under a specific magnetic field in which the adhesion of the magnetic particles with the size of 400 and 600 nm will be enhanced by \( \sim 49.4\% \) and \( \sim 59.7\% \), respectively. In recent numerical studies, we investigated the drug delivery ability of various MBs and nanoliposomes to abdominal aortic aneurysm (AAA) (Ebrahimii et al., 2021; Shamloo et al., 2020). It was concluded that the size and type of MBs, as well as the size of nanoliposomes, can affect their adhesion to the AAA lumen. It was also revealed that the flow pattern inside the AAA can significantly influence the adhesion of MBs and nanoliposomes to the AAA lumen. Studies have revealed that no study has been conducted to investigate the delivery of drug carriers in a TDD system upon the application of both magnetic and ultrasound forces in the case of atherosclerosis. Therefore, it is necessary to conduct a comprehensive study on this disease under these two forces to improve further
our understanding of the TDD mechanism for a more effective treatment of the disease.

The application of magnetic and ultrasound fields to enhance the TDD using nano-microcarriers could potentially enhance targeted drug delivery to atherosclerosis sites. The present study addresses the drug delivery performance of nano-microcarriers to the carotid atherosclerotic plaque under magnetic and ultrasound fields (Figure 1(a)). The value of airbox and body tissues were considered around the magnetic and ultrasound transducers. Based on Equation (1), 500889 elements were considered for One Magnet and FUS transducer. Two transducers (disk and focused) at various powers were considered to study the influence of the ultrasound field on the drug delivery to the atherosclerotic plaque. Nanoliposomes at the size ranges of 200 – 800 nm and MBs at the size ranges of 1 – 4 μm were studied as the nano and microcarriers, respectively. Magnetic nanoparticles (NPs) were coated on these carriers, while the nanomicrocarriers were coated by P-selection aptamers to promote their binding to the surface of P-selection-containing plaque.

2. Materials and methods

2.1. Model geometry

A schematic representation of our carotid atherosclerotic plaque under the magnetic (permanent magnet) and ultrasound fields is showed in Figure 1. The present study addressed a two-dimensional (2D) cylinder model for the carotid artery with an asymmetric plaque and stenosis 50% (based on the previous studies (Ahmed & Giddens, 1983; Manzoor et al., 2020; Sanyal & Han, 2015)), which was designed by SOLIDWORKS software (Figure 1(a,b)). The thickness of the artery wall and the surrounding tissues of the carotid artery is denoted by t and h, respectively. A permanent magnet is placed on the neck skin. The ultrasound transducer is also placed on the other side of the neck, and the focal region of focused ultrasound (FUS) transducer was adjusted inside of the artery. To avoid the effects of the boundary conditions, airbox and body tissues were considered around the magnetic and ultrasound fields (Figure 1(a)). The value of parameters in Figure 1 is shown in Supplementary Table 1 (Jain et al., 2012; Sanyal & Han, 2015; Waller et al., 1992).

The whole geometry was meshed by triangular elements (Figure 1(c)). The number of the applied elements varied by changing the magnets and type of the ultrasound transducers. Based on Figure 1(a), 500889 elements were considered for One Magnet and FUS transducer.

2.2. Blood flow and boundary conditions

Blood flow inside the carotid artery was assumed laminar and non-Newtonian. Experimental studies on blood rheology have shown the dependence of the blood viscosity on the shear rate. There is a nonlinear relation between the shear stress and shear rate of the blood, which determines the non-Newtonian properties of the blood (Sriram et al., 2014). Carreau–Yasuda model is often used to describe the shear thinning behavior of the blood (Kwon, 2008). In the present study, this model was applied. Based on this model, apparent blood dynamic viscosity can be determined by:

\[ \eta_{\text{app}} = \eta_{\infty} + (\eta_0 - \eta_{\infty})[1 + (\lambda \dot{\gamma})^2]^{(a-1)/2} \]  

where \( \eta_0 \) is the viscosity at zero shear rate and \( \eta_{\infty} \) is the viscosity at infinite shear rate. \( \lambda \) refers to relaxation time constant. \( \dot{\gamma} \) and \( a \) are the local shear rate and power-law index, respectively. The values of the parameters mentioned for Equation (1) are \( \eta_0 = 0.161 [\text{Pa.s}] \), \( \eta_{\infty} = 0.00345 [\text{Pa.s}] \), \( \lambda = 39.418 [\text{s}] \), and \( a = 0.479 \) (Forouzan-dehmehr & Shamloo, 2018; Kwon, 2008).

To include the effects of the apparent dynamic viscosity (i.e. non-Newtonian properties of the blood) in the hydrodynamic motion of incompressible blood flow, the Navier–Stocks equations governing the generalized Newtonian fluid (GNF) (Gori & Boghi, 2011, 2012) for mass conservation:

\[ \nabla \cdot \mathbf{u} = 0 \]  

and for momentum (‘Fundam. Mech. Fluids, Third Ed.,’ 2017):

\[ \rho \frac{\partial \mathbf{u}}{\partial t} + \rho \mathbf{u} \cdot \nabla \mathbf{u} = -\nabla p + \nabla \tau + \mathbf{F} \]  

are solved to determine the velocity and pressure values in the entire domain.

In the above equations, \( \rho \) denotes the density, and \( \mathbf{u} \) presents the fluid velocity vector. \( p \) is the fluid static pressure and \( \mathbf{F} \) is the vector of the volumetric forces on the fluid. \( \tau \) also represents the stress tensor of the fluid which is a function of strain rate tensor \( (S_{ij}) \) and Kronecker delta function \( (\delta_{ij}) \) whose tensor notion can be expressed as:

\[ \tau_{ij} = 2\eta_{\text{app}} S_{ij} - p\delta_{ij} \]  

\[ S_{ij} = \frac{1}{2} \left( \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) - \frac{1}{3} \frac{\partial u_k}{\partial x_k} \delta_{ij} \]  

\[ \delta_{ij} = \begin{cases} 1 & \text{if } i = j \\ 0 & \text{if } i \neq j \end{cases} \]  

As mentioned earlier, the flow regime inside the carotid artery was considered laminar which is a proper assumption for a 50% stenosis based on the study by
Figure 1. A schematic representation of the carotid artery in the human body with atherosclerosis plaque (50%) in the blood circulation path as well as the applied fields to improve the drug delivery to the target site (a) Geometrical modeling of a carotid artery with the length of $L = 60 \text{ mm}$ along with its surrounding tissues. To influence the magnetic NPs-coated nano-microcarriers, a permanent magnet is attached to the body on one side of the carotid artery at the site of atherosclerosis. The distance from the artery to the skin is set to $\sim 12 \text{ mm}$. The tissue properties were taken for this region. A region is also considered around the magnet to simulate the closed magnetic field lines. This region is known as the airbox and was considered to make the results closer to reality. An ultrasound transducer is embedded on the other side of the atherosclerosis plaque whose resulting field pushed the drug carriers passing from the disease area to the target site. (b) An atherosclerosis plaque with a length of $17.5 \text{ mm}$ in a carotid artery with an internal diameter ($d_i$) of $4 \text{ mm}$. In this region, the blood flow could only pass through a path with a diameter of $d_s = 2 \text{ mm}$. The thickness of the artery wall is $t = 1 \text{ mm}$. (c) Dividing the plotted geometry into nodes by triangular elements to calculate the simulation parameters at each node. (d) Different arrangements of the permanent magnets to investigate the distribution of the magnetic field in the vicinity of the target site and their impact on improving the drug delivery by magnetic NPs. (e) The configuration of ultrasound setup for drug delivery and its boundary conditions. The transducers’ boundaries were subjected to normal displacement, and other boundaries were assumed to be sound soft boundaries.
Ahmed and Giddens (1983). Pulsed velocity and pressure were applied to the inlet and outlet of the carotid artery within three cardiac cycles, as depicted in Supplementary Figure 1. The experimental data used for the pulsed velocity and pressure have a phase delay (Hirata et al., 2006; Manzoori et al., 2020).

