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A review on: Novel Drug Delivery System in Magneto Electric Nanoparticles.

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Abstract:

Magneto nanoparticles (MNPs) have undergone significant advancements in recent years, largely due to the rapid growth of nanotechnology and their highly active magnetic core with a high surface-to-volume ratio. The functionalization of their surface has led to a wide range of applications in medicine, gene therapy, and bioactive patch immobilization. By utilizing various colourful functionalization methods, the reactivity of the magnetic core has been effectively controlled, resulting in MNPs that are tailored for the diagnosis and treatment of cardiovascular or neurological disorders, tumours, and cancer. Superparamagnetic iron oxide nanoparticles (SPIONs) are integral components of drug delivery systems and have the potential to serve as efficient agents for magnetic fluid hyperthermia (MFH). With diverse functionalization strategies and unique morphological characteristics, MNPs now offer a wide spectrum of applications, which will be discussed in this comprehensive review.

Keyword: nanoparticles, Magnetoelectric nanoparticles, Drug delivery system.

Introduction:

In recent years, the biomedical area has been dominated by discoveries on the characteristics of micro and nanoparticles (NPs) and their formulations.(1) Because of their small size and huge surface area, nanoparticles have garnered a lot of attention in a variety of application sectors in recent years. This is especially true in situations where high reactivity and mobility in a microchannel are crucial factors.(2) Due to these benefits, current research is moving toward enhancing the range of uses by giving nanoparticles many multifunctionalities for use in environmental and medicinal applications.(3) As a result, scientists have been working extremely hard to create new intelligent materials that can be analyzed for their special qualities and made into nanostructures with special functional capabilities.(1) In order to target point-specific excrescences and perfectly achieve a controlled-release profile appropriate for complaint therapy, magnetic nanoparticles, or MNPs, are the real heart and soul of magnetic delivery systems.(4) Magnetoelectric nanoparticles (MENPs) have a plethora of potential uses in medicine. To far, no other nanoparticle has demonstrated such a strong magnetoelectric (ME) effect.(5) Targeting and triggering mechanisms are the main

methods used to deliver antiviral and anticancer medicines to specific sites using magnetoelectric nanoparticles (MENPs) or ME nanocarriers (MENCs).[1]

Specifically, two phases make up magnetoelectric structures: 1) the magnetostrictive phase, which strains when exposed to an external magnetic field, and 2) the piezoelectric phase, which transducesthe electric charges' absorption of mechanical deformation[6] With their tunable physio-chemical packages and a remarkably high face-to-volume ratio characteristic of nanoparticles, MNPs can be manipulated to fit into drug delivery systems that have sizes similar to those of the body's own proteins or antibodies for improved biocompatibility, while incorporating therapeutic agents that would otherwise be difficult to get to the cancer cells. Systems with improved colloidal stability and decreased aggregation propensity are achieved when biologically acceptable polymers of adipose acids are carpeted over superparamagnetic nanoparticles (SPIONs).[4] There are various multifunctions that have been applied to nanoparticles, including the magnetoelectric (ME) phenomenon, which generates an electric field from an applied magnetic field or vice versa. It is mostly used in research domains where using a magnetic field as the driving source is beneficial.[7] Various applications related to the ME phenomenon, such as magnetic or current sensors, memory devices, high energy density capacitors, energy harvesters, gyrators, resonators, inductors, ME antennas, and magneto-mechano-electric generators, have been developed based on these interactions. The application of multiferroic magnetoelectric nanoparticles (MENPs) with high efficiency requires a high ME coupling effect. In most applications, ME composite structured MENPs are synthesized as core-shell structured composites consisting of a magnetostrictive material and a piezoelectric material. The magnetostrictive material converts a magnetic field into strain, while the piezoelectric material converts stress from the magnetostrictive strain into an electric field. Core-shell MENPs are commonly fabricated using sol-gel and hydrothermal methods. The evaluation of ME voltage coefficients in MENPs involves diverse methods, including the assessment of physics-to-physics conversion efficiency and the mechanical interface coupling between the magnetostrictive core and piezoelectric shell. Various methods have been explored to accurately and reliably characterize ME voltage coefficients by minimizing the artifact error of small nanoparticles.[3]

