Int. J. Nano Dimens., 15 (1): 80-92, Winter 2024

ORIGINAL ARTICLE

A method for macromolecule transport to the spinal cord nervous system trauma with a combination of ultrasound and magnetic fields

*Fatemeh Mokhtari [1], Majid Pouladian *[1] , Amir Shamloo [2]*

[1] *Department of Biomedical Engineering, Science and Research Branch, Islamic Azad University, Tehran, Iran*

[2] *Department of Mechanical Engineering, Sharif University of Technology, Tehran, Iran*

Received 14 September 2023, revised 19 October 2023, accepted 26 October 2023, available online 02 Novemberber 2023

Abstract

Damage to the central nervous system causes severe consequences for patients and increases medical costs. In spinal cord injuries, due to sensitive nerves, there is a need for a high-precision and non-invasive method to transfer macromolecules to the damaged area of the spinal cord for nerve repair. The main objective of this study is a high-impact strategy for optimal delivery of macromolecules to spinal cord injuries using ultrasound and magnetic fields. Several permanent magnets and transducers of ultrasound waves with different arrangements, sizes, and angles are used. Their effect on the efficiency of delivering macromolecules to the target area is analyzed. The results determined that utilizing three or four magnets along with the transducer of ultrasound waves could have a precise performance in the delivery of macromolecules. Advances in combining ultrasound and magnetic fields in delivering macromolecules to the target area are associated with increased efficiency and accuracy. The interaction between ultrasound and magnetic forces balances the rotation of macromolecules and their useful movement toward the destination.

Keywords: *Central Nervous System; Delivery; Magnet; Spinal Cord ; Ultrasound.*

How to cite this article

Mokhtari F., Pouladian M., Shamloo A., A method for macromolecule transport to the spinal cord nervous system trauma with a combination of ultrasound and magnetic fields. Int. J. Nano Dimens., 2024; 15(1): 80-92.

INTRODUCTION

Magnetic macromolecules have unique properties that differ from other types of macromolecules developed and have particular advantages for medical applications with magnetic properties. The importance of delivery of macromolecules, including drugs, stem cells, etc., for treating many diseases has increased in recent years. Physicochemical and biological barriers, macromolecule delivery routes, formulation, dynamic issues, and cell culture models used in macromolecule delivery are topics that make macromolecule delivery an exciting field for researchers [1]. In research, the dynamic model of the movement of particles by magnetic field in three-dimensional vascular networks has been investigated by simulation and in vivo.

Based on this model, a stochastic magnetic conduction method with a time-varying gradient can control the particles well. Also, the numerical model of the movement of heterogeneous flows in three-dimensional vascular networks has been simulated [2].

In research for Amyotrophic Lateral Sclerosis (ALS), a drug delivery method with ultrasound was presented. The motor performance of the animals was evaluated after drug delivery. Focused ultrasound with microbubbles can deliver specific molecules temporarily. The results show that targeting cells using ultrasound to improve spinal cord functions can be a rational therapeutic strategy for this debilitating disorder [3].

The non-invasive method of irradiating ultrasound waves to the tumor destroys tumor cells due to the increase in temperature and

* Corresponding Author Email: *pouladian@srbiau.ac.ir*

mechanical pressure. Depending on the type and structure of the tumor, the waves can be changed to increase the effectiveness of the treatment. Also, nanomedicines can be transferred to the exact location of the tumor by ultrasound waves. Advances and limitations in the delivery of nanomedicines for cancer treatment with ultrasound waves determined in previous research [4].

In another study, magnetic nanoparticles were coated with paclitaxel and polyethylene glycol. Then, they were guided by the magnetic field so that the paclitaxel drug reaches the target point. Magnetic nanoparticles were made by laser with different wavelength characteristics. This method makes it possible to prepare nanoparticles with the desired size and shape. This research was carried out in animal experiments on mice and has had significant results in improving the treatment of tumors [5].

Methods to control drug release can improve therapeutic effects. Microparticles and nanoparticles can work well in drug transport and release mechanisms. Magnetic nanoparticles surround the drugs and are guided by changes in the magnetic field. There are numerous ways to transport drugs, such as ultrasound, light, radio frequency, electric, and magnetic fields. These techniques remain under laboratory conditions due to various challenges, including safety [6].

In research, colon cancer cells are exposed to pulsed ultrasound field combined with a magnetic field. In this approach, the efficiency of drug delivery to the target area increased by 40%. By applying mechanical and electrical stimuli, the improvement of cancer cells was observed. Mechanical and electrical waves cause changes in the stability and permeability of the cell membrane, which can inhibit cancer cells [7].

In a study, drug transfer to the anterior and posterior parts of the eye was investigated. In this method, ultrasound waves were used to transfer eye medicine. This method was examined anatomically and physiologically, and the fundamental aspects of ultrasound physics related to drug delivery were discussed. This method is more effective than the standard methods of ocular drug delivery [8].

In a study, hollow magnets were applied for macromolecule transfer. Hollow magnets with high surface area and large pore size can perform better in absorbing magnetic nanoparticles. These magnets have a low density and perform magnetic separation better than ordinary magnets. Synthesis of magnetic particles was analyzed and the efficiency of this procedure was calculated for various shapes and sizes of particles. The results show the improvement of the method compared to previous method [9].

In recent years, new, innovative and intelligent strategies have been presented for drug delivery. One of the methods is the use of polymers. Using polymers to make drug delivery scaffolds is easy and biocompatible and can be combined with different materials and drugs. To solve this problem, 3D printers were used to make synthetic polymers, but they are less biocompatible than natural polymers. This method has high flexibility in model making and is economical. Disadvantages of polymers include their low mechanical properties and their movement in fluid flow and porous media [10]. To improve the movement of drug-containing polymers in fluid and porous medium, the proposed method of this research can be used based on guidance with magnetic and ultrasound fields.

Electrospinning is a method for drug delivery. Among the advantages of using electrospun nanofibers in pharmaceuticals is the ability to encapsulate hydrophilic and hydrophobic agents. The porous structure of these nanofibers can accommodate drugs. These nanofibers have better mechanical properties and less side effects than polymers [11]. The combination of liposomes with cells is a professional method for drug delivery. The reactions of the combination are considered for safe drug delivery and effective treatment [12].