2.3. Magnetic field and magnetic force

The movement of the electrical charges within a substance can generate forces at the atomic level, which is known as a magnetic field. The magnetic field produced by a permanent magnet can be calculated using Maxwell’s equations, known as the Ampere and Gauss’ laws (Babinec et al., 2010; Lunnoo & Puangmali, 2015). Specifically, Ampere’s law:

\[ \nabla \times \mathbf{H} = \mathbf{J} \]  

(4)

where \( \mathbf{H} \) is magnetic field intensity (A/m), and \( \mathbf{J} \) is current density (A/m\(^2\)). There is no electric current in this study, so the value of \( \mathbf{J} \) is set to zero.

Gauss’ law:

\[ \nabla \cdot \mathbf{B} = 0 \]  

(5)

where \( \mathbf{B} \) is magnetic flux density (T), and it is determined inside the domain of the permanent magnet with bellow equation (Lunnoo & Puangmali, 2015):

\[ \mathbf{B} = \mu_0 \mu_r \mathbf{m} \mathbf{H} + \mathbf{B}_{\text{rem}} \]  

(6)

In Equation (6), \( \mu_0 = 4\pi \times 10^{-7} \) N/A\(^2\) is magnetic permeability of vacuum, \( \mu_r \mathbf{m} \) is relative permeability of the permanent magnet, and \( \mathbf{B}_{\text{rem}} \) is remanent magnetic flux density (T). Here, to gain the highest effect of magnetic field from a permanent magnet, a permanent magnet \( \text{NdFeB} \), grade \( N52, \mu_r \mathbf{m} = 1.05, \mathbf{B}_{\text{rem}} = 1.5(\text{T}) \) was utilized such that the limitations regarding the body exposure to the magnetic field were completely obeyed (Owen et al., 2015; Pyröhönen et al., 2013). In stronger magnetic fields, it is necessary to include the possible effects of the fields and the electric currents induced in the circulation due to the movement of electrolytes in the blood. Such currents may reach a level that causes extraneous nerve or muscle excitation (Schenck, 2000; Ziegelberger, 2014). In the presence of strong magnetic fields, the tissue components with a positive magnetic susceptibility relative to water will experience a force and are drawn toward high field areas. Theoretically, this phenomenon will arrange the paramagnetic components of the tissue. Another effect that poses an even more serious hazard than the translational force is that the diamagnetic components of the tissue tend to rotate in the presence of a magnetic field. This magnetic torque increments the tendency of the axis with the least negative susceptibility to align along the field (Schenck, 2000).

Equilibrium rates or positions of some chemical reactions that provide the proper metabolic function of tissues may alter under the influence of high magnetic fields which can be associated with variations in spin chemistry. The presence of a high magnetic field shifts the equilibrium of a chemical reaction in favor of products that are more paramagnetic than the reactants. For example, diamagnetic oxygen-bound hemoglobin molecules are decomposed into separate paramagnetic molecules: hemoglobin and oxygen (Motta et al., 1998; Schenck, 2000). Blood has a relatively low electrical conductivity, thus, magnetohydrodynamic (MHD) forces are very small compared to hemodynamic ones. Nevertheless, by applying magnetic fields larger than \( \sim 15 \text{T} \), MHD slowing of blood flow is expected to reach more than \( \sim 10\% \). Prior studies have been shown that small MHD forces functioning on the endolymphatic tissue of the inner ear can lead to sensations of nausea and vertigo at higher magnetic fields (Schenck, 2000; Tenforde, 2005). Moreover, it has been reported that significant modification in depolarizing currents – the currents that are accountable for nerve propagation and muscle activity potentials – only occurs with the presence of a high magnetic field because the motion of ions and electrons is changed under Lorentz force (Schenck, 2000; Ziegelberger, 2014). Therefore, a permanent magnet having a moderate magnetic flux density would be a safe instrument for enhancing drug delivery inside the human body.

On the other hand, the magnetic flux density (magnetic induction) around the permanent magnet including the blood, walls, tissues, and air can be defined by Manshadi et al. (2018):

\[ \mathbf{B} = \mu_0(\mathbf{H} + \mathbf{M}) \]  

(7)

where \( \mathbf{M} \) is magnetization vector (A/m). The linear relationship between \( \mathbf{M} \) and \( \mathbf{H} \) is represented through bellow equation (Babinec et al., 2010):

\[ \mathbf{M} = \chi \mathbf{H} \]  

(8)

\( \chi \) is material magnetic susceptibility. By substituting Equation (8) in Equation (7), the following equation is obtained:

\[ \mathbf{B} = \mu_0(1 + \chi)\mathbf{H} \]  

(9)

\( \chi \) is also a dimensionless scalar related to relative permeability (Furlani, 2006).

\[ \chi = \mu_r - 1 \]  

(10)
Therefore, Equation (9) yields:

\[ B = \mu_0 \mu_r H \]  \hspace{1cm} (11)

Here, \( \mu_r \) was considered 0.99999095 for the blood and tissue, 0.999991 for the walls, and 1 for the air (Pyrhönen et al., 2013; Schenck, 1996).

The difference in the magnetic permeability of the magnetic NPs and their surrounding results in the magnetization of the magnetic NPs upon exposure to the external magnetic field. That is, the NPs experience a transforming force in the direction of ascending field gradient, a phenomenon referred to as magnetophoresis. The force on a magnetic NP in an external magnetic field (\( H_a \)) can be determined by the following equation (Babinec et al., 2010):

\[ F_m = \mu_r (m_{np, eff} \nabla)H_a \]  \hspace{1cm} (12)

where \( m_{np, eff} \) is the ‘effective’ dipole moment of the magnetic NP.

Various sizes of magnetic NPs exhibit different magnetic behaviors under external magnetic field. Magnetic domains of the NP will be aligned with the field direction upon exposure to the magnetic field. This process, known as magnetization of the NP, is linearly correlated with the applied field strength. Under a sufficiently strong field, all the magnetic domains will be aligned resulting in magnetic saturation. For a NP with the radius of \( r_{np} \) and volume of \( V_{np} \), \( m_{np, eff} \) will be (Babinec et al., 2010; Kelly et al., 2015):

\[ m_{np, eff} = V_{np} f(H_a)H_a \]  \hspace{1cm} (13)

and below the saturation value:

\[ M_{np} = \chi_{np} H_{in} \]  \hspace{1cm} (14)

Here, \( M_{np} \) is the magnetization vector of NP and \( \chi_{np} \) is the magnetic susceptibility of the NP. At magnetic saturation, \( M_{np} = M_{np, sat} \) where \( M_{np, sat} \) indicates saturation magnetization of the NP. \( H_{in} = H_a - H_{demag} \) and \( H_{demag} = M_{np, sat}/3 \) is self-demagnetization of the NP and opposite of \( H_a \). When the NP is dissolved in a magnetically linear fluid with susceptibility of \( \chi_f \), \( f(H_a) \) can be defined as (Babinec et al., 2010):

\[
f(H_a) = \begin{cases} 
3(\chi_{np} - \chi_f) / (\chi_{np} - \chi_f) + 3, & H_a < (\chi_{np} - \chi_f) + 3/\chi_{np} M_{np, sat} \\
M_{np, sat} / H_a, & H_a \geq (\chi_{np} - \chi_f) + 3/\chi_{np} M_{np, sat} 
\end{cases} \hspace{1cm} (15)
\]

In the above equation \( H_a = |H_a| \).

