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RESEARCH ARTICLE

Magnetic Nanoparticles in Targeted Drug Delivery Systems: Overcoming the Blood-Brain Barrier for Central Nervous System Therapeutics

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ABSTRACT: The blood-brain barrier (BBB) presents one of the most substantial and drastic challenges in delivering therapeutic agents to the brain. Iron oxide nanoparticles have emerged as a promising strategy for overcoming this barrier due to their nanoscale, tunable surface properties, and potential for targeted drug delivery. These nanoparticles play a crucial role in delivering effective treatments to the brain, particularly by traversing the BBB via processes like magnetic hyperthermia, where an alternating magnetic field (AMF) disrupts tight junctions, improving the permeability of nanoparticles without any lasting impact. Moreover, external magnetic fields, such as the AMF, can direct iron oxide nanoparticles to localized regions in the brain for efficient drug delivery. Additionally, surface modifications and coatings have drawn attention to improving cellular uptake, targeting efficiency, and drug release. Guiding iron oxide nanoparticles using an external magnetic field enables precise delivery, minimizing side effects and toxicity, thereby enhancing the effectiveness of medicine. To explore this, experiments involving ferrofluid—a substance composed of iron oxide nanoparticles—were conducted to observe how magnetic fields affect nanoparticle mobility. This research highlights the potential of iron oxide nanoparticles to revolutionize neurological disease treatments by enhancing drug delivery across the BBB and ensuring effective, targeted therapies.

KEYWORDS: Biomedical and Health Sciences, Cell, Organ, and Systems Physiology, Central Nervous System, Drug Delivery, Magnetic Nanoparticles.

Introduction

The blood-brain barrier (BBB) presents numerous challenges related to its high selective permeability for medical treatments, particularly in the form of drugs and other therapeutic substances. To overcome this barrier, specifically engineered nanoparticles could be used. The use of magnetic nanoparticles, particularly iron oxide nanoparticles, for drug delivery across the blood-brain barrier has been studied and proposed as an effective method for enhancing brain permeation. Most studies focus on the prospect of various nanoparticles simply transporting medicine across the BBB and eventually mitigating negative brain disorders. However, these nanoparticles must efficiently travel across the BBB to deliver medicine and target the brain parenchyma without massive disturbance to other bodily functions. Subsequently, further studies should be conducted to explain the effects of iron oxide nanoparticles in the human body. The use of various fields to improve the drug delivery process, such as implementing external magnetic fields (EMFs) outside of the brain to guide magnetic nanoparticles, has also remained a highly recognized theory. Data is needed to demonstrate the correlation between EMFs and iron oxide nanoparticles for drug delivery.

Additionally, drug delivery of iron oxide nanoparticles using external magnetic fields has been tested in the reticuloendothelial system, including organs such as the liver and spleen, where significant nanoparticle accumulation demonstrates promising therapeutic potential for treating tumor areas in this system.[1]

According to a study, the application of an external magnetic field in mice facilitated magnetic nanoparticles to cross the BBB with no apparent damage to its integrity and functionality, which is the key to maintaining homeostasis.[2]

The use of the EMF for the specific targeting of malicious cells in the brain parenchyma was investigated in a study. Researchers have concluded that magnetic nanoparticles, guided by an external magnetic field, can deliver drugs to any poorly accessible site of inflammation, such as the brain, and can be used for the treatment of various neurological diseases. The EMF can drive magnetic nanoparticles toward damaging cells, delivering medicine to the proper place in the brain.[3]

The high surface area-to-volume ratio of the magnetic nanoparticles allows for the attachment of various molecules, making them suitable for drug delivery applications. Additionally, the various coatings and surface modifications, such as liposomes, can increase their biocompatibility, improve permeation through the blood-brain barrier, and increase the ability to control drug release. The surface charge of the magnetic nanoparticles can also be modified to tune their properties and functions.[4]

This study is meant to showcase the extensive ability of magnetic nanoparticles for drug delivery across the challenging BBB to treat life-changing neurological disorders. While these nanoparticle methods are certainly useful for biomedical applications, they may pose significant health risks and safety concerns by accumulating in organs within the body and serv-

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ing an unintended purpose. We discuss the effects of external magnetic fields, surface charges, and surface coatings on the targeted drug delivery applications of iron oxide nanoparticles.

Literature Review

The Blood-Brain Barrier:

The blood-brain barrier (BBB) is a natural, semipermeable, and selective membrane that prevents pathogens and toxic substances from crossing into the central nervous system (CNS) and into the brain (Figure 1). The BBB's function could be a significant disadvantage for potential drug remedies and treatments since it recognizes them as toxins. Large compounds, such as proteins and drug molecules, are unable to permeate the BBB due to their larger size compared to other molecules. A recent study estimates that the BBB excludes approximately 98% of small-molecule drugs and nearly all large-molecule therapeutics.[5] Generally, only lipid-soluble (lipophilic) molecules with a low molecular weight (under 400–600 Da) can cross the BBB. In contrast, the rest of the molecules require certain cell endogenous transport systems, such as carrier-mediated transport, receptor-mediated transport, or absorptive-mediated transport.[6] That poses a major challenge for the administration of vital medicine into the brain because the BBB rejects the drugs, and it is instead released into the bloodstream. The blood-brain barrier is an extremely important factor to consider when determining treatments for different neurological diseases, since the disruption of the BBB can lead to severe pathology observed in many different diseases, but also because crossing the BBB is an essential consideration in the development of CNS-acting therapeutics.[7]

To effectively provide beneficial drugs and biopharmaceuticals into the brain, the development of methods to bypass the BBB has become a necessity. However, some strategies may have limited drug penetration, potential toxicity, and difficulty in targeting specific areas of the brain, emphasizing the need for effective drug delivery methods and prompting scientists to continue formulating and improving the methods of delivery. Similarly, insufficient drug delivery into the brain leads to low therapeutic efficacy as well as aggravated side effects due to the accumulation in other organs and tissues.[8] Mainly, there are two primary pathways for substances to cross the BBB: paracellular transport, which involves passing in between the endothelial cells, and transcellular transport, which involves passing across the luminal side of the endothelial cell, crossing the cytoplasm, and then passing across the abluminal side of the endothelial cell into the brain interstitial fluid.[9]

The BBB mainly consists of capillary endothelial cells, tight junctions, pericytes, astrocytes, and basement membranes that serve as primary parts of the BBB situated inside the brain capillaries (Figure 1). Specifically, the property of low permeability is controlled by tight junction (TJ) protein complexes that seal the passageway between opposing brain microvascular endothelial cells.[10] For specific substances like water and small molecules to enter the brain, they must pass the tight junctions and travel into the bloodstream through the BBB, which is highly restrictive.