In a research, metal oxide nanoparticles were synthesized and used for drug delivery. The sol-gel method was used for the synthesis and celecoxib was delivered by magnetite nanoparticles. In this research, the amount of drug loading and release was analyzed. The results showed that the proposed method has a better performance in drug absorption and release than the previous methods [13].

In another study, a method was presented for the characterization of functionalized metal oxide nanoparticles. In this method, cerium oxide was used to functionalize magnetite nanoparticles. Nanoparticles prepared using dynamic light scattering techniques were used to deliver celecoxib. This research provided favorable results in the measurement of particle size and

the production of nanocomposites in the drug delivery system [14].

Development and research on nanostructures for targeted drug delivery and cellular interactions can help in improving the choice of drug delivery method with effective treatment. The combination of polymer, liposome and nanoparticle drug delivery methods with magnetic and ultrasound fields can increase accuracy and efficiency in the safe delivery of cells and drugs, which is addressed in this research. In this method, the movement of macromolecules in a fluid and porous medium is improved with the guidance of magnetic and ultrasound fields. In this method, various layouts of sharp tip magnets, and ultrasound transducers are analyzed. The research goal is a strategy desgin to improve the efficiency of the transfer of macromolecules.

MATERIALS AND METHODS

Model geometry

In this research, we considered the conduction of magnetic nanoparticles in the spine from the origin of the L4 vertebra to the L1 destination. Spinal cord injury is considered a circle with a radius of 0.1 mm in the area of the L1 vertebra. The human spine is almost cylindrical in the distance from the origin to the destination, and we considered this distance to be a complete cylinder with 20 mm length and, 0.5 mm width. Macromolecules can be stem cells or various drugs that are coated with iron magnetic nanoparticles. Macromolecules are magnetized by Fe_3O_4 particles, and after being injected into the white matter in L4, they are driven to the target site with the external magnetic and ultrasound field. The distance between the skin and the studied spine is 23 mm. A schematic of the studied geometry is shown in Fig. 1. The different number of sharp tip magnets and ultrasound transducer is used to guide magnetic macromolecules to the exact target site.

The current study uses permanent sharp tip magnets in different numbers and arrangements to deliver nano-microcarriers to the spinal cord injury site. Sharp magnets can produce a more concentrated magnetic field than ordinary magnets. In addition,two transducers are used to analyze the performance of the ultrasound field on the transport of macromolecules. Two Bowl-shaped focused ultrasound transducers with 90 degrees are located adjacent to the skin near the injection site. Focused bowl transducers with on-axis pressure push macromolecules toward the target. The Specifications of Bowl-shaped focused ultrasound transducers are 1 MHz resonance frequency, 30 mm bowl radius of curvature and, 30 mm bowl aperture diameter.

The different arrangement of the permanent sharp tip NdFeB magnet with a side of 0.7 mm is considered. The sharp tip magnets are embedded adjacent to the skin around the target location.

Dynamic model

The movement of macromolecules in the CSF fluid depends on the impact of external magnetic and ultrasound fields in the CSF fluid flow. Therefore, the effect of the magnetic and ultrasound fields on the CSF liquid is investigated.

To investigate how the macromolecules move towards the target, it is necessary to calculate the forces acting on it at every moment. The forces applied on a particle in the cerebrospinal fluid located in the spinal cord are given by [15]

$$\mathrm{Mp}\frac{\mathrm{dv}}{\mathrm{dt}} = \mathrm{F_{drag}} + \mathrm{F_{gravity}} + \mathrm{F_{lift}} + \mathrm{F_m} + \mathrm{F_{rad}} + \mathrm{F_{buoyancy}} + \mathrm{r} + \mathrm{d} \quad (1)$$

where F_{lift} is the hydrodynamic lift force, r is the random Brownian force, F_{drag} is the hydrodynamic drag force, fm is the magnetic force, mp is the particle mass, v is the particle velocity, F_{rad} is ultrasound force, $F_{buoyancy}$ is the buoyancy force, and d is the particle interaction forces.

The particle interaction force d can be neglected due to its smallness. Buoyancy and lifting force for less than micron- size particles are ignorable. Besides, the inertia of particles is very low and is negligible [16].

The gravity force is [17].

$$\mathrm{f_{gravity}} = -\mathrm{v_{particle}}(\rho_{\mathrm{particle}} - \rho_{\mathrm{fluid}})\mathrm{g}\hat{\mathrm{z}} \quad (2)$$

Where $\rho_{particle}$ is particle density, $v_{particle}$ is particle hydrodynamics volume, g is earth gravity with a value of 9.8 m/s2 and, , ρ_{fluid} is fluid density.

Gravity force in z coordination is considered.

Magnetic forces

Magnetic particles are microscopic in an external magnetic field, and act as point dipoles. Electromagnetic fields are given by Maxwell equations [18].

$$\nabla \times \vec{\mathrm{H}} = \vec{\mathrm{j}} \quad (3)$$

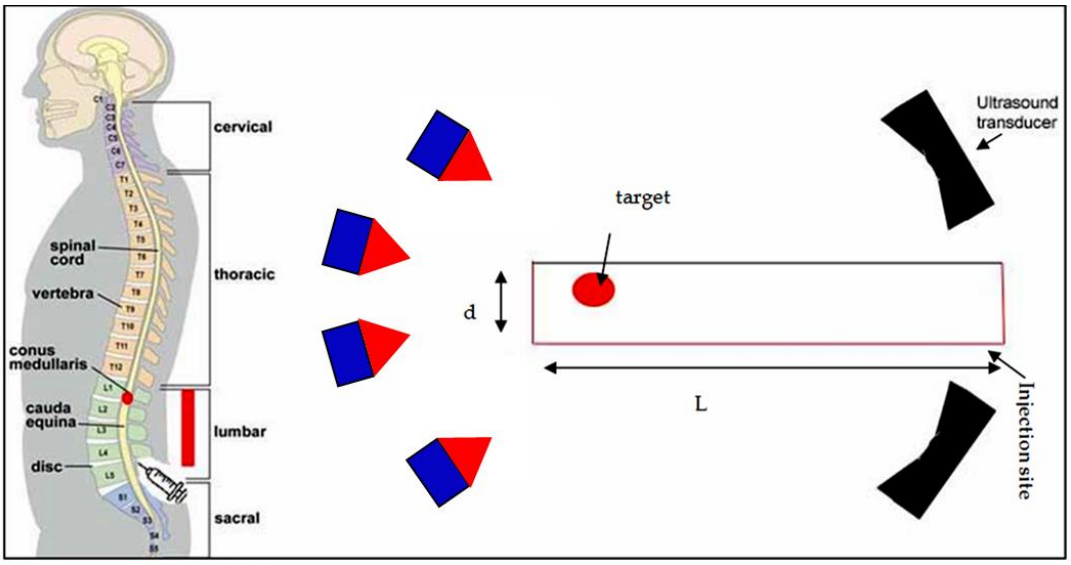


Fig. 1. A schematic of research geometry.