Migration and movement of magnetic NP-coated particles are influenced by a number of key parameters such as the permanent magnet size, magnitude and direction of the magnetic field, and arrangement of the permanent magnets. Researchers have experimentally investigated the use of the magnetic field for TDD with various arrangements and alignments of the permanent magnets (Beguin et al., 2019; de Saint Victor et al., 2019; Nacev et al., 2012; Owen et al., 2018). In this study, we explored the effect of factors like size and longitudinal position of the permanent magnet relative to the plaque, and the arrangement of the permanent magnet with respect to the adhesion and collision of magnetic NP-coated nanoliposomes and MBs with atherosclerotic plaque (Figure 1(d)). Moreover, Fe3O4 NPs with magnetic susceptibility of 1.186 and a diameter of 10 nm were used for effective delivery of MBs and nanoliposomes (Owen et al., 2015). The saturation magnetization of this NPs was about 4480000 A/m (Xu et al., 2005). Maximum external magnetic field (\( H_a \)) of the simulated permanent magnets was obtained in the blood. The highest value (191577.65 A/m) was related to the Halbach arrangement (Xu et al., 2005). Therefore, according to Equation (15), the Fe3O4 NPs did not reach saturation, i.e. they were paramagnetic.

### 2.4. Ultrasound field and force

#### 2.4.1. Ultrasound field calculation

To determine the ultrasound forces that contribute to the drug delivery process requires the ultrasound wave (field) variables, via solving the sound propagation equation. Thus, the Helmholtz equation with attenuation in the frequency domain must be solved (Peng et al., 2017):

\[
\nabla \left( -\frac{1}{\rho_c} \nabla p_c \right) - \frac{k_{eq}^2 p_c}{\rho_c} = 0 \hspace{1cm} (16)
\]

In the above equation, \( p_c \) is the ultrasound pressure, \( \rho_c \), and, \( k_{eq} \) are complex density and equivalent wave number, respectively. The equivalent wave number can be defined as:

\[
k_{eq} = \left( \frac{\omega}{c} - i\alpha \right) \hspace{1cm} (17)
\]

where \( \alpha \) is the attenuation coefficient, and \( c \) stands for the speed of sound in the medium.

In order to better evaluate the effect of ultrasound field on enhancing the drug delivery process, two 2D ultrasound sources were examined to generate the fields. A FUS transducer with the resonance frequency of 1.1MHz and 50mm focal length (Haddadi & Ahmadian, 2018) and a disk transducer with the same resonance frequency and radius of 10mm were considered as the wave source (Figure 1(e)). The disk transducer was modeled from a
piezoelectric ultrasound source in our Lab with the ultimate power of 30 W. A normal displacement was applied on the transducers as the amplitude of the sinusoidal wave as follows:

\[- n \left( - \frac{1}{\rho_c} \nabla p_c \right) = - \omega^2 d_n \quad (18)\]

where \(d_n\) denotes the normal displacement. Other boundary conditions are depicted in Figure 1(e). The maximum size of each edge of the elements was adjusted to approximately 1/6th of the wavelength, which led to approximate ly 249.445 for FUS transducer and 29,360 for the disk transducer (Figure 1(e)).

### 2.4.2. Nonlinear effects of ultrasound field

#### 2.4.2.1. Acoustic radiation force

In the next step, the ultrasound field forces acting on the nano-microcarries are calculated. This type of force is known as the acoustic radiation force (ARF) and can be obtained with the equations below:

\[ F_{\text{rad}} = - \pi a^3 \left[ \frac{2 \kappa_f}{3} \text{Re}(f_1 p_c \nabla p_c) - \rho \text{Re}(f_2 v_c \nabla v_c) \right] \quad (19a) \]

\[ f_1(\kappa) = 1 - \kappa \quad (19b) \]

\[ f_2(\rho, \delta) = \frac{2[1 - \Gamma(\delta)](\delta - 1)}{2\rho + 1 - 3\Gamma(\delta)} \quad (19c) \]

\[ \Gamma(\delta) = -\frac{3}{2} [1 + i(1 + \delta)] \delta \quad (19d) \]

\[ \tilde{\kappa} = \frac{\kappa_p}{\kappa_f} \quad (19e) \]

\[ \tilde{\rho} = \frac{\rho_p}{\rho} \quad (19f) \]

\[ \tilde{\delta} = \frac{\delta}{a} \quad (19g) \]

\(\kappa_f\) and \(\kappa_p\) denote the compressibility of fluid and particle, \(\delta\) is defined as the viscous penetration depth of fluid, \(v_c\) is the ultrasound velocity in the domain, and \(a\) and \(\rho_p\) are the particle’s radius and density, respectively.

#### 2.4.2.2. Acoustic streaming

When ultrasound waves pass through a free bulk liquid, it can generate a steady-state flow. This phenomenon is called acoustic streaming and it can be simulated as a volume force acting on the liquid in the Navier-Stokes equation (Huang et al., 2004):

\[ F_{\text{uf}} = - \rho (v_c \nabla) v_c + v_c (\nabla v_c) \quad (20) \]

where \(F_{\text{uf}}\) stands for volume force vector. Since the value of streaming force in the \(y\)-direction is much bigger than that in the other direction, we can ignore streaming force in the \(x\)-direction. Furthermore, Equation (20) can be simplified as (Huang et al., 2004):

\[ F_y = \frac{2\alpha I}{c} \quad (21) \]

In the equation above, \(I\) denotes the magnitude of acoustic intensity per area and \(y\) is the direction of propagation of ultrasound waves. The ultrasound parameters are listed in Supplementary Table 2 (Huang et al., 2004).

### 2.5. Particle tracking for fluid flow

Simulations were carried out representing injection of the Optison MBs with surface tension and dynamic viscosity of \(~0.072 \text{ N/m}\) and \(~0.001 \text{ Pa.s}\), respectively, and nanoliposomes with surface tension and dynamic viscosity of \(~0.0075 \text{ N/m}\) and \(~0.001 \text{ Pa.s}\), respectively. These particles were released through four injections in the inlet of the carotid artery at the presence of the external fields. The release was in the onset of one-second intervals while the injection times of 0, 1, 2, and 3 s were selected during the total three cardiac cycles plus a ramp (Shamloo et al., 2019, 2020). The particles were randomly introduced (Figure 2(a)).

To investigate the effect of the roughness of the endothelial surface on the particles’ motion, scattering diffusion, and specular reflection methods were selected to include the interaction of particles with the target wall. The possibility of a particle to be specularly reflected from the surface, occurring in a tangential plane, was 0.5 (\(\gamma = 0.5\) ). The collision angle of the particle coincided with its reflection angle relative to the surface normal (Shamloo et al., 2019).

\[ q' = q \quad (22a) \]

\[ v' = v - 2(n \cdot v)n \quad (22b) \]

where \(q\) and \(q'\) determine the position vector of the particle before and after contact with the surface, respectively. \(v\) and \(v'\) are pre-contact and post-contact particle velocity vectors, respectively, and \(n\) is the surface normal vector. The particle was diffusively reflected from the surface with a velocity vector according to Knudsen’s cosine. The particle position can be determined according to Equation (22a) and the velocity can be obtained by:

\[ v_{11} = |v_c| \sin \theta \sin \phi \quad (23a) \]

\[ v_{12} = |v_c| \sin \theta \cos \phi \quad (23b) \]

\[ v_n = |v_c| \sin \theta \quad (23c) \]

\(v_c\) is the velocity of the moment that the particle hits the surface. \(v_{11}\) and \(v_{12}\) are the outgoing-tangential components of velocity, and \(v_n\) is the normal component of
Figure 2. Deviation of the drug carriers toward the target site as a result of external forces. (a) The injected drug carriers move toward the atherosclerosis plaque site along with the blood flow. The surface of these magnetic NPs-coated nano-microcarriers is covered with ligand by avidin. Upon facing the lipid plaque, they form a bond with the receptors on the plaque surface and release their drug content to fulfill the drug delivery. (b) In the path of drug carriers, two external forces, one due to the permanent magnet and the other due to the ultrasound transducer, caused transverse transfer of drug carriers in the blood flow further guiding the drug carriers toward the target site. In addition to the external magnetic force ($F_m$) and ultrasound force ($F_{rad}$), some forces are also applied to the carriers from the fluid flow. Drag force ($F_d$) is due to the displacement of the fluid around the carrier along its path. This force can cause a relative displacement for carrier along the flow direction. In addition to the drag force, an additional transverse force is also applied to the carriers known as the lift force ($F_l$) which results in lateral migration of the carriers. Brownian force ($F_b$) originates from the collision of carriers. The Lennard-Jonse potential is also applied to include the carrier-carrier interactions.

velocity. Angle $\theta$ is a random number that uniformly distributed between zero and $2\pi$. The angle $\theta$ is also expressed according to the following relation:

\[
\theta = \sin^{-1} \left( \sqrt{\Gamma} \right)
\]

$\Gamma$ is a uniformly distributed random number. The probability distribution of the normal component of the velocity is directly related to the cosine of the angle ($\Gamma$). Moreover, to track the particles, the GMRES solver was adopted using the generalized-alpha time-stepping method by a nonlinear finite element code. Furthermore, a constant damping factor was employed as a nonlinear method for damped Newton iterations.