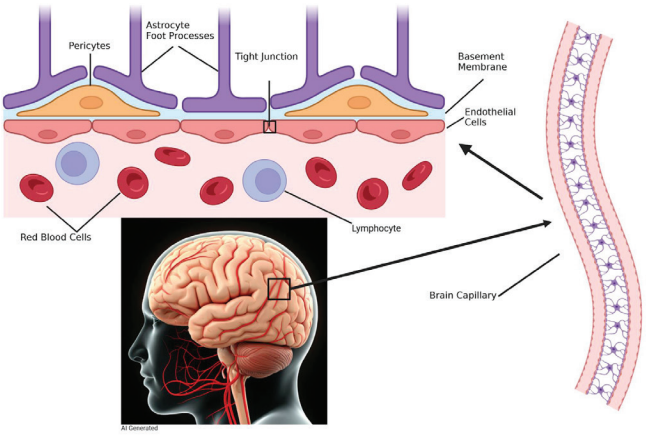

Figure 1: Diagram of the blood-brain barrier. The location of the brain capillaries inside the brain, a representation of the brain's capillary (enlarged), and parts of the blood-brain barrier (enlarged), including endothelial cells, pericytes, astrocyte foot processes, tight junctions, basement membranes, red blood cells, and lymphocytes, are depicted within this image. A visual representation of the parts of the blood-brain barrier is shown, which work together to maintain the passageway into the brain. On the inside, there are red blood cells, lymphocytes, water, and other substances that get distributed throughout the brain from capillaries. The figure was created using BioRender.

Nanoparticles for Drug Delivery:

Nanoparticle drug delivery has been proposed as an effective method of brain permeation within the scientific community and continues to be researched extensively. Nanoparticles have various advantages for drug delivery across the BBB because of their small size (1 to 100 nm), tunable surface properties, and the ability to act as carriers.[11] For nanoparticles to carry drugs and medicine into the brain, they must pass through the blood-brain barrier (BBB) properly and efficiently.

Due to their small size, nanoparticles can penetrate the tissue system, facilitating the easy uptake of the drug by cells, permitting efficient drug delivery, and ensuring action at the targeted location.[12] A study examining the use of nanoparticles for drug delivery states that the nanoparticles also possess enhanced bioavailability, an additional ability to cross the blood-brain barrier (BBB), and can be absorbed through the tight junctions of the endothelial cells.[13]

Magnetic nanoparticles, particularly iron oxide nanoparticles, are important nanoparticles for drug delivery and imaging applications. Iron oxide nanoparticles are nanoscale forms of iron oxides with unique magnetic and surface properties. Since these nanoparticles are typically less than 100 nanometers, they are small enough to cross the BBB. When synthesized using a variety of complex methods, iron oxide nanoparticle size can range from 3 nanometers to 11 nanometers, which would make them less recognizable by the BBB.[14]

The iron oxides magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) exhibit magnetic properties, which make them capable of magnetic navigation. The crystal structure of magnetite is shown in Figure 2. Magnetite (Fe_3O_4) and maghemite (γ–Fe_2O_3 or $Fe_{8/3}O_4$) are the reduced and oxidized end–members of a spinel solid solution.[15] Stoichiometric magnetite Fe_3O_4 has an inverse spinel structure with one Fe^{3+} per formula unit on tetrahedral sites and Fe^{2+} and the remaining Fe3+ randomly distributed on the octahedral sites. Maghemite (magnetite –

hematite), γ–Fe_2O_3 or $Fe_{8/3}O_4$, has a defect spinel structure with one-third mole of cation vacancies per four moles of oxygen, compensating for the oxidation of Fe^{2+}.[16]

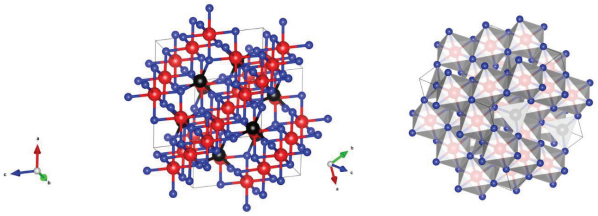

Figure 2: Crystal structure of magnetite. On the left side: black atoms – Fe^{2+}, and the red ones – Fe^{3+}. The blue atoms represent oxygen. On the right side: octahedral and tetrahedral sites. Source: American Mineralogist Crystal Structure Database CIF data. VESTA software was used for visualization.

Iron oxide nanoparticles are also biocompatible. However, it is important to note that factors such as dosage, cellular effects, and long-term exposure can lead to the accumulation of these nanoparticles in various organs, potentially disrupting homeostasis. Like most nanoparticles, iron oxide nanoparticles can be coated or functionalized with various agents to aid in the drug delivery process and improve the nanoparticles' efficiency in transporting drugs to the BBB (Figure 3).