$$\nabla \times \vec{B} = 0 \quad (4)$$

$$\vec{B} = \mu_0(\vec{H} + \vec{M}) = \mu_0(\vec{H} + \chi\vec{H}) \quad (5)$$

Where j is the current density, M is the material magnetization, B is the magnetic field, H is the magnetic field intensity, μ_0 is the vacuum permeability, and χ is the magnetic susceptibility.

Magnetic force on a particle is defined as [19].

$$\overrightarrow{F_M} = \frac{4\pi a^3}{3}\frac{4\pi a^3}{(1+\chi/3)}[\frac{d\vec{H}}{d\vec{x}}]^T\vec{H} = \frac{2\pi a^3}{3}\frac{\mu_0\chi}{(1+\chi/3)}\nabla(|H|^2) \quad (6)$$

Where a is particle radius [m], ∇ is the gradient operator [1/m] and, T is matrix transpose. The force applied on the saturated particle is given by:

$$\overrightarrow{F_M} = \frac{4\pi a^3}{3}\frac{4\pi a^3}{(1+\chi/3)}[\frac{d\vec{H}}{d\vec{x}}]^T\vec{M}_{sat} \quad (7)$$

Where $\vec{M}_{sat}$ is the particle's saturated magnetization

The magnetic force applied to the volume of magnetic element is [20].

$$\overrightarrow{F_M} = \frac{2\pi a^3}{3}\frac{\mu_0\chi}{(1+\chi/3)}C\nabla(|H(x,y)|^2) \quad (8)$$

In the above equation, C is the particle concentration [number/m3].

Drag force

The drag force applied on a particle is given by [21]

$$F_{drag} = \frac{18\mu C_D Re}{24{d_p}^2\rho_p} \quad (9)$$

Here, d_p is particle diameter (m), ρ_p is the particle density (kg/m3), μ is fluid viscosity (Pa·s), and Re is the Reynolds number that is [22]:

$$Re = \frac{d_p\rho|u_p - u_f|}{\mu} \quad (10)$$

Where u_f is the velocity of the fluid, and u_p is the velocity of the particle.

Ultrasound force

An ultrasound field is needed to apply sound pressure to the macromolecules to drive them. The sound propagation equation is expressed by [23]:

$$\nabla.\left(-\frac{1}{\rho_c}\nabla p_c\right) - \frac{k_{eq}^2 p}{\rho_c} = 0 \quad (11)$$

Where *pc* is the ultrasound pressure, *ρc is* complex density. *keq* the equivalent wave number is given by:

$$k_{eq} = (\frac{w}{c} - i\alpha) \quad (12)$$

Where α is the attenuation coefficient, and c is the sound speed. In this research, the Bowl-Shaped Focused Ultrasound Transducer is considered. The position c, sphere center on the bowl lies is given by[24]:

$$C = \frac{r}{\|f-b\|}(f - b) + b \quad (13)$$

Where b is the position of the center of the bowl's rear surface, r is the radius of curvature of

the bowl, and f is the focus position.

Two Bowl-shaped focused ultrasound transducers with 1 MHz resonance frequency, 30 mm bowl radius of curvature, and 30 mm bowl aperture diameter are considered. Two Transducers with 90 degrees are located adjacent to the skin near the injection site.

Ultrasound power is known as sound radiation power and is obtained as follows:

$$F_{rad} = -\pi a^3 [\frac{2k_f}{3} Re(f1 p_c . \nabla p_c) - \rho Re(f2 v_c . \nabla v_c) \quad (14a)$$

$$f_1(\bar{k}) = 1 - \bar{k} \quad (14b)$$

$$f_2(\bar{\rho}, \bar{\delta}) = \frac{2[1-\Gamma(\bar{\delta})](\bar{\rho}-1)}{2\bar{\rho}+1-3\Gamma(\bar{\delta})} 1 - \bar{k} \quad (14c)$$

$$\Gamma(\bar{\delta}) = -\frac{3}{2}[1 + i(1+\bar{\delta})]\bar{\delta} \quad (14d)$$

$$\bar{k} = \frac{k_p}{k_f} \quad (14e)$$

$$\bar{\rho} = \frac{\rho_p}{\rho} \quad (14f)$$

$$\bar{\delta} = \frac{\delta}{a} \quad (14g)$$

k_f is the compressibility of fluid, k_p is compressibility of particles, δ is the viscous penetration depth of fluid, v_c is the ultrasound velocity, a is the radius of the particle, and ρ_p is the density of the particle.

Ultrasound waves in the fluid create a steady flow, which is expressed by the Navier-Stokes equation [25]:

$$F_{uf} = -\rho(v_c . \nabla)v_c + v_c(\nabla . v_c) \quad (15)$$

Where ***Fuf*** is the volume force vector. Ultrasound waves in the fluid in *y*–direction are minimal compared with those in the *x*–direction. So, force from Ultrasound waves in the *y*–direction of fluid is ignorable. So Equation (15) is simplified as :

$$F_x = \frac{2\alpha I}{c} \quad (16)$$

In the above equation, *x* is the propagation direction of ultrasound waves, and *I* is the magnitude of acoustic intensity per area.

Macromolecules Transport Equation

The transport of macromolecules through the cerebrospinal fluid is given by [16].

$$\frac{\partial}{\partial t} C(x,y,t) = -\nabla . [-D_{Tot} \nabla C + C\overrightarrow{V_C}(y) + CU] \quad (17)$$

Where $\overrightarrow{V_c}$ is the cerebrospinal fluid velocity, C is macromolecules concentration, and U is drift velocity:

$$U = \mu F \quad (18)$$

$$\mu F = F_m + F_{rad} + F_d + F_g + r \quad (19)$$

One dimension of the transport equation 17 is:

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial z}(D\frac{\partial c}{\partial z} - Uc) \quad (20)$$

The finite volume method is used to solve equation 20.