To determine the surface density of particles adhered to the atherosclerotic plaque, a specific variable was defined on each element of the plaque boundary. This variable was under the influence of all the particles attached to the boundary elements. Upon attachment of a particle to the boundary element, the value of the defined variable which was set to 1 by the source term will be increased. Then the source term was divided by the area of the boundary element (Amani et al., 2021; Shamloo et al., 2020).

2.6. Forces acting on the drug carriers

When the magnetic NP-coated particles pass the disease site through the blood circulation, they will experience two external forces arising from magnetic and ultrasound fields in addition to the drag and lift forces due to the fluid flow (Figure 2(b)). The forces acting on these particles can be classified into volumetric and surface forces. Here, blood is under the influence of external magnetic and ultrasound fields. Therefore, magnetic force ($F_m$), acoustic radiation ($F_{rad}$), and acoustic streaming ($F_{af}$) are among the volumetric forces. It was assumed that the patient is lying horizontally on the bed. In this regard, the volumetric gravity force is perpendicular to the blood flow, hence it can be neglected in the calculations. Virtual mass force is another volumetric force; previous
studies have shown that this force can be also neglected (Umbackar & Kleinstreuer, 2015). Drag and lift forces, as well as particle-particle interactions, are among the surface forces. The drag force \( F_D \) is due to the interaction between the particle and the moving fluid or vice versa. This force is applied to the particle in the direction of the fluid velocity and in the opposite direction to the final velocity of the particle. The lift force \( F_L \) is due to the velocity difference and hence the pressure gradient in the upper and lower parts of the particle. The direction of this force is normal to the fluid flow. The particles may also collide within the blood flow. The force exchanged during these collisions is called particle-particle interaction \( F_{p−p} \). These forces are formulated in Supplementary Table 3 (Ebrahimi et al., 2021; Shamloo et al., 2019).

The second law of Newton can determine the superposition of the forces applied on the magnetic NPs-coated particles with the mass of \( m_p \) (Shamloo et al., 2019):

\[
\frac{d}{dx}(m_p v) = F_D + F_L + F_m + F_{rad} + F_{af} + F_{p−p} \tag{25}
\]

where \( m_p \) and \( v \) are particle’s mass and velocity vector. It must be noted that as the diameter of the particles is larger than 50 nm, the brownian force can be neglected (Shamloo & Forouzandehmehr, 2019).

The Lagrangian-Eulerian model was used in this study in which the blood and nano-microcarriers were formulated as continuous and discrete phases using Eulerian and Lagrangian frameworks, respectively (Forouzandehmehr & Shamloo, 2018; Shamloo & Forouzandehmehr, 2019; Tan et al., 2013). In this approach, Equation (25) was solved for individual particles to determine their position and velocity as a function of time. Moreover, as the blood has low particle concentration (based on the distributed drug dosage), one-way coupling was assumed in this method. dilute models refer to the models in which the volume fraction of particles is below 1% (Umbarkar & Kleinstreuer, 2015).

The density of MB and nanoliposomes as nano and microcarriers is \( \sim 1000 \text{ kg/m}^3 \) (Van Rooij, n.d.). It was assumed that NPs cover all the surface of MB and nanoliposome. Therefore, the total density of magnetic NPs coated nano-microcarriers can be determined by:

\[
\rho_T = \frac{\rho_{\text{nano or microcarriers}} \times V_{\text{nano or microcarriers}}}{\rho_{\text{magnetic NPs}} \times V_{\text{magnetic NPs}}} = \frac{\rho_{\text{nano or microcarriers}} \times V_{\text{nano or microcarriers}}}{V_{\text{nano or microcarriers}} + V_{\text{magnetic NPs}}} \tag{26}
\]

The density of magnetic NPs with a diameter of 10 nm is \( 5100 \text{ kg/m}^3 \) (Owen et al., 2015). In the above equation the volume of nano-microcarriers or magnetic NPs (\( V \)) can be determined based on the radius (\( r \)) of nano or microcarriers and magnetic NPs:

\[
V_{\text{nano or microcarriers}} = \frac{4}{3} \pi r^3_{\text{nano or microcarriers}} \tag{27a}
\]

\[
V_{\text{magnetic NPs}} = \frac{4}{3} \pi ((r_{\text{nano or microcarriers}} + 2r_{\text{magnetic NPs}})^3 - r_{\text{nano or microcarriers}}^3) \tag{27b}
\]

The calculations for MB and nanoliposome with diameters of 2 \( \mu \text{m} \) and 200 nm surrounded by a layer of magnetic NPs showed that \( \rho_T \) is \( 1120.58 \text{ kg/m}^3 \) and \( 209.61 \text{ kg/m}^3 \). In this study, the simulation of the nano-microcarriers coated by magnetic NPs was carried out considering the mentioned densities.

### 2.7. Drug carrier adhesive dynamics model

Studies have demonstrated that P-selection aptamers (PSA) have a higher adhesion tendency compared to the other antibodies (Amani et al., 2021; Maul et al., 2010). In this study, it was assumed that the particles are coated by this type of aptamer. The adhesion probability of the particles to the target site (plaque) can be determined by the ligand–receptor binding formula. This equation was first introduced by Decuzzi and Ferrari (2006). Wall shear stress \( \eta_{app}S \), shape and size of the particle \( d_p \) are among the factors affecting the force and dislodge torque on a spherical particle from the fluid flow (Decuzzi & Ferrari, 2006).

\[
F = 3\pi d_p l \eta_{app} S F^S \tag{28a}
\]

\[
T = \frac{1}{2} \pi d_p^3 \eta_{app} S T^S \tag{28b}
\]

where \( l \) is the separation distance of the particles from the substrate. \( F^S \) and \( T^S \) are constant parameters that depend on the particle aspect ratio (\( \gamma = a/b \) ). In the case of spherical particles \( \gamma \) is 1, and the numerical values of \( F^S \) = 1.668 and \( T^S \) = 0.944 were adapted from the classic results of Goldman et al. (1967).

The probability of having at least one ligand–receptor bond is known as the probability of adhesion \( (P_a) \) which can be determined by Equation (29). This parameter is directly related to the adhesion ability; that is, the higher the \( P_a \), the greater the particle adhesion to the endothelium.

\[
P_a = \pi r_0^2 m_r m_l K_{a}^0 \times \exp \left[ -\frac{\beta d_p \eta_{app} S}{K_B T_0 m_r} \right] \times \left[ 3 \left( \frac{d_p}{2} + \delta_{eq} \right) F^S + \frac{d_p^2}{r_0} T^S \right] \tag{29}
\]

where \( m_r \) and \( m_l \) are the surface densities of receptors and ligands, respectively. \( K_{a}^0 \) is the association constant when
the ligand–receptor bound load is zero. \( \beta \) is the reactive compliance, \( \delta_{eq} \) is the equilibrium separation distance between the spheroidal and the vascular substrate, \( K_B T \) is the thermal energy of Boltzmann, \( h_0 \) is the maximum distance of the particle from the vascular wall where a specific bond can be formed, and \( r_0 \) is the radius of the circular section of the spheroid that exists at a separation distance \( h_0 \) from the substrate.