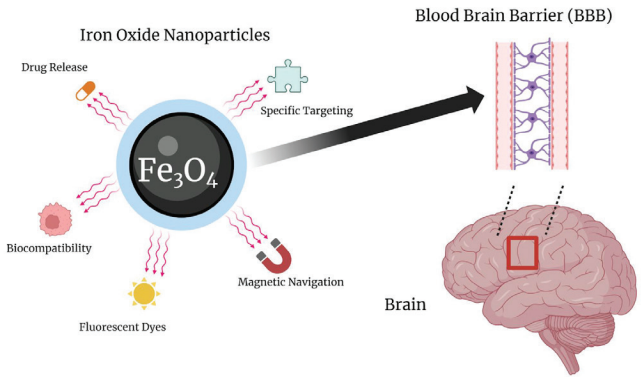

Figure 3: Iron oxide nanoparticle abilities for drug delivery purposes. The various abilities that iron oxide nanoparticles have are depicted in this image. These properties are all necessary when the iron oxide nanoparticle enters the brain and crosses the blood-brain barrier. A visual representation showing the particle traveling towards the blood-brain barrier with these helpful properties emphasizes the potential of iron oxide nanoparticles to improve disorders within the brain. Drug release, specific targeting, biocompatibility, fluorescent dyes, and magnetic navigation all impact iron oxide nanoparticles for drug delivery. The figure was created using BioRender.

External Magnetic Field Technology:

Iron oxide nanoparticles offer the enhanced benefit of magnetic targeting due to their ability to respond to magnetic forces. When an external magnetic field (EMF) is applied outside the human body, the resonating magnet draws iron oxide nanoparticles towards localized areas and targets, releasing the drugs, which then target pathogens and invasive cells within the brain (Figure 4).

Apart from the normal drug delivery process, utilizing an EMF reduces the negative drug side effects of the nanoparticle drug delivery, drawing nanoparticles towards localized areas and minimizing nanoparticle concentrations in unwanted regions of the brain, ensuring drugs are shifted towards the proper location. Furthermore, nanoparticles can release amounts of toxicity, causing inflammation and cell death, by drugs that may distribute in healthy tissues, causing them to die. While iron oxide nanoparticles have less toxicity than other nanoparticles, using an EMF to draw iron oxide nanoparticles away from susceptible areas is better for the body and maintains brain homeostasis.

In addition, the EMF's strength can manipulate iron oxide mobility depending on the magnetic field intensity. Low or high magnetic attractions can change the location and the distance of the iron oxide nanoparticles traveling inside the brain. Furthermore, a typical EMF has an intensity barely sufficient to control a moving nanoparticle but is usually stronger than a low-intensity magnet. If the EMF is too strong, then the surrounding tissues will be damaged by the magnetic field. As stated, when an external magnetic field is present, a force is exerted on the magnetic nanoparticles, effectively pulling them towards the magnet, as shown in Figure 4. The formula represents the magnetic force of an external magnet:

$$F_{mag} = (\chi_1 - \chi_2)V\frac{1}{\mu_0}B(\nabla B)$$

Where V is the volume of the magnetic particle, μ0 is the magnetic permeability of free space, B is the magnetic field strength, ∇B is the magnetic field gradient, or how fast the strength or direction of the magnetic field changes over a given distance, χ_2 is the magnetic susceptibility, or how much magnetic nanoparticles will respond to the applied magnetic field, χ_1 is the magnetic susceptibility of the medium, which is very small in comparison to χ_2 and is therefore disregarded in biological systems.

Based on this information, the important parameters for considering the capture of the magnetic nanoparticles are the magnetic properties, volume of the nanoparticles, the magnetic field strength, and the magnetic field gradient. It is clear that as the external magnetic field strength decreases, the ability of the magnet to capture the nanoparticles decreases.[17]

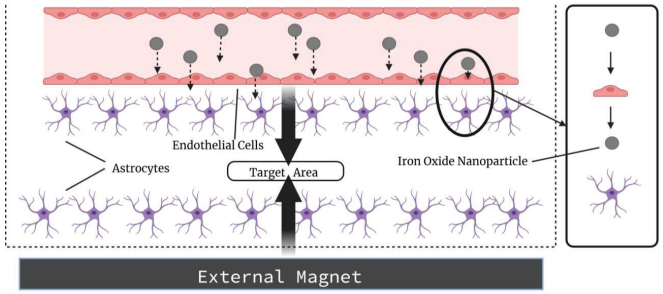

Figure 4: An external magnetic field affects the mobility of iron oxide nanoparticles. Iron oxide nanoparticles are traveling across the BBB to the target area. The iron oxide nanoparticles must pass the endothelial cells and astrocytes before reaching the target site. Then, the EMF may be pulled away when the nanoparticles reach the target, and the nanoparticles can release medicine to cure cognitive diseases. The external magnetic field is key for magnetic targeting, since it allows iron oxide nanoparticles to successfully penetrate the blood-brain barrier and reach the target area. The figure was created using BioRender.

Alternating Magnetic Field Technology:

Another important magnetic field helping magnetic nanoparticles target harmful cells within the brain is the al-

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ternating magnetic field (AMF). The AMF is a specific type of external magnetic field that produces heat, where only the magnetic components alternate and the direction of the alternating magnetic field changes constantly, resulting in vibrations and heat. The alternating magnetic fields (AMFs) amplitudes vary in time, causing vibrations and secured motions towards a certain place or target.[18] The AMF can be defined with characteristics such as differing alterations, frequency, and strength. Depending on their frequencies, they may have low or high amplitudes, which can control vibrations. These magnets are commonly used in technological applications, particularly for manipulating electrical and magnetic particles.