The macromolecule path from L4 to L1 in the spinal cord is considered a cylinder with length z. The length z is $z_l \le z \le z_r$, where z_l is in the L1 location, z_r is in the L4 location, and $U(z) = \mu F(z)$.

The FVM discretization of equation 20 is

$$c_i^{n+1} = c_i^n - \frac{\partial t}{\partial z}\left(P_{i+\frac{1}{2}} - P_{i-\frac{1}{2}}\right) \quad (i = 1,2,\dots,N_z) \quad (21)$$

the length of a cell is ∂z , and ith node concentration at time n,n+1 is c_i^n and c_i^{n+1} . $P_{i\mp 1/2}$ is particle flux at the end of the cell $z_{i\mp 1/2}$. Then

$$P_{i+\frac{1}{2}} = -[D\frac{c_i^{n+1} - c_i^n}{\partial z} - (\min(U_i, 0)\, c_i^n + \max(U_{i-1}, 0)\, c_{i-1}^n)] \quad (22)$$

Neumann boundary condition in z_r, and Dirichlet condition z_l are defined.

RESULTS AND DISCUSSIONS

In the present study, the transfer of macromolecule for repairing spinal cord injury by magnetic fields and ultrasound has been considered and discussed. Matlab and FEATool software are applied to solve the problem. The constants used for stimulation are shown in Table 1.

Performance determination of the macromolecule delivery techniques depends on the macromolecule's successful presence in the target site under external fields. It needs the analysis of different parameters, including the

Table 1. Simulation constants.

variable	value	units	
Particle density	7870	Kg/m^3	ρ_P
Number of particles	1000		
Particle Saturation magnetization	$4.78*10^5$	A/m	Msp
Flow viscosity	0.001	$N.sec/m^2$	μ
Flow density	0. 59	Kg/m^3	ρ
permeability of a vacuum	$4\pi*10^{-7}$	$^7N/A^2$	μ_0
Csf velocity	10	Mm/s	Vf
particle velocity	20	Mm/s	Vp
susceptibility of the fluid	0		χf
susceptibility of the particle	20		χp
Shear rate	10	s-1	$\dot{y}$
Solid fraction	40%		f
Spinal cord diameter	15	mm	d
White matter diameter	6	mm	
Distance between l1 to l4	20	mm	
Distance between spinal cord to the skin	30	mm	
k_B	$1.38*10^{-23}$	$M^2kgs^{-2}k^{-1}$	
Spinal cord in L1 diameter	7	mm	
wound diameter	0.1	mm	

mode, magnitude, external magnets direction, and ultrasound fields, to optimize the technique. Examining techniques by the experimental method of macromolecule delivery to the site of spinal cord injury is complex and not affordable. In this study, a macromolecule delivery technique with high efficiency is presented to be a tool to investigate these parameters considering human pathophysiological limitations.

Macromolecule delivery systems, such as drugs and stem cells, have the limitations of biological barriers and low accuracy in target detection. To overcome these shortcomings, in the present study, a non-invasive method is proposed that includes different sharp tip magnetic fields and ultrasound waves to deliver macromolecules into the spinal cord.

The location and arrangement of sharp tip magnets affect the speed of macromolecules. For macromolecule delivery optimization, the performance of different configurations of permanent sharp tip magnets and ultrasound transducers was evaluated.

Different arrangements for sharp tip magnets have been made in this modeling. In all these sharp tip magnet arrangements, two sound transducers are fixed at the beginning of the path at a 90-degree angle to each other, and their focus point is the target location.

Fig. 2 shows the magnetic fields of sharp tip magnets layout. In the Figures two transducers with 90 degree is considred in the beginning of the path adjucent the injection site.

Layout 1 uses only one sharp tip is placed above the target location, and its magnetic field is shown in Fig. 2a. Layout 2 has two sharp tip magnets at an angle of 180 degrees, and the target location is placed in the middle of these magnets. The poles of these two magnets are opposite each other. The magnetic field of this layout is shown in Fig. 2b. Layout 3 contains three sharp tip magnets with angles of 90 degrees that are placed in three directions of the injured site. All three magnetic pole directions are the same. The magnetic field of this Layout can be seen in Fig. 2c. Layout 4 also consists of three sharp tip magnets, which is like Layout 3, except that the adjacent magnets have opposite poles, and is shown in Fig. 2d. Layout 5 uses four sharp tip magnets that have an angle of 45 degrees and the target location is in the center of the intersection of the magnets. In this Layout, all magnets have the same pole and their magnetic field is shown in Fig. 2e.

Layout 6, like Layout 5, consists of four sharp tip magnets, but the adjacent magnets have opposite poles. The magnetic field of this Layout is shown in Fig. 2f.

Layout 7 also consists of four sharp tip magnets like Layout 5, but the first and last magnets have the same pole, and the two middle magnets have