The shear stress due to the velocity gradient of fluid near the wall is the main cause of particles adhesion to the wall (Decuzzi & Ferrari, 2006; Godin et al., 2010). The mean shear stress \( (\eta_{app}S) \) was determined throughout the atherosclerosis plaque at the presence of volumetric forces due to magnetic and ultrasound fields under pulsed fluid flow. Then, Equations (28a,28b) were substituted in the equation for the probability of adhesion \( (P_a) \). The constants of this equation were derived from a previous molecular dynamics study for P-selection aptamers (PSA) (Supplementary Table 4). Therefore, \( P_a \) only depends on the particle diameter. It was determined for particles with various diameters and the rest of the calculations for the surface density of particles adhered to atherosclerosis plaque continued.

For spherical particles, studies have indicated that the adhesion ability will be enhanced by raising the surface density of receptors and ligands as well as the growth of the affinity coefficient (Decuzzi & Ferrari, 2006). Maul et al. (2010) introduced the optimization of ultrasound contrast agents using a numerical model for the blood vessels to determine a method for a better selection of ligand and adhesion ability. The values considered in their numerical model are listed in the Supplementary Table 4.

In a TDD system by magnetic NPs-coated nano-microcarriers, the drugs are loaded inside the nano-microcarriers and injected into the artery. The nano-microcarriers will then migrate to the plaque site by the blood circulation. The external forces can cause transverse movements in the nano-microcarriers. These forces perform as follows: ultrasound force pushes the nano-microcarriers toward the target site while the magnetic force absorbs them to the target site due to the presence of the magnetic NPs on the nano-microcarriers. The effective interaction of these forces causes desirable direction along with the blood flow. The presence of antibodies on the nano-microcarriers will facilitate their adhesion to the target wall. Ultrasound treatment provides the cavitation process of the nano-microcarriers; thus, their drug content will be released. Higher and better guidance of the nano-microcarriers to the disease site by the two external forces will result in the small transfer of the released drug to the artery downstream with the blood circulation (Figure 2(a)) (Shamloo et al., 2020; Wang, Searle, et al., 2018).

### 2.8. Mesh study and solution dependence to time

In the present study, Laminar Flow module, Magnetic Fields (No Currents module), Pressure Acoustics (Frequency Domain module), and Particle Tracing for Fluid Flow module were used to simulate the motion of the magnetic NPs-coated nanoliposomes and MBs inside the carotid artery under magnetic and ultrasound fields. To assess the mesh-independence of the mentioned modules, the simulation results were obtained for One Magnet and FUS transducer for several number of elements (Supplementary Table 5). According to this table, for number of elements above \( \sim 500889 \), the difference in the results of the three mentioned modules was less than \( \sim 3\% \). Besides, a mesh quality study was performed to ensure that poor element quality will not affect the outcomes. For this goal, Skewness mesh quality measurement was applied to the different meshes of this study. This measurement gives us a criterion of how the angles of a real element differ from the ideal element. By applying this measurement to our meshes, we find that the average element quality in our study is good enough not to have a significant impact on our final results. For example, this value was calculated as \( \sim 0.9535 \) for the ultrasound part mesh. Moreover, it is worth mentioning that the ideal number for the average element quality is 1. Thus, to decrease the costs and time, the mentioned number of elements was chosen. To explore the time-independence of the simulation results, the simulations were carried out in five cardiac cycles. It was observed that the difference in the results of the fourth and fifth cycles was less than 1% relative to the third cardiac cycle, indicating that three cardiac cycles are a proper choice to avoid the initial conditions of the modeling.

### 2.9. Validation

The particle tracking and deposition within a Y-shaped single branch tube were experimentally and theoretically assessed for various particle diameters and flow rates by Kim et al. (1989). To verify the fluid flow and particle tracking solutions in this study, a geometry similar to that of Kim et al. (1989) was considered. As shown in Supplementary Figure 2(a) \( L_1 = 10 \text{cm}, L_2 = 5 \text{cm}, a = 0.5 \text{cm}, b = 0.4 \text{cm}, \text{and} \theta = 37.5^\circ \). The laminar airflow entered the inlet boundaries with a density of \( \sim 1.78 \text{kg/m}^3 \) and viscosity of \( \sim 1.78 \times 10^{-5} \text{Pa.s} \) in flow rates of \( \sim 4, \sim 8, \) and \( \sim 12 \text{L/min} \). The boundary conditions of the outlets and walls were exit pressure and no-slip, respectively. The velocity profile in flow rate of \( \sim 8 \text{L/min} \) is depicted in Supplementary Figure 2(a). Particles with a density of \( \sim 5230 \text{kg/m}^3 \) and diameters of \( \sim 3, \sim 5, \) and \( \sim 7 \mu\text{m} \) were selected for simulation. In each simulation, \( \sim 1000 \)
particles were randomly released at the inlets, which moved toward the outlets (with the boundary condition of disappear) at sticky boundary conditions for the walls. The tracing of \( \sim 5 \mu m \)-diameter particles at \( t = 0.005s \) and 0.5 s was depicted in Supplementary Figure 2(b,c), respectively. As depicted in Supplementary Figure 2(c), a stagnation point exists in the particles’ trace bifurcation point. The presence of such a region can decrease the fluid velocity and hence induced particle decomposition in the bifurcation point. Some particles moving near the walls also stick to the tube walls due to their initial position and defined boundary conditions. In different flow rates, the particle decomposition percentage is shown in Supplementary Figure 2(c) for particles at various diameters. A proper agreement between the numerical results of the present study and experimental results of Kim et al. (1989) can be observed, indicating the validation of the present study and experimental results of Kim et al. (1989). The tracing of disappearance at sticky boundary conditions for the walls.

Nano-microcarriers experience the magnetic force due to the magnetic field applied by a permanent magnet. This force can influence the path of the drug-carriers and deviate them toward the atherosclerosis plaque at which the permanent magnet is placed. The magnetic flux density in the vicinity of the cubic magnet can be determined along the central axis of the permanent magnet by the equation proposed by Camacho and Sosa (2013):

\[
B(y) = \frac{\mu_0 M}{\pi} \left[ \arctan \frac{ab}{(y - c)\sqrt{a^2 + b^2 + (y - c)^2}} - \arctan \frac{ab}{(y + c)\sqrt{a^2 + b^2 + (y + c)^2}} \right]
\]  

(28)

In which, \( \mu_0 M \) shows the magnetization and \( a, b, \) and \( c \) denote the dimensions of the permanent magnet. Manshadi et al. (2018) modeled the distribution of magnetic field around a permanent magnet with \( B_{rem} = 0.8(T) \) whose dimensions are depicted in Supplementary Figure 3(a). In their study, the value of \( a \) was considered 3 mm based on Equation (28). Here, a permanent magnet with characteristics similar to that of Manshadi et al. (2018) was modeled and the results are presented in Supplementary Figure 3(b,c). The magnetic flux density in the form of a diagram is also illustrated in Supplementary Figure 3(c) compared with theoretical relationship (Equation (28)) considering \( \mu_0 M = (0.87 \pm 0.07 \, (T)) \). A proper agreement between distribution of magnetic field around the permanent magnet obtained in this study with previous numerical study and the theoretical relationship presented by Camacho and Sosa (2013) verified the proposed solution.

Acoustic pressure profiles of average transducer power value of each transducer are shown in Supplementary Figure 4. As shown in this figure the results are in good agreement with the reported pressure profile by Haddadi and Ahmadian (2018). To better validating the results, values of maximum pressure at focal zone are demonstrated and compared with the same data reported by Haddadi and Ahmadian (2018) in Supplementary Figure 4. This figure shows that the obtained pressure can follow the results of Haddadi and Ahmadian (2018). Noting that the sound pressure and velocity depends on the inherent characteristics of the source, each transducer generates different ARFs and streaming forces. Thus, it is not possible to validate the exact values of these forces with the past studies. However, the distribution and direction of ARF and acoustic streaming force can be compared with those reported by Rudenko et al. (1996) and Slama et al. (2019), respectively.