The AMF can be used for nanoparticle interactions, influencing materials that have magnetic properties like a common EMF. However, the AMF plays a different role for these magnetic nanoparticles within the brain. When an AMF is projected at iron oxide nanoparticles within the brain, they start to rotate and vibrate as a result of the amplitudes directed by the AMF. This causes the iron oxide nanoparticle to heat up as it travels across the BBB, resulting in temporary structural changes in the endothelial cells. Due to the AMF's alterations and vibrating motion, the tight junctions and tight junction proteins in the endothelial cells, which are necessary to secure the BBB, lose their structural integrity temporarily. In the tight junctions, vital proteins such as claudin and occludin lose their function, causing openings in the BBB. This method of penetration through the BBB is called magnetic hyperthermia, which is an applicable method that may be implemented specifically for iron oxide nanoparticles. This makes the BBB more permeable and, in turn, aids iron oxide nanoparticles in reaching the brain without potential backlash.[19]

The AMF can be implemented to assist the drug delivery targeting malicious cells, particularly tumors and similar abnormal cells, using iron oxide nanoparticles. The iron oxide nanoparticles engineered for drug delivery are typically coated with specific molecules to enhance the process's efficiency and facilitate binding to harmful cells within the brain. In fact, they can be conjugated to antibodies that bind to specific antigens expressed on the membranes of targeted cells.[20] Via this means, cells in suspension, like blood samples, can be specifically targeted, and upon applying a low magnetic field gradient, the target cell population can be separated from all other cells. This means that iron oxide particles can bind to target cells, ultimately releasing drugs to eliminate harmful molecules. Moreover, the AMF's function can cause iron oxide nanoparticles to vibrate and rotate, thereby creating heat that propels them toward target cells, interferes with their functions, and eventually kills them. Examples typically refer to tumor and cancerous cells within the brain that get immobilized and killed due to magnetic hyperthermia.[19]

Surface Charges and Surface Functionalization:

Nanoparticle surface charge relates to the electrical charge that exists on the surface of the nanoparticle. It usually results from interactions with particles in environments. Surface charges can be introduced on nanoparticle surfaces by attaching charged molecules to the nanoparticle surface. These charges affect the stability, cellular interactions, and chemical reactivity of a specific nanoparticle. Surface charges typically interact with charged particles or other materials that have opposite charges. For example, positively charged iron oxide nanoparticles exhibit stronger interactions with negatively charged biomolecules, while negatively charged iron oxide nanoparticles interact more strongly with positively charged biomolecules. Both positively charged iron oxide nanoparticles and negatively charged nanoparticles have different properties and can be utilized for various applications, such as drug delivery across the BBB.

In fact, magnetic effects are caused by movements of particles that have both mass and electric charges. This includes magnetic fields like EMFs, surface charges, and other important iron oxide characteristics.[21]

It is important to note that specific coatings may be applied to iron oxide nanoparticles to change the nanoparticles' surface charge and overall functionality. The preparation of surface functionalized MNPs using iron oxide NPs (MNPs), poly (lactic-co-glycolic acid) (PLGA), and sodium alginate via co-precipitation, emulsification, and electro-spraying, respectively. Additionally, the surface functionalization of MNPs with selective polymers alters the surface chemistry to improve biocompatibility. To test the utmost functionality of iron-oxide nanoparticles for drug delivery, it may be coated or functionalized on its surface to ensure that the iron oxide has more capability for drug delivery and crossing the BBB.[22]

Positively charged iron oxide nanoparticles have numerous advantages for overcoming the BBB and performing the drug delivery process efficiently. After a study evaluated the surface charge of biological membranes within the blood-brain barrier (BBB), it was found that the surface charge of brain endothelial cells forming the blood-brain barrier (BBB) is highly negative due to phospholipids in the plasma membrane and the glycocalyx.[23] Additionally, positively charged nanoparticles are known to be more easily internalized than neutral or negatively charged nanoparticles.[24] This is because positively charged nanoparticles respond better with negative counterparts like the brain's endothelial cells, which are key for the BBB crossing. As a result, the positively charged iron oxide nanoparticles are preferred in drug delivery over negatively charged ones due to their specific advantages. The advantages and disadvantages of negatively and positively charged iron oxide nanoparticles (Table 1) regarding their potential for drug delivery are notable. Notably, the positively charged nanoparticles are most popular among experiments pertaining to drug delivery.

On the other hand, negatively charged iron oxide nanoparticles facilitate safer interactions with molecules, have better stability, but are less efficient as drug delivery nanocarriers. In addition, they induce a lower cytotoxic response compared to positively charged nanoparticles and neutral charged nanoparticles.[25] However, the negatively charged nanoparticles could cross the BBB effectively and complete the process with appropriate surface modifications and functionalization. In a study considering the surface charge of negatively charged nanoparticles and evaluating other surface coatings, it was deduced that negatively charged nanoparticles targeted with an RVG

peptide can also penetrate across a human BBB model effectively.[26] The pros and cons of surface charges used in iron oxide nanoparticle drug delivery are listed in Table 1.

Table 1: Advantages and Disadvantages of Iron Oxide Nanoparticle Drug Delivery. A comparison of iron oxide nanoparticle drug delivery across the BBB. The advantages of positively charged iron oxide nanoparticles, negatively charged iron oxide nanoparticles, and neutrally charged iron oxide nanoparticles are depicted. Positively charged iron oxide nanoparticles were identified as the best candidates for drug delivery to the brain.

	Advantages	Disadvantages
Positively Charged Iron Oxide Nanoparticles (+)	Enhanced Cellular Uptake	Higher Rates of Toxicity
	Can Target Specific Cells for Drug Release	More Instability and Aggregation
	Bioavailability	
	High Interaction with Magnetic Targeting	
Negatively Charged Iron Oxide Nanoparticles (-)	Lower Rates of Toxicity	Lower BBB penetration
	Better Stability in Blood Circulation	Lower Cellular Uptake
Neutrally Charged Iron Oxide Nanoparticles	Better Interactions with Molecules	Weaker Interactions with Magnetic Targeting comparatively
	Low Inflammatory Response	
	Bioavailability	Low Cellular Uptake
	Better Stability	Little Targeting Efficiency
	Lower Rates of Toxicity	Difficulty with Functionalization

Note: Iron oxide nanoparticles typically need coatings, ligands, or other materials for full optimization and improvement. This is especially required for neutral (no charge) iron oxide nanoparticles.