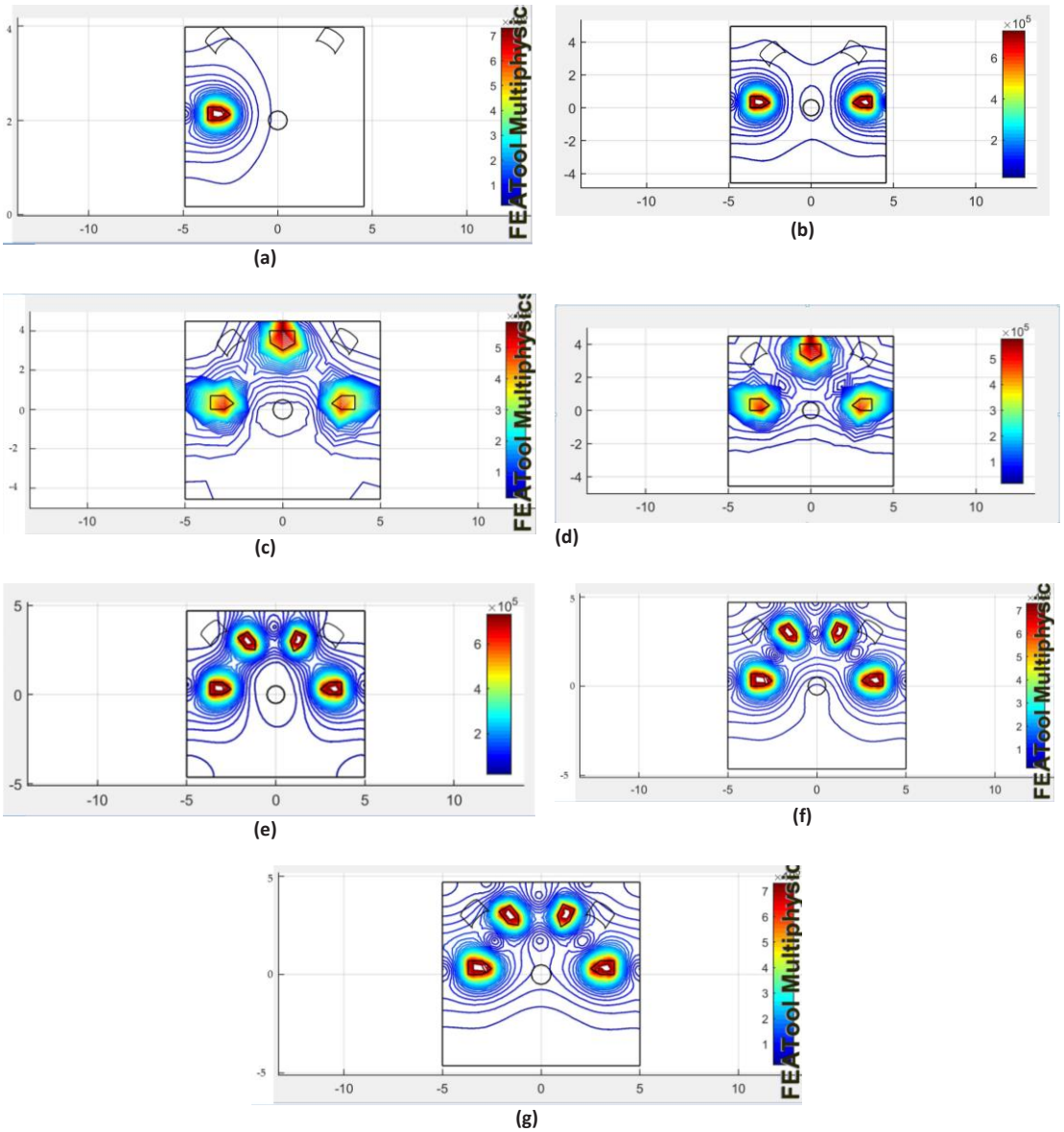


Fig. 2(a, b, c, d, e, f, g). Magnetic field of layouts.

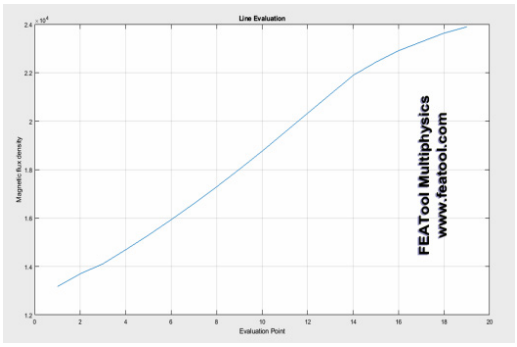
the same pole. The magnetic field of Layout 7 is shown in Fig. 2g.

To analyze the movement of macromolecules in the path from the source to the destination, it is necessary to calculate the intensity of the magnetic flux along the path in different arrangements of magnets.

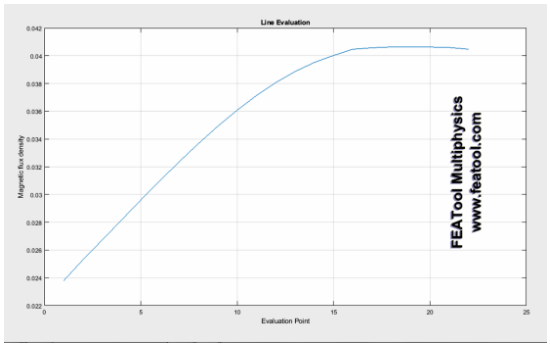
In Fig. 3, line evaluation of magnetic flux density from the injection site to target of magnet layouts is demonstrated. Fig. 3a, relates to layout1, Fig. 3b relates to layout 2, Fig. 3c indicates layout 3, Fig. 3d relates to layout 4, Fig. 3e relates to layout 5, Fig. 3f relates to layout6 and, Fig. 3g relates to layout 7 in the magnetic flux density.

The Figures show that in the arrangement of one sharp tip magnet, the intensity of the magnetic flux is higher, but in the arrangement of several sharp tip magnets, we have more magnetic stability, which causes more concentration in guiding the magnetic nanoparticles to the destination. The results show that in layout 5, four sharp tip magnets with the same poles, there is an unstable and chaotic magnetic field.

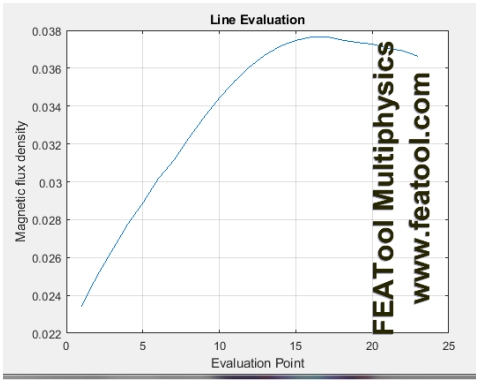
The magnitude and range of applied magnetic force change by changing the arrangement of magnets and affect the movement of macromolecules. The location of force can affect the speed of macromolecules. The simulation



(a)



(b)