3. Results and discussions

The use of external fields to enhance TDD via nano-microcarriers to atherosclerotic plaques has recently received attention as a potential therapeutic method (Beguin et al., 2019; Duan et al., 2016; Gao et al., 2016; Owen et al., 2018). Investigation of the delivery performance of nano-microcarriers based on their adhesion to the target walls under the external fields requires examination of the various parameters such as type and size of nano-microcarriers and mode, magnitude, and direction of the external fields. Clinical and experimental optimization of the mentioned parameters for better drug delivery to atherosclerotic plaques is difficult and time-consuming due to the complexity and limitations imposed by the physiological and pathophysiological environments in the human body. Herein we set out to develop a computational model as a powerful tool for the investigation of these parameters considering the (patho)physiological conditions of the patient body. In the present research, the drug delivery performance of nano-microcarriers to the atherosclerotic plaque in a carotid artery was investigated under magnetic and ultrasound fields in terms of the carrier adhesion by ligand–receptor binding. To this end, first, the fluid flow inside a carotid artery was examined by the entrance of pulsed blood flow. As expected, the results indicated that the highest blood flow velocity occurs in the stenosis region followed by recirculations as were also reported in the experimental and numerical studies on the fluid flow within carotid atherosclerosis (Biglarian et al., 2020; Kaaeinpour-Mofrad et al., 2005; Manzoori et al., 2020; Razavi et al., 2011). Next, the influence of external magnetic field was investigated at different
Figure 3. The velocity values of blood flow in a cardiac cycle and the velocity profile in the simulation domain for the carotid artery with atherosclerosis in (a) The first peak of the velocity, \( t = 2.31 \) s, (b) minimum velocity \( t = 2.50 \) s, and (c) The second peak of the velocity \( t = 2.62 \) s. When blood flows upstream of the plaque with the highest velocity in the first peak (a), in addition to over-increasing the blood velocity in the disease site downstream will cause some vortices around the plaque. The vortices at the back of the plaque will extend by the decrease of the blood velocity (b). With the re-increase of the velocity in the second peak, the high-velocity region around the plaque will be enhanced which decreases the vortices.

location, arrangement, and strength of the permanent magnets. Finally, the effect of the ultrasound field was investigated inside the artery using two common transducers at various powers.

3.1. Fluid flow, magnetic field, and ultrasound field

The present study investigates the adhesion of nanomicrocarriers to the carotid atherosclerosis plaque under the magnetic and ultrasound fields. Previous studies have shown that the motion of the particles in the artery under the influence of external fields depends on the blood flow pattern within the artery, the magnitude and direction of the magnetic field, and the ultrasound field pattern (Kayal et al., 2011; Owen et al., 2015). Here, the fluid flow within the carotid artery is briefly described, then the fields generated as a result of permanent magnet and ultrasound transducer will be analyzed.

The blood flow streamlines inside a clogged carotid artery are shown in Figure 3 at three different times in the cardiac cycle, namely related to the highest inlet flow velocity in the first peak (Figure 3(a)), the lowest inlet flow velocity (Figure 3(b)), and the highest inlet flow velocity in the second peak (Figure 3(c)). As expected, the highest flow velocity occurred at the clogged section. Additionally, vortices can be seen immediately after the plaque, which is more abundant at the maximum inlet velocity of the first peak and minimum inlet velocity.

The effects of the size, location, and arrangement of the magnets were also assessed on the performance of drug delivery to plaque using nano-microcarriers. The magnetic flux density patterns (whose colors are proportional to the field magnitude) are shown in Figure 4 along with the magnetic force along y-direction on nanoliposomes (\( \sim 200 \) nm) using One Magnet and Halbach arrangement. The results for the other sizes, locations, and arrangements are depicted in Supplementary Figures 5–7. It should be mentioned that the magnetic force along y-direction on MBs (\( \sim 2 \) \( \mu \)m) in different sizes, locations, and arrangements of magnets are similar in pattern with nanoliposomes (\( \sim 200 \) nm). According to Equation (12), the magnitude of the magnetic force is found to be proportional to the cube of the diameter of the particle, so the force on MBs (\( \sim 2 \) \( \mu \)m) was \( 10^3 \) times higher than the force experienced by nanoliposomes (\( \sim 200 \) nm). As suggested in Figure 4(a) and Supplementary Figures 5–7, the changes in the size, location, and arrangement of the magnets drastically affected
the direction and magnitude of magnetic flux density inside the artery. As a result, based on Figure 4(b), the magnitude and domain (domain refers to an area where the magnitude of the magnetic flux density is high) of the applied force also changed by varying from One Magnet to Halbach arrangement. The maximum force enhancement in the Halbach arrangement was 6-fold higher than that with the One Magnet. An increase in the magnet height enhanced the magnitude of force applied to the nano-microcarriers, but the force application domain was not affected. By increasing the length of the magnet, the force application domain was increased, but no significant change was observed in the magnitude of applied force (Supplementary Figure 5). The longitudinal displacement of the magnet, although not changing the magnitude of the magnetic field, can dramatically alter the force application site (Supplementary Figure 6) which can affect the adhesion of nano-microcarriers to the plaque. Simulation results indicated that the change in the magnet angle (One Magnet-45°) significantly altered the magnitude and direction of the force as well as the force application domain. The use of the Two Magnet-45° arrangement increased the magnitude and domain of the force application at the stenosis site. The 3Up arrangement also improved the domain of the applied force at the stenosis site; however, it had a lower force magnitude compared to the Two Magnet-45° arrangement. By changing the arrangement of the magnets to Down–Up-Down, the stenosis region was less engaged with the domain of applied force (Supplementary Figure 7).

The ultrasound pressure and acoustic radiation force (ARF) determined from the Helmholtz equation (Equation (16)) in a carotid artery are shown in Figure 5 for a mean sound, i.e. 20 W for the disk transducer and 45 W for the FUS transducer. The results for the other powers are depicted in Supplementary Figure 8. As reported in Figure 5(a), the disk transducer created compressive fronts throughout the domain, but the FUS transducer concentrated the ultrasound energy in the focal region. This means that ARF produced by the disk transducer will influence a larger area of the artery while the maximum ARF of the FUS transducer is 5 times higher than that of the disk transducer at the
mean sound energy (Figure 5(b)). By changing the nano-microcarriers’ radius from $\sim 200$ nm to $\sim 2 \mu m$, the maximum acoustic radiation force showed a 1000-fold enhancement (see Equation (19)).

### 3.2. The delivery efficiency of nano-microcarriers under magnetic field

In this section, the surface density of nanoliposomes and MBs with various diameters adhered to the plaque is investigated by ligand–receptor binding under an external magnetic field from permanent magnets with different sizes, locations, and arrangements. The surface density patterns of nanoliposomes ($\sim 200$ nm) and MBs ($\sim 2 \mu m$) adhered to the plaque are shown in Figure 6 for various sizes, locations, and arrangements of the magnets. In the case of nanoliposomes, the presence of magnetic field from One Magnet enhanced the surface density of nanoliposomes adhered to the plaque by $\sim 12\%$ as compared to the absence of magnetic field. By increasing the height of magnet from $\sim 15$ mm to $\sim 20$ and $\sim 30$ mm, the surface density of nanoliposomes adhered to the plaque showed $\sim 16\%$ and $\sim 28\%$ enhancements, respectively. Moreover, the length increase from $\sim 15$ mm to $\sim 20$ and $\sim 30$ mm increased the surface density of nanoliposomes adhered to the plaque by approximately $\sim 46\%$ and $\sim 51\%$, respectively. Simulation of the motion of magnetic NPs-coated nanoliposomes and MBs under the magnetic field indicated an increase in the adhesion of nano-microcarrier to the plaque by increasing the magnet size. This phenomenon was also observed in the numerical study by Manshadi et al. (2018) on the delivery of magnetic particles at different flow rates. However, the results of the present study revealed that the increase in the length of the magnet can cause a more significant effect on the drug delivery by nano-microcarriers compared to that with magnet height variations. The reason could be the increase in the magnetic force domain in the stenosis region (Supplementary Figure 5).