The BBB is a vital component of drug delivery, since it hinders the ability of therapies to travel effectively into the brain. Iron oxide nanoparticles have been proposed as effective nanocarriers because of their magnetism, which allows for effective BBB permeation using EMFs. The potential of these nanoparticles for facilitating effective drug delivery has been recognized. However, the lack of *in vitro* BBB models to test iron oxide nanoparticles for predictive outcomes has limited accurate results, and this gap in experimental modeling continues to make magnetic targeting difficult for translation into real-world applications such as drug delivery. In this study, we conducted multiple experiments to simulate BBB permeation and assessed whether iron oxide nanoparticles could react to external magnets properly.

Methods

The goal of this paper is to evaluate the effect of magnetic nanoparticles, and particularly the iron oxide nanoparticles, for drug delivery across the blood-brain barrier. This paper assesses the efficacy and effect of these magnetic nanoparticles.

Two separate experiments were conducted to determine the application of iron oxide nanoparticle properties for drug delivery, focusing primarily on mobility and the presence of a magnetic field. All three trials in the second experiment were maintained for 24 hours, so that the results could be compared under consistent time conditions.

Experiment 1: Evaluating the Magnetism of Iron Oxide Nanoparticles using Ferrofluid:

The first experiment was conducted to measure how ferrofluid (an iron-oxide-based liquid that is attracted to the poles of a magnet) reacts to a magnetic field and then use those measurements to create a distance versus magnetic field graph, uncovering the scope of iron oxide magnetism in real-life scenarios. During this experiment, a magnetic field was applied to determine how the amount of ferrofluid, which is made up of iron oxide nanoparticles, responds to an external magnetic field. We measured how the ferrofluid properties changed, collected data, and plotted them on a graph to see the common relation between field strength and nanoparticle behavior, proving that iron oxide nanoparticles have sustained magnetism and can be applied for drug delivery purposes.

Initially, a Gauss meter was used to measure the magnetic field strength (H), which is a measure of the intensity of a magnetic field produced by an external source such as the neodymium magnet (5mm height x 20mm length x 10mm width) used in this experiment. The magnet was positioned at distances ranging from 20 centimeters to 2 centimeters from the ferrofluid, which had been measured beforehand, and the corresponding magnetic field strength (in mT) was recorded at each point using a Gauss meter. Starting from 20 centimeters, the neodymium magnet was moved closer by 2 centimeters to 10 centimeters, where it was then moved closer by 1 centimeter onward for consistent results. The ferrofluid was contained within a petri dish to avoid inconsistent results, including prior magnetization. The data collected from the setup in Figure 6 were then analyzed to observe the relationship between the distance and magnetic field strength of the standard iron oxide nanoparticles. For all the materials used in this experiment, see Figure 5.

This step-by-step experiment was recorded for varying amounts of ferrofluid, including 5 mL, 8 mL, and eventually 12 mL of ferrofluid, for the magnetic field strength (H) to compare results and test different ferrofluid inputs.

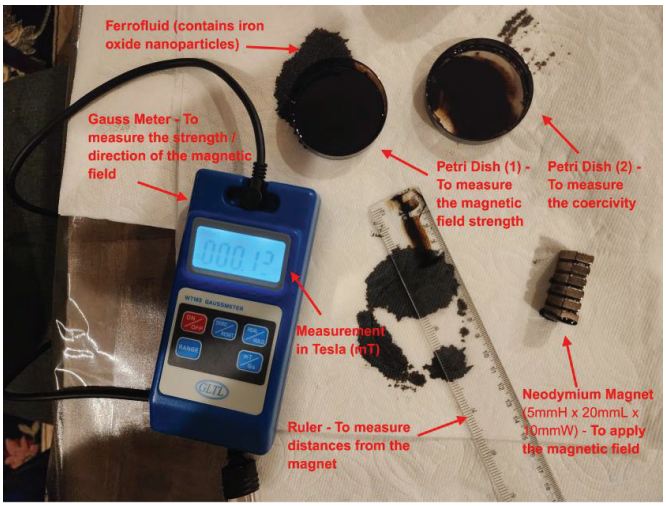

Figure 5: Materials used in experiment 1 to represent the magnetism of ferrofluid. Ferrofluid for testing, a Gauss meter to measure in Tesla (mT), a ruler for measuring distances, two petri dishes to contain the ferrofluid, and a neodymium magnet as the active source of magnetic force were all used in testing and described in the visual.

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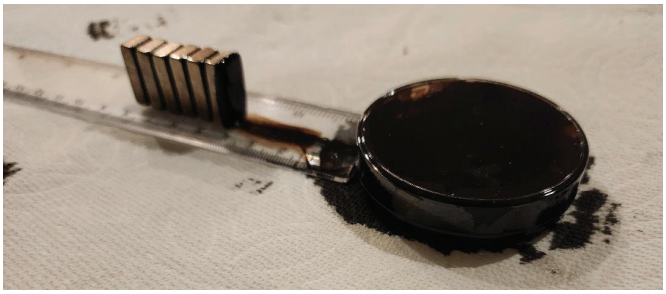

Figure 6: Experimental setup and material utilization as depicted in Figure 5. A small neodymium magnet was placed on the ruler at centimeter marks in increments, and ferrofluid, acting as the magnetic substance used for measuring magnetic field strength, was placed at the end of the ruler. From the experiment, the magnetic field strength exponentially grew as the neodymium magnets moved closer to the ferrofluid.

Experiment 2: Conducting Systematic Trials to Simulate Iron Oxide Nanoparticle Permeability Across the Blood-Brain Barrier:

Three trials were conducted to evaluate the extent to which iron oxide nanoparticles could penetrate the blood-brain barrier (BBB) effectively, with each covering an aspect vital to iron oxide nanoparticle permeation past the BBB and into the brain's cerebrospinal fluid, enabling drug release.