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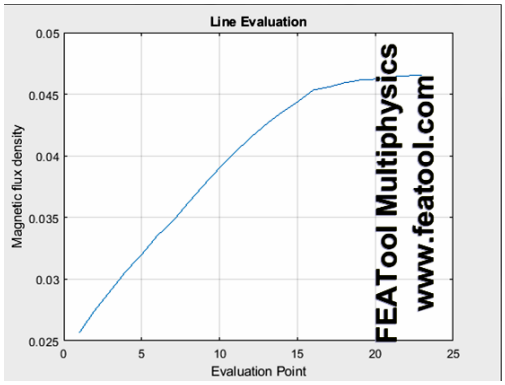
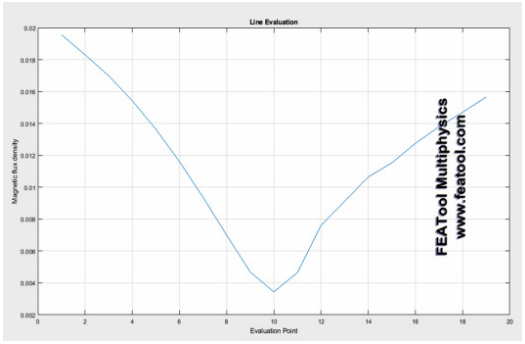
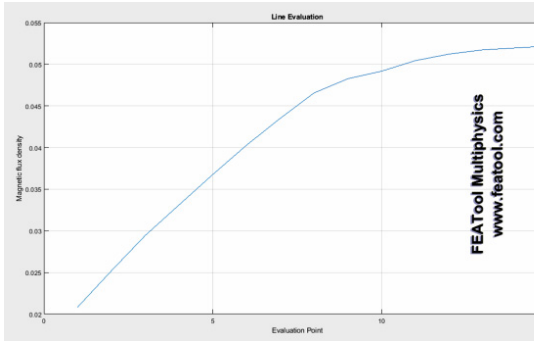


(d)



(e)



(f)

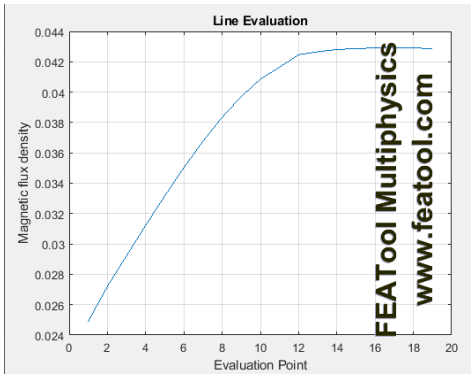


Fig. 3 (a, b, c, d, e, f, g). Line evaluation of magnetic flux density from injection site to target of magnet layouts.

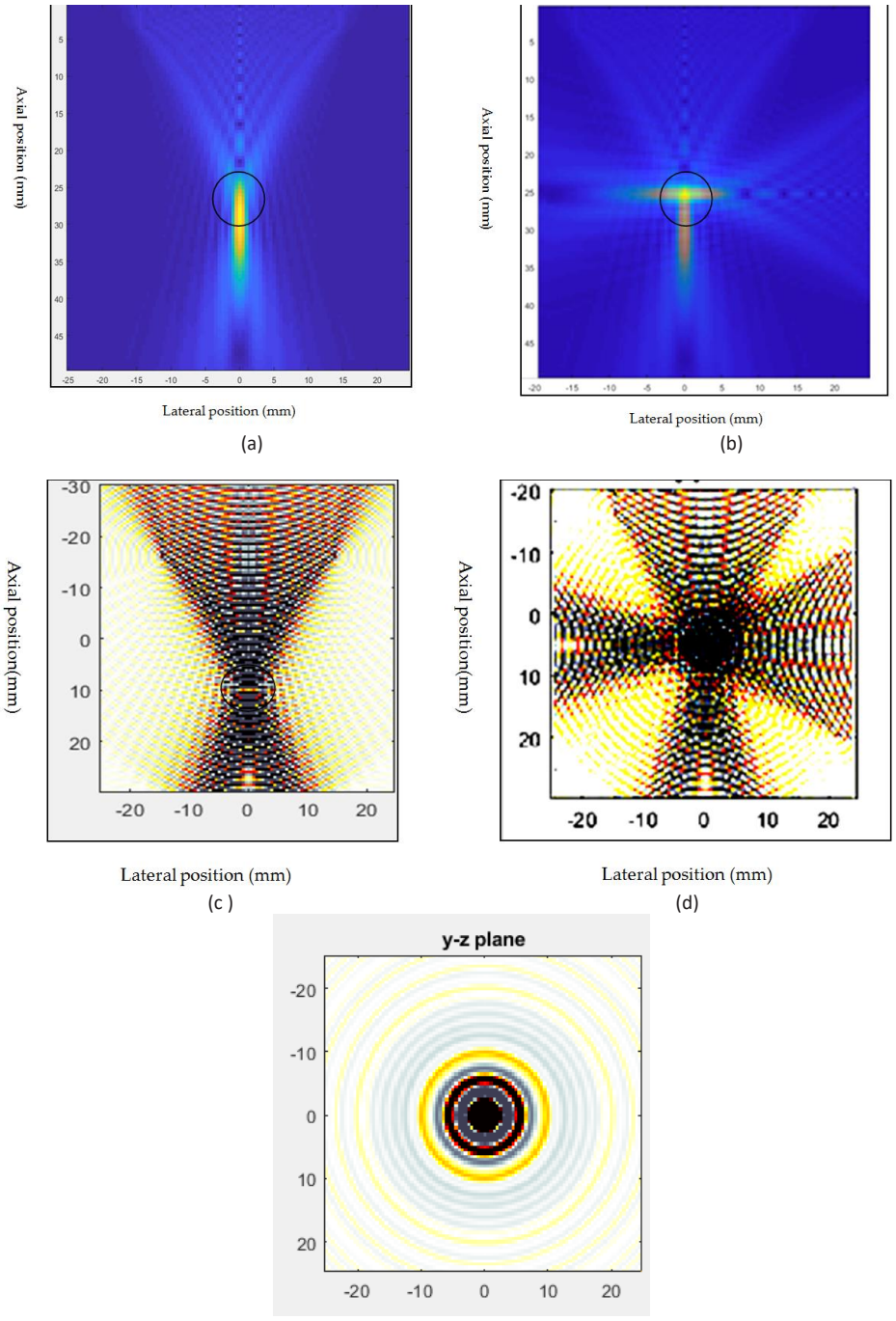
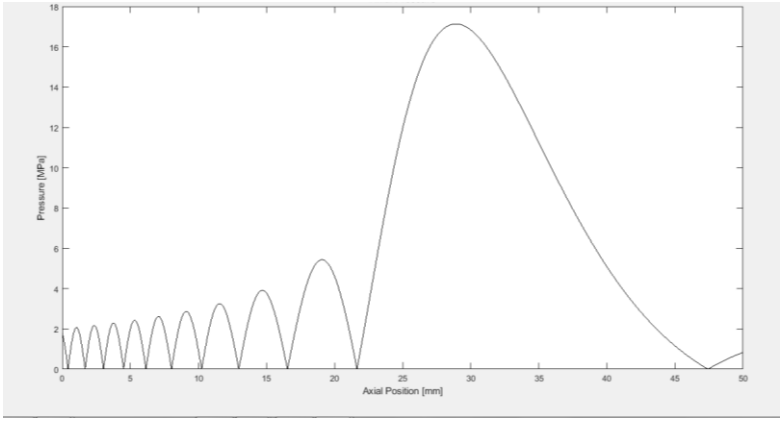