Longitudinal displacement of the magnet along the artery by $\sim 5$ mm opposite to the blood flow direction increased the surface density of nanoliposomes adhered to the plaque. This phenomenon can be assigned to the deviation of the magnetic NPs-coated nano-microcarriers toward the plaque before reaching the stenosis region; they will eventually collide with the plaque by the drag force due to the fluid flow, which can
Figure 6. The effect of (a) increase of the size of the magnet along with the length and height, (b) displacement of the One Magnet along the longitudinal direction relative to the atherosclerosis plaque position and (c) various arrangements of magnets on the surface density of (i) nanoliposomes (200 nm) and (ii) MBs (2 μm) adhered to the plaque. The presence of the magnet enhanced the surface density of the nano-microcarriers adhered to the plaque. As the increase of the longitudinal size of the magnet will engage a larger part of the disease site to the magnetic field in y-direction, it causes more increase on the surface density of nano-microcarriers adhered to the plaque compared to the height enlargement of the magnet. The effect of the longitudinal displacement of the magnet on the surface density of nano-microcarriers adhered to the plaque depends on the direction of displacement. Various magnet arrangements caused different impacts on the surface density of nano-microcarriers adhered to the plaque.
Figure 7. (a) The effect of the magnetic field (Halbach arrangement) on the surface density of (i) Nanoliposomes with diameters of 100, 200, 400, and 800 nm and (ii) MBs with diameters of 1, 2, 3, and 4 μm adhered to the plaque. The adhesion of nano-microcarriers improved by their enlargement. In the case of carriers with the same diameter, an external magnetic force also enhanced the surface density of nano-microcarriers adhered to the plaque. The effect of (b) Disk transducer and (c) FUS transducer at various powers on the surface density of (i) Nanoliposomes (200 nm) and (ii) MBs (2 μm) adhered to the plaque. An external ultrasound field enhanced the surface density of the nano-microcarriers adhered to the plaque as compared with the case lacking ultrasound field. The increase in the power of the transducers increased the adhesion of the nano-microcarriers as higher pressure will be exerted along y-direction.
enhance their adhesion to the plaque. If the magnet location was altered along the flow direction or is farther from the plaque opposite the flow direction, the effectiveness of the magnet will severely decrease, which will decrease the drug delivery performance. While the results showed that by moving the magnetic source ~5 mm and ~10 mm toward the direction of the blood flow, the surface density of nanoliposomes adhered to the plaque decreased, and the same scenario occurred with ~10 mm of movement through the opposite direction.

Simulation results showed that the Down–Up–Down arrangement of the magnet decreased the surface density of nanoliposomes adhered to the plaque by ~13% as compared with the One Magnet. However, the 3Up arrangement enhanced the surface density of nanoliposomes adhered to the plaque by ~50% as compared with the One Magnet. The 45° change in the magnet angle for One Magnet-45° and two adjacent magnets (Two Magnet-45° arrangement) enhanced the surface density of nanoliposomes adhered to the plaque by ~7% and ~78%, respectively (Figure 6). Halbach arrangement increased the surface density of nanoliposomes adhered to the plaque by ~96% as compared with the One Magnet. The trend of variations in the surface density of MBs (~2 μm) adhered to the plaque in various sizes, locations, and arrangements of magnets were similar to that of the nanoliposomes (~200 nm). Various arrangements of the magnets can dramatically alter the magnitude and direction of the magnetic field applied to the stenosis (Supplementary Figure 7). Such alteration can significantly influence the force experienced by the nano-microcarriers; hence affecting their adhesion to the plaque. The simulation results indicated that the drug delivery performance of the magnetic NPs-coated nano-microcarriers would be enhanced upon using Halbach arrangement and One Magnet-45° as compared with the One Magnet. Previous numerical and experimental studies on TDD by One Magnet-45° (de Saint Victor et al., 2019) and Halbach arrangement (Beguin et al., 2019) exhibited a increasing in the drug delivery performance. In the present study, several magnet arrangements were addressed to optimize how they are placed next to each other to achieve the highest efficiency for drug delivery to the plaque using nano-microcarriers. The simulation results indicated that the Halbach arrangement would result in the best performance for drug delivery for three adjacent magnets compared to the 3Up and Down–Up–Down arrangements. Contrary to the Down–Up–Down arrangement, the 3Up arrangement can positively affect the surface density of nano-microcarriers adhered to the plaque. The change in the magnet angle to 45° (One Magnet-45°) can significantly improve the drug delivery performance compared with One Magnet. Moreover, the use of two adjacent magnets at the angle of 45° (Two Magnet-45° arrangement) exhibited better adhesion of nano-microcarriers to the plaque when compared with the three-magnet arrangement of 3Up. At all, the Halbach arrangement exhibited the best drug delivery performance for three magnets, while Two Magnet-45° arrangement and One Magnet-45° displayed the best drug delivery efficiencies for the two- and one-magnet cases, respectively.

The surface density distributions of nanoliposomes and MBs with various diameters adhered to the plaque are shown in Figure 7(a) at the presence of Halbach arrangement and the absence of magnet. The increase in the surface density of nanoliposomes adhered to the plaque at the presence of magnetic field was ~134%, ~59%, ~46%, and ~41% for the nanoliposome diameters of ~100, ~200, ~400, and ~800 nm, respectively, for the case of MBs with diameters of ~1, ~2, ~3, and ~4 μm, the increase in the surface density of MBs adhered to the plaque at the presence of magnetic field was ~112%, ~93%, ~66%, and ~55%, respectively.

Investigation of the TDD by nanoliposomes and MBs with different diameters indicated that the effectiveness of the magnet on the adhesion of carriers to the plaque decreased with increasing the diameter. However, the magnetic field positively influenced the adhesion of nano-microcarriers at all diameters. The decreasing effectiveness of the magnetic field by enlarging the particle diameter was also observed in an experimental study by Shamsi et al. (2018) considering the particle delivery to the cancer cells. In our previous study (Shamloo et al., 2019), targeted drug delivery to atherosclerosis site was investigated by the use of magnetic NPs in which a point magnetic field was equally applied throughout the coronary artery. It was observed that at elevated diameters of magnetic NPs, the magnetic field negatively affected the delivery of magnetic NPs to the target site. Here, arrangement of permanent magnets with maximum magnetic field generation (Halbach arrangement) was used, which is close to the real physiological conditions and in vivo assessment, hence dramatically affecting the results.

3.3. The delivery efficiency of nano-microcarriers under ultrasound field

The ultrasound force can push the nano-microcarriers toward the target site; this capability can be exploited in targeted drug delivery. In this section, the surface density of nanoliposomes and MBs with various diameters adhered to the plaque is investigated under the ultrasound fields. The surface density of nanoliposomes
augmentation was liposomes (∼FUS transducer, an increase in the transducer power from 30, 40, and 60 W) are shown in Figure 7(b,c). For both types of transducers, the surface density of nanoliposomes and MBs adhered to the plaque exhibited a dramatic increase in the presence of ultrasound fields. In the case of disk transducer with the lowest power (∼10 W), the surface density of nanoliposomes (∼200 nm) and MBs (∼2 μm) adhered to the plaque increased by ∼28% and ∼25% compared to the case without the ultrasound fields, respectively. This increase was ∼18% and ∼12% for the case of the FUS transducer with the lowest power (∼30 W) for the same nanoliposomes and MBs, respectively. The simulation of the motion of nano-microcarriers within the carotid artery under the ultrasound fields indicated that the surface density of nanoliposomes (∼200 nm) adhered to the plaque by ∼14% and ∼22% when the disk transducer power was increased from ∼10 W to ∼20 W and ∼30 W, respectively. This increase was ∼9% and ∼25% in the case of MBs (∼2 μm). For the case of the FUS transducer, a increase in the transducer power from ∼30 W to ∼45 W and 60 W increased the surface density of nanoliposomes (∼200 nm) adhered to the plaque by ∼21% and ∼42%; for the case of MBs (∼2 μm), this augmentation was ∼13% and ∼41%, respectively.