The materials used within each trial remain constant; however, the amount of each substance used varies per trial to progressively test multiple scenarios. Throughout all 3 trials, the amount of ferrofluid remained 8 milliliters to ensure consistent results. The materials included within the 3 trials are agar (agarose gel), water, and glycerin (mixed in a 3:1 ratio, respectively), a toothpick, ferrofluid (8mL), a neodymium magnet (5mm height x 20mm length x 10mm width), plastic containers and glass cups, a ruler, and a syringe.

For all trials, agar (agarose gel) was used to simulate the blood-brain barrier because it acts as a semi-permeable medium; water and glycerin (mixed 3:1, respectively) were used to mimic blood consistency within the human body. The tiny, punctured holes (made with a toothpick 1.5 mm in diameter) were used to replicate tight junctions (TJs) in the agar (representing the blood-brain barrier) (Figure 7). The agar or the blood-brain barrier in this case served as a benchmark that the ferrofluid had to reach past to travel into the outside interstitial fluid (under the agar).

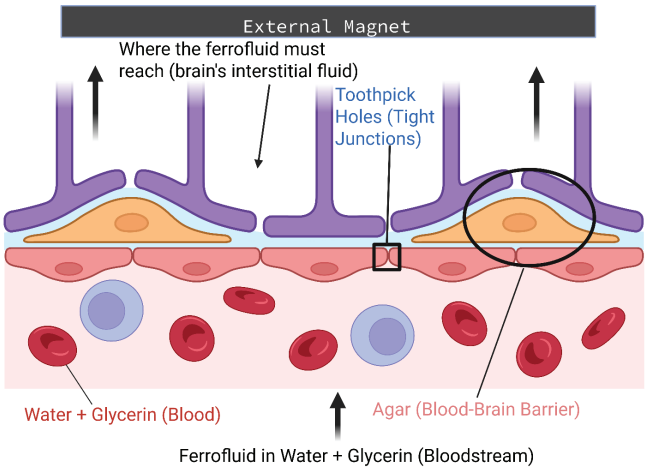

Figure 7: Modeling Magnetically Guided Transport Across an In Vitro Blood-Brain Barrier Model. The materials used in experiment 2 correspond to a function of the blood-brain barrier process. Water and glycerin mimic blood, while agar represents the blood-brain barrier due to its matrix-like formation, with toothpick holes that form tight junctions. Ferrofluid, which contains iron oxide nanoparticles, is used, and an external magnetic field acts as a pull factor for the ferrofluid. The ferrofluid successfully passed through the toothpick holes and past the agar using the external magnet. The figure was created using BioRender.

Trial 1: Ferrofluid Diffusion Through Simulated Blood-Brain Barrier with Pierced Tight Junctions (without magnet):

In the first trial, ½ inch of agar (agarose gel), ½ inch of water and glycerin, 8 mL of ferrofluid, and toothpicks were the materials used. Initially, the agar (representing the blood-brain barrier) was placed on the bottom level, and water and glycerin (representing blood) were placed directly above the agar. Five evenly spaced toothpick holes were pierced into the agar to act as tight junctions for the iron oxide nanoparticles to follow through. Then, 8 mL of ferrofluid was carefully measured using a syringe and dropped into the glass cup containing water and glycerin. This solution was left alone for approximately 24 hours and kept at a constant room temperature (70˚F). This will serve as the control, from which the following trials will build upon.

Trial 2: Ferrofluid Diffusion Through Simulated Blood-Brain Barrier with 5 Pierced Tight Junctions (with magnet):

The materials used in the second trial were ½ inch of agar (agarose gel), ½ inch of water and glycerin, 8 mL of ferrofluid, a neodymium magnet (5mm height x 20mm length x 10mm width), and toothpicks to pierce 5 evenly spaced holes. The neodymium magnet is an addition to this trial, compared to the previous trial, to test the relation between the strong magnet and the ferrofluid within the blood-brain barrier or agar in this case. Following a similar procedure, the agar (representing the blood-brain barrier) was placed on the bottom level, and water and glycerin (representing blood) were placed directly above the agar. Five evenly spaced toothpick holes were pierced into the agar to act as tight junctions for the iron oxide nanoparticles to follow through. Then, 8mL of ferrofluid was carefully measured using a syringe and dropped into the glass cup containing water and glycerin. The neodymium magnet was placed at the bottom of the cup or below the agar, where it could pull

the ferrofluid through the pierced holes. This solution was left alone for approximately 24 hours and kept at a constant room temperature (70˚F).

Trial 3: Ferrofluid Diffusion Through Simulated Blood-Brain Barrier with 1 Pierced Tight Junction (with magnet):

In the third trial, the materials used were 1 ½ inches of agar (agarose gel), ½ inch of water and glycerin, 8mL of ferrofluid, a neodymium magnet (5mm height x 20mm length x 10mm width), and a toothpick to pierce 1 hole in the center of the agar. As stated, the neodymium magnet was used in this trial to compare whether an external magnet has a significant impact on the movement of the ferrofluid in the cup. Once again, the agar (representing the blood-brain barrier) was placed on the bottom level, and water and glycerin (representing blood) were placed directly above the agar. Only one center hole was pierced to impede the ferrofluid compromise under the agar. Then, 8mL of ferrofluid was carefully measured using a syringe and dropped into the glass cup containing water and glycerin. The neodymium magnet was placed at the bottom of the cup or below the agar, where it could pull the ferrofluid through the one pierced hole. This solution was left alone for approximately 24 hours and kept at a constant room temperature (70˚F).