Fig. 4(a, b, c, d, e). Distribution of the ultrasound field of transducers.

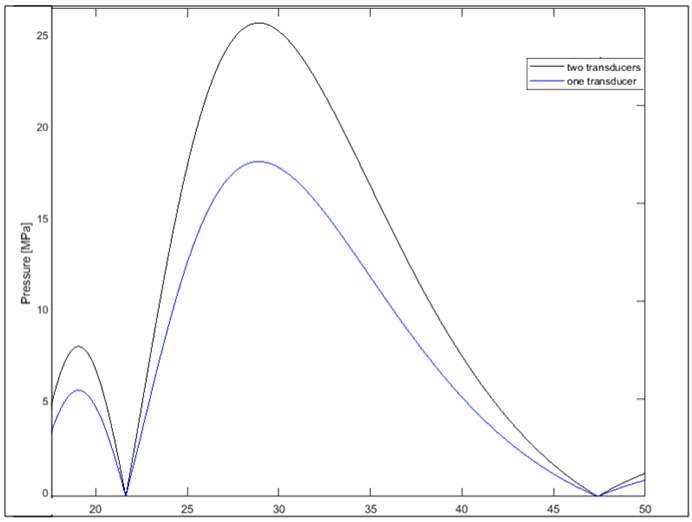
results showed that changing the angle of the magnet changes the amount and direction of the forces.

The ultrasound field distribution of transducers and its effective range on the nanoparticles path in the spinal cord is shown in Fig. 4. Two Bowl-shaped focused ultrasound transducers with 90 degrees are located adjacent to the skin near the injection site. The distance from each bowl center to the injured area in the spinal cord is 30mm. The Transducers with 90 degrees are located near the injection site.

Two focused bowl transducer in three dimensions are modeled. In this research, the bowl-shaped focused ultrasound transducer is considered. Two bowl-shaped focused ultrasound



(a)



(b)

Fig. 5 (a, b). The ultrasound pressure in axial position.

transducers with 1 MHz resonance frequency, 30 mm bowl radius of curvature, and 30 mm bowl aperture diameter are considered. Two transducers with 90 degrees are located adjacent to the skin near the injection site. The ultrasound field distribution of two transducers and their area of effectiveness on the injured site in the spinal cord are shown in Fig. 4. The pressure field generated from one disk transducer is shown in Fig. 4a, and Fig. 4b indicates the pressure field of two transducers. Besides, the pressure fields in the x-y plane of one and two disk transducers are shown in Fig. 4c, and Fig. 4d, respectively. The pressure fields of two disk transducer in the y-z plane are shown in Fig. 4e.

The figure shows that when one transducer is used, a forward pressure is felt, but when two transducers are used at an angle of 90 degrees, we have two ultrasound forces, and when these two forces meet, the total force is increased. This resulting pressure fields pushes the nanoparticles on the path toward the magnets and increases the speed of the magnetic nanoparticles. Results show that the pressure field of two transducers is more effective than one transducer.

Fig. 5 shows the ultrasound pressure field in the axial position. Fig. 5a shows the ultrasound pressure field of one transducer. From the injection site to the target pressure field is increased. The maximum pressure field is around 30 mm, that is the target site. This increase in pressure causes the macromolecules to be directed towards the target.

The Fig. 5b shows the comparison of the

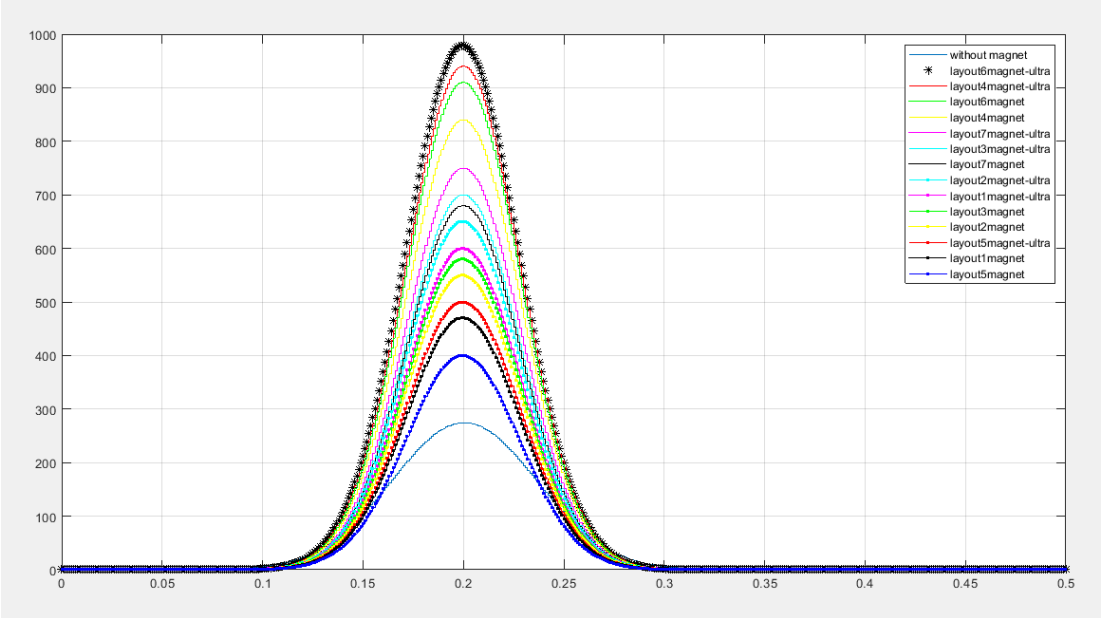


Fig. 6. Macromolecule count in the destination.