Next, we examined the surface densities of nanoliposomes (∼100−800 nm) and MBs (∼1−4 μm) adhered to the plaque in absence and presence of ultrasound field (FUS transducer-60 W) (see Figure 8). Simulation results demonstrated an increase in the surface density of nanoliposomes and MBs with various diameters adhered to the plaque at the presence of ultrasound field. The increase in the surface density of nanoliposomes with diameters of ∼100 nm, ∼200 nm, ∼400 nm, and ∼800 nm adhered to the plaque at the presence of ultrasound field was ∼86%, ∼65%, ∼56%, and ∼47%, respectively. This increase was ∼75%, ∼58%, ∼48%, and ∼40% for the MBs with diameters of ∼1 μm, ∼2 μm, ∼3 μm, and ∼4 μm, respectively.

A main goal of this study was to evaluate the use of ultrasound field for targeted drug delivery of nano-microcarriers to the atherosclerotic plaque as a potential therapeutic solution. Simulation of the motion of the nano-microcarriers under the ultrasound field revealed that the use of ultrasound field can significantly enhance the adhesion of the drug carriers to the plaque, thus, promising to improve targeted drug delivery to the patients suffering from carotid artery disease. Moreover, ultrasound field is compatible with the body. Our results indicated that an increase in the power of both transducers (disk transducer and FUS transducer) increased the adhesion of nano-microcarriers to the plaque. This increase was not linear, i.e. the increase in the transducer power did not cause the same increase in the drug delivery efficiency. At very high powers, the drug delivery performance did not exhibit a significant alteration. It was observed that the FUS transducer with the power of ∼60 W led to the highest impact on the delivery of nano-microcarriers to the atherosclerotic plaque. However, the performance of the disk transducer was considerable at lower powers as compared to the FUS transducer, possibly because the relatively wider domain of the applied pressure from the disk transducer to the plaque region of the carotid artery (Figure 5). By increasing the diameter of nanoliposomes and MBs, the ultrasound field positively influenced the drug delivery performance at all carrier diameters. However, the larger the diameter of the nano-microcarriers, the lower the extent of the positive impact of ultrasound field on the carrier adhesion to the plaque.

3.4. The delivery efficiency of nano-microcarriers under magnetic and ultrasound field

Two magnetic and ultrasound forces were simultaneously applied to nano-microcarriers to investigate the surface density of nanoliposomes and MBs adhered to the plaque. The surface densities of nanoliposomes (∼200 nm) and MBs (∼2 μm) adhered to the plaque are presented in Figure 8(b) for four states: without external field, at the presence of magnetic field (Halbach arrangement), at the presence of ultrasound field (FUS transducer-60 W), and at the simultaneous presence of magnetic and ultrasound fields. Compared to the case without external fields, the simultaneous application of magnetic and ultrasound fields increased the surface density of nanoliposomes (∼200 nm) and MBs (∼2 μm) adhered to the plaque by ∼148% and ∼121%, respectively. The presence of magnetic field alone increased the surface density of nanoliposomes (∼200 nm) and MBs (∼2 μm) adhered to the plaque by ∼148% and ∼121%, respectively. The presence of magnetic field alone increased the surface density of nanoliposomes (∼200 nm) and MBs (∼2 μm) adhered to the plaque by ∼148% and ∼121%, respectively. The presence of the ultrasound field alone caused ∼67% and ∼58% increase in the surface density of nanoliposomes (∼200 nm) and MBs (∼2 μm) adhered to the plaque, respectively. It was observed that the simultaneous use of magnetic and ultrasound fields synergistically increased the targeted drug delivery (TDD) to atherosclerotic plaque. Examination of the performance of each field indicated that the magnetic field generated by the Halbach arrangement presented the highest impact on the delivery of drug carriers. This arrangement, in comparison to the most efficient ultrasound transducer (FUS transducer at the
Figure 8. (a) The effect of the ultrasound field (FUS transducer-60 W) on the surface density of (i) Nanoliposomes with diameters of 100, 200, 400, and 800 nm and (ii) MBs with diameters of 1, 2, 3, and 4 μm adhered to the plaque. The increase in the carrier diameter and presence of ultrasound field can improve the adhesion of the nano-microcarriers to the plaque. (b) Co-application of two external forces on nano-microcarriers. The surface density of (i) Nanoliposomes (200 nm) and (ii) MBs (2 μm) without any external field, as the presence of magnetic field (Halbach arrangement), at the presence of ultrasound field (FUS transducer-60 W) and at the simultaneous presence of magnetic and ultrasound fields adhered to the plaque. The rate of the increase in the surface density of the nano-microcarriers adhered to the plaque was higher in the presence of the magnetic field, when compared with the presence of the ultrasound field. The co-application of the two fields caused the highest surface density of the nano-microcarriers adhered to the plaque.

3.5. Limitations and future works

The present study has several limitations. First, the geometry of the carotid atherosclerosis plaque is 2D. In this research, the delivery of nano-microcarriers at various diameters to the plaque was investigated. Moreover, different sizes, locations, and arrangements of magnets, as well as ultrasound transducers with diverse powers were considered to optimize their impact on the TDD. Thus, numerous simulation runs were conducted. Additionally, consideration of the airbox and body tissue around the artery (to avoid the adverse impact of the boundary conditions) substantially enhanced the number of elements and prolonged the simulation time. In this regard, using three-dimensional geometry will be highly time-consuming and costly or even impossible. Therefore, a 2D model was considered. Based on the previous studies, 2D geometries can offer an acceptable accuracy and broaden our insight on the TDD to the atherosclerosis plaque (Lunnoo & Puangmali, 2015; Manshadi et al., 2018). Secondly, two types of drug carriers (nanoliposomes and MBs) were considered to investigate the TDD to the carotid atherosclerosis plaque under magnetic and
ultrasound fields. Other drug carriers such as gold, SiO\textsubscript{2}, Fe\textsubscript{3}O\textsubscript{4}, and silver with various densities and properties have been employed in the drug delivery application (Amani et al., 2021), whose performance should be explored under the magnetic and ultrasound fields. In this research, N52 permanent magnet was applied to evaluate the influence of the magnetic field on the delivery of nano-microcarriers to the target site. Some studies, however, have revealed that the force generated by electromagnetic field can also improve drug delivery performance (Dames et al., 2007; de Saint Victor, 2016). This issue should also be addressed in the delivery of nanoliposomes and MBs to the plaque in future studies.

4. Conclusions

In our previous studies, we used numerical simulation for investigating different biological phenomena (Ebrahimi et al., 2021; Forouzandehmehr & Shamloo, 2018; Shamloo, Manuchehrifar, et al., 2015; Shamloo, Mohammadaliha, et al., 2015; Shamloo et al., 2016, 2017, 2019). In this study, the drug delivery performance of magnetic nanoparticles (NPs)-coated nanoliposomes and microbubbles (MBs) by ligand–receptor binding to the carotid atherosclerotic plaque was investigated under isolated and combined external magnetic and ultrasound fields. Our simulations revealed that the increase in the length of the magnet and changing its location opposite to the fluid flow direction can enhance the drug delivery performance of the nano-microcarriers to the plaque. It was also observed that the three-, two-, and one-magnet arrangements will exhibit the best performance in respective arrangements of Halbach, Two Magnet-45°, and One Magnet-45°. Moreover, a focused ultrasound (FUS) transducer at the power of 60 W offered the best drug delivery efficiency. The results, however, indicated the most significant effect of the disk transducer in the delivery of nano-microcarriers to the plaque was obtained at lower powers. The increase in the diameter of the nano-microcarriers decreased the positive influence of the magnetic and ultrasound fields on the drug delivery to plaque. The influence of the magnetic field on the delivery of nano-microcarriers to the plaque was higher than the impact of the ultrasound field. Finally, the simultaneous employment of magnetic and ultrasound fields will markedly facilitate the adhesion of nano-microcarriers to the plaque, and hence this combined mode is recommended for enhanced targeted drug delivery to the atherosclerotic plaque site.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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