Results and Discussion

Based on our literature review, we suggest that iron oxide nanoparticles with smaller sizes, a positive surface charge, and a biocompatible coating should be the most suitable nanocarriers for BBB permeation and targeted drug delivery. They can be synthesized using the method suggested in a study, which results in nanoparticles with a diameter of around 1 nm.[27] The product will be a thermodynamically stable solid solution between magnetite and maghemite, i.e., partly oxidized magnetite with a formula $Fe_{3-x}O_4$ where x is between 0 and 0.33.[15] The primary method of verifying the phase purity and crystal structure will be powder X-ray diffraction with Rietveld refinement to determine the lattice parameters.[28,29] The average particle size will be determined from the surface area measured using the five-point Brunauer-Emmett-Teller (BET) technique, a standard method for nanoparticles.[28-30] The particle size distribution and morphology will be determined using Transmission Electron Microscopy (TEM), a standard technique for characterizing nanomaterials.[28,29,31] Fourier-transform infrared spectroscopy (FTIR) will be used to determine the type of organic molecules adsorbed on the surface.[28] The magnetic moment will be measured on MPMS superconducting quantum interference device (SQUID) magnetometers.[27]

The rate of cellular uptake can be increased by altering the surface charge of the nanoparticles. We suggest using positively charged nanoparticles to confer a higher internalization rate in the brain cells. They can be obtained using a method that describes the process of getting positively charged iron oxide nanoparticles.[32] Iron oxide nanoparticles were synthesized with designed charged ligands via reversible addition fragmentation chain transfer (RAFT) polymerization for stability. A positive charge was obtained by stabilizing the iron oxide nanoparticles with a catechol-derived dopamine ligand along with polyethylene glycol (PEG), carboxylic acid, and amine groups. The tertiary amine group ((N-[3-(dimethylamino)propyl]acrylamide)) was used as a positive charge. The zeta potential of the positively charged iron oxide nanoparticles after completing this process was +32mV, respectively.[32]

Lipids will coat the iron oxide nanoparticles to ensure effective drug delivery for the BBB influx. A study suggests that lipid-based magnetic nanocapsules with a 12 wt.% iron oxide content exhibit magnetic behavior, making them suitable for biomedical applications that require external magnetic fields (EMFs).[33] Moreover, the lipid coating showed increased biocompatibility against human cerebral endothelial cells and pericytes. Guided by an EMF, the coated iron oxide nanoparticle displayed an enhanced targeting ability across the BBB. Additionally, a lower exposure time was required for this targeted delivery to pericytes, demonstrating targeting efficiency.[33]

Adding an external magnetic field will further improve properties by driving iron oxide nanoparticles towards localized areas to reduce minimal effects, disrupting healthy cells, and generally enhancing the therapeutic potential of the drug delivery system. We suggest using an alternating magnetic field (AMF), which causes localized heating and disrupts the tight junctions between endothelial cells. The spatial distribution of the iron oxide nanoparticles can be controlled by modulating the strength of the magnetic field.

Experiment 1:

In the first experiment, where a magnetic field was introduced to iron oxide nanoparticles, we found that the closer the magnet approached the ferrofluid, the more the iron oxide nanoparticles within the ferrofluid began to react. Data were collected by measuring the distance and observing the magnetic strength of the field using a Gauss meter (Tables 2 and 3). The closer the magnet was, the more intense the magnetic field displayed by the ferrite iron oxide nanoparticles and the magnet. All three samples of ferrofluid (5mL, 8mL, and 12mL) showed relatively the same exponential increase. As the magnet inched closer to the ferrofluid, there was an exponential increase in the magnetic field intensity during the experiment (Figure 8), meaning the closer the magnet traveled, the more magnetic intensity was put on the ferrofluid. This experiment demonstrates the prominence of a magnetic field when iron oxide nanoparticles are exposed to magnetic objects, specifically magnets. External magnets seem to demonstrate a strong correlation with the magnetic nanoparticles and most likely can be used to control iron oxide nanoparticles for drug delivery applications.

Based on the experiment conducted, iron oxide nanoparticles show promising results for drug delivery, crossing the blood-brain barrier, and enhancing treatments for individuals with neurological disorders, particularly when an external magnet is used.

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Table 2: Recorded Results for Magnetic Field Strength (H) in Experiment 1. Data on how distance correlates to the magnetic field using 5 mL, 8 mL, and 12 mL samples of ferrofluid. As the distance between the neodynium magnet and the ferrofluid decreased, a more magnetic field intensity occurred in all of the samples.

Distance (cm)	Magnetic Field (H) (mT) - 5 mL ferrofluid	Magnetic Field (H) (mT) – 8 mL ferrofluid	Magnetic Field (H) (mT) - 12 mL ferrofluid
20	1.02	0.9	0.94
18	1.07	1.09	1.03
16	1.14	1.13	1.18
14	1.25	1.17	1.2
12	1.4	1.27	1.48
10	1.75	1.52	1.64
9	2.2	2.05	2.26
8	3.0	2.52	2.75
7	4.36	3.24	3.28
6	6.18	4.31	4.48
5	12.41	5.36	6.93
4	20.5	12.56	11.52
3	55.53	25.3	23.25
2	164.46	155.57	168.39

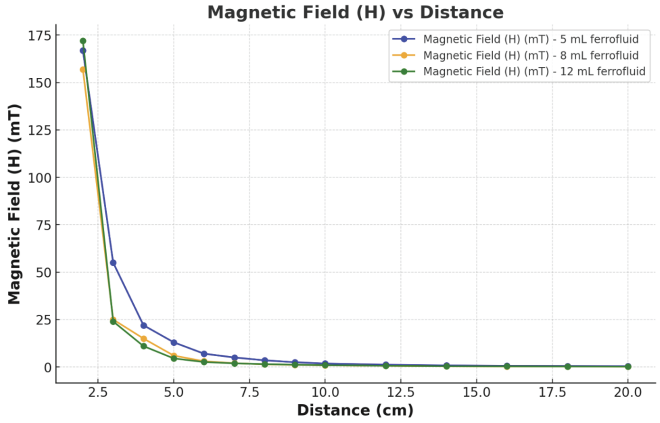

Figure 8: Distance vs. Magnetic Field (H) in Experiment 1 of the 5, 8, 12 mL Samples. Based on the results, there is a prominent exponential relationship between distance and the magnetic field for all 5 mL, 8 mL, and 12 mL ferrofluid samples. As the distance reduces and the magnet slowly approaches the ferrofluid, more magnetic field (H) exposure is available.