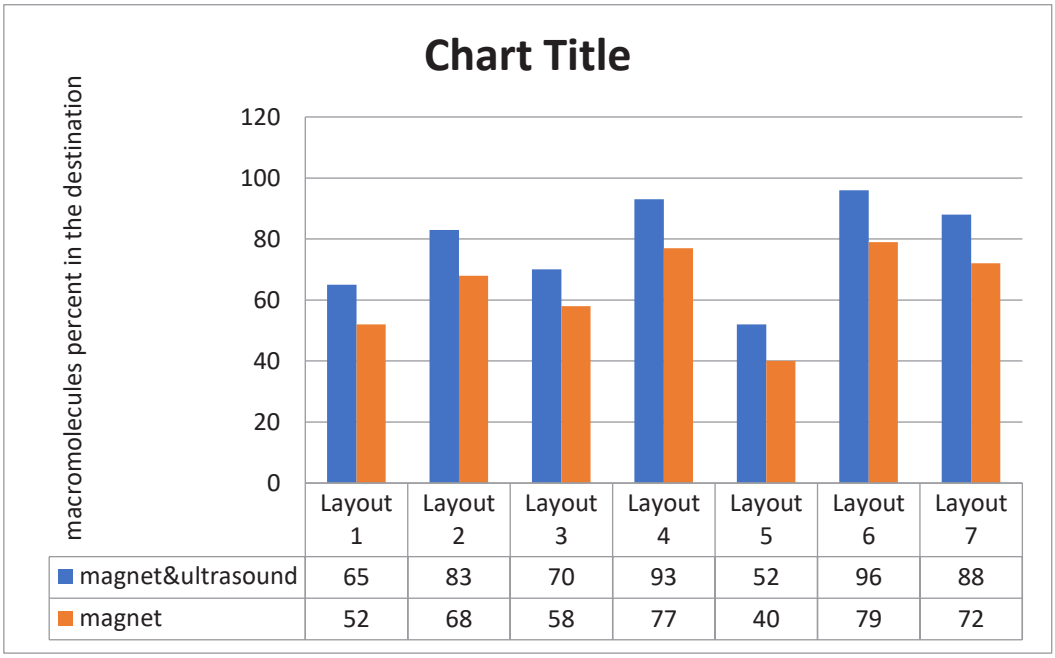


Fig. 7. Comparison of macromolecules percent in the destination.

ultrasound pressure field of one and two transducers around the target area. When the radiated waves from two transducers with 90 degrees reach together, a stronger wave is formed.

It seems that in the two transducers' case, more pressure is applied to the macromolecules, especially around the target site.

The Figure shows that an acceptable pressure can be observed from two transducers in the selected range of spinel cord and it can push the nanoparticles forward towards the magnets.

Fig. 6 shows the macromolecule count in the destination. Fig. 6 shows the macromolecule count in the destination with only magnetic fields

and with magnetic and ultrasound fields. It seems that using both magnetic and ultrasound fields are more effective than using magnetic field. It shows that the ultrasound transducers created pressure fronts across the trajectory of the macromolecules and concentrated the ultrasound energy at the site of the target. The size of macromolecules 200 nm is considered.

To compare the efficiency of magnet and ultrasound transducer layouts models, the macromolecules percent in the destination is analyzed and is shown in Fig. 7. Among the various layouts of sharp tip magnets and ultrasound transducers for the transfer of macromolecules, it seems that layout 6, which consists of four sharp tip magnets with different adjacent poles, has had better results. After that layout 4, consisting of three sharp tip magnets with different adjacent poles, shows better performance. In addition, the use of ultrasound fields has a positive effect on the performance of all arrangements and is able to increase the concentration of macromolecules in Layout 6 and 4 to a very desirable level.

The interaction of magnetic and ultrasound forces helps macromolecules reach their destination. When the magnetic forces pull the magnetic nanoparticles towards them at the destination, the ultrasound force pushes the nanoparticles forward from the origin. The result of the forces of two ultrasound transducers with an angle of 90 degrees is an effective force moving toward the destination. The result of the magnetic forces of magnets is also an effective attraction force in the destination. The interaction between these forces balances the rotation of macromolecules and their useful movement toward the destination.

One of the limitations of the research is the lack of experimental testing of the model. To get more accurate results, it is necessary to apply the proposed strategy on laboratory samples.

To simplify the geometry of the spinal cord model, we considered it to be an approximate cylinder. In future research, the proposed method can be applied on a more precise geometry of human spinal cord. In addition, the proposed method can be used for clinical applications related to the treatment of spinal cord injury.

CONCLUSIONS

Macromolecule delivery systems have characteristics such as high doses of macromolecule, biological, and low accuracy in target detection. One of the challenges of targeting magnetic macromolecules is the accurate delivery of macromolecules to the spinal cord space under complex physiological conditions. To manage these limitations, in the present study, a new non-invasive method is proposed to deliver macromolecules to the injured spinal cord. In this method, various layouts of magnets and ultrasound transducers are analyzed. Two sound transducers are used at the beginning of the path and one to four magnets at the end of the path are used to concentrate the macromolecules exactly in the damaged site. The simulations show that the layout of four magnets and three magnets with different poles side by side has better results than other methods. In addition, using two ultrasound transducers can play a role in improving the efficiency of the transfer of macromolecules. In future studies, the combination of other force sources that can help macromolecule movement can be analyzed. Besides, more dynamic analysis of macromolecule transport in the spinal cord, including the dynamics of white and gray matter and the space around damaged vessels and nerves, is needed. Besides, more arrangements of different ultrasound transducers with permanent magnets can be investigated to increase the performance of nanoparticle transfer. This study can help to understand the practical concepts of macromolecule transfer, and can be used experimentally for the treatment of spinal cord injury in the future. Macromolecules are stem cells or different drugs that help to treat the injury by transferring to the place of injury in the spinal cord. This research is able to provide a precise non-invasive method for the transfer of macromolecules in the form of simulation, and proves it can be an effective method experimentally.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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