Experiment 2:

In the second experiment, which involved numerous trials to gather information on the mobility of iron oxide nanoparticles in concentrated solutions and through obstructing barriers like the blood-brain barrier (BBB), we found that iron oxide nanoparticles were able to pass through the BBB via the tight junctions successfully.

Trial 1: Ferrofluid Diffusion Through Simulated Blood-Brain Barrier with Pierced Tight Junctions (without magnet):

The ferrofluid containing the iron oxide nanoparticles was able to pass through the selective tight junction areas scattered in the agar during the 24 hours; however, this process was gradual, with the ferrofluid being immobilized for long periods of time. All three ferrofluid samples were successful.

Trial 2: Ferrofluid Diffusion Through Simulated Blood-Brain Barrier with 5 Pierced Tight Junctions (with magnet):

The ferrofluid containing iron oxide nanoparticles was able to pass through the selective, tight junction areas scattered in the agar almost instantly over the 24 hours. Once the magnet was centered under the tight junctions, it passed through immediately. Using external magnets to divert and mobilize iron oxide nanoparticles is key in the drug delivery process, so brain regions affected by harmful cells are targeted.

Trial 3: Ferrofluid Diffusion Through Simulated Blood-Brain Barrier with 1 Pierced Tight Junction (with magnet):

The ferrofluid containing iron oxide nanoparticles was able to pass through the selective tight junction areas scattered in the agar almost instantly over the 24 hours. Once the magnet was centered under the tight junctions, it passed through immediately again. This trial was conducted to make it significantly harder for ferrofluid to pass through the punctured holes, even by using a magnet. However, the external magnet's force was strong enough to bring the ferrofluid past the agar, deeming this trial successful.

In the second experiment, which included each of the trials, we found that the iron oxide nanoparticles were able to pass through the agar via the toothpick holes or tight junction formations; however, the ferrofluid took hours to drift past the agar without any immediate result (Trial 1). Upon applying an external magnetic force, such as a neodymium magnet, the ferrofluid swiftly entered the tight junctions and traversed the agar or blood-brain barrier within minutes (Trials 2, 3). On a larger scale, iron oxide nanoparticles are considered effective drug delivery carriers, as they are small enough to pass through tight junctions and exhibit magnetic properties, allowing for individual control over their movement.

Conclusion

In conclusion, magnetic nanoparticles, particularly iron oxide nanoparticles, are promising carriers for drug delivery that can cross the blood-brain barrier (BBB). The BBB limits the efficiency of many therapeutic drugs attempting to enter the brain, as it serves as a membrane that shields the brain from substances like drugs and pathogens. The nanoparticles provide significant improvement for drug delivery systems due to their small size, unique properties, and tunable surface. External magnetic fields can control the iron oxide nanoparticles due to their magnetic properties. The surface charges of iron oxide nanoparticles hold distinct properties like biocompatibility, which proves beneficial in drug delivery applications across the BBB. Positively charged iron oxide nanoparticles are typically used for drug delivery compared to other surface charges because their properties are mainly tailored towards drug delivery. Surface charges on iron oxide nanoparticles allow for clinical variability in specific situations and are important for delivering drugs across the BBB.

Advancements in the magnetic nanoparticle-based drug delivery have opened new pathways for surface functionalization and coatings, which ultimately aid in the delivery process because of their ability to enhance iron oxide nanoparticle abilities and the permeability of the BBB. Furthermore, surface coatings like other therapeutic ligands can assist iron oxide nanoparticles in the drug delivery process across the BBB,

thereby enhancing the performance of these nanoparticles. With surface charges, surface functionalization can additionally be added to iron oxide nanoparticles to boost separate properties that are hindered by the specific surface charge. For example, positively charged nanoparticles may have instability for drug delivery across the BBB; however, adding extra coatings will improve stability rates.

Additionally, magnetic fields may be implemented in the drug delivery process to help iron oxide nanoparticles pass through the BBB and deliver drugs in the brain. External magnetic fields (EMFs) help draw iron oxide nanoparticles towards target sites in the brain, capturing the iron oxide magnetic properties, and reducing side effects in the body. Since the magnetic field controls iron oxide nanoparticle mobility, it ensures effective drug usage in the brain and throughout the bloodstream, which also minimizes harmful side effects. The alternating magnetic field (AMF), a type of external magnetic field, uses the iron oxide nanoparticle properties of magnetism to mobilize iron oxide nanoparticles across the BBB by disruption. In addition, techniques involving the use of BBB disruptors, such as magnetic hypothermia, which effectively allow iron oxide nanoparticles to pass through the BBB, make the delivery process more accessible in clinical applications. These magnetic fields may be amplified based on clinical settings and prove to be significant elements able to aid in iron oxide nanoparticle drug delivery across the BBB.

Despite ongoing research on iron oxide nanoparticles as promising candidates for drug delivery across the blood-brain barrier (BBB), limitations must be considered when evaluating their primary clinical success. As mentioned, external magnets present challenges related to optimization and standards-based trials for drug delivery. Therefore, accuracy in medical situations might prove to be significantly difficult, especially since iron oxide nanoparticles can be immensely enhanced by using external magnets. More experiments to address the effect of specific molecules in the brain, mainly for prolonged exposure, are essential for proper performance. In this study, multiple experiments were conducted to simulate BBB diffusion using ferrofluid; however, the biological complexity of the BBB is not explicitly represented through these experiments. Research addressing the roles of iron oxide nanoparticles and the BBB in relation to each other should be considered. In addition, more research targeting aspects and limitations contributing to the iron oxide drug delivery process must be evaluated to provide safe and effective treatments for neurological diseases. One major limitation is the inconsistent ability to predict results in preclinical studies, making it challenging to predict outcomes in human trials. The size, surface charge, and functionalization of iron oxide nanoparticles complicate the generalization of results across studies. Furthermore, external magnetic field (EMF) manipulations are difficult to translate into clinical experiments due to the limited information surrounding their overall functionality and factors involving their magnetism.

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