MNPs were also employed in magnetic resonance imaging (MRI) as discrepancy agents. Functionalization of the receptor antibodies or aptamers for epithelial growth factor results in an efficient opinion tool for many cancer kinds and the identification of brain inflammation. MNPs are Because to their superparamagnetic packages, high reflexivity, high biocompatibility after face functionalization, and low blood toxin content, they are utilized as essential discrepancy agents in MR imaging.[4] Nanoparticles (NPs) and magnetic resonance imaging (MRI)-related diagnostic applications, as well as various theranostic applications involving imaging, often face challenges with undesired distribution leading to side effects on healthy cells and tissues. Therefore, researchers are focusing on modifying materials to improve pharmacokinetics (PK) and biodistribution (BioD) profiles, as well as incorporating targeting ligands for precise delivery of therapeutics. This has led to the development of stimuli-directed nanomaterials for targeted therapy, with magnetic drug delivery systems being a promising technology due to their ability to be directed to specific regions using magnetic fields. Magnetic nanoparticles (MNPs) have been extensively

studied since the 1980s and have shown potential in hyperthermic treatment, site-specific drug delivery, MRI, and overcoming biological barriers. Recent literature reviews have emphasized the significance of magnetic particles, including paramagnetic and superparamagnetic particles, in cancer diagnostics and therapies. These materials respond to externally applied magnetic fields by generating induced magnetic fields, making them attractive for various applications.(1)

Currently, bioactive compounds have been utilized to decorate ME nanoparticles for various purposes, including on-demand drug delivery, nano-electroporation, and brain stimulation. Numerical simulation studies have specifically emphasized that ME materials can serve as facilitators for a detailed mapping of the brain. This is because they generate a magnetic moment when in close proximity to a neuron that is firing its action potential, thereby enabling a "sensing-type" of readout through the inverse magnetoelectric effect. In addition to this crucial function, ME particles have also been suggested as nanoelectrodes for wireless brain stimulation. They have been studied on embryonic hippocampal cells in vitro, delivered to cortical slices ex vivo, or administered via intranasal route or injection at the subthalamic region to remotely modulate neuronal response and customize the local brain activity wirelessly in a mouse model.(6)

Magneto Electric Nanoparticles:

M-NCs-based drug delivery systems face several problems and opportunities in the future. One of these is the drive to create and develop novel materials, like ME NCs. Since ME-NCs have both ferroelectric and ferrromagnetic characteristics in one phase and exhibit dual effect (magnetic and electronic), they are unable to pair with other parameters to exhibit novel properties, i.e., the ME effect. Controlling both electrical polarization and magnetization in a single phase is made possible by this phenomenon. Utilizing the ferroelectric phase's piezoelectric capabilities, energy is converted from magnetic to electric. Ferromagnetic phase's piezomagnetic characteristics . Structurally compatible, very stable (chemical, thermal, and mechanical), and simple to prepare are the main benefits of ME-NCs over M-NCs. ME-NCs are typically core-shell structures with a shell that has the appropriate electrical properties and a magnetic core that is retained.(8) Materials with tunable properties and repeatable features are produced as a result of the careful tuning of the structure and phase fraction of the ME-NCs formulation made possible by the control over the core size and shell thickness. Traditionally, the synthesis of core-shell nanoparticles is done in two consecutive Steps:

(i) the ferrite NPs precipitate; (ii) each NP is surrounded by a shell.

Because of the aforementioned special qualities, ME nanostructures have been applied to transduction, spintronics, optical devices, and sensors in addition to drug delivery. Furthermore, low remote ME field can be used to create ME-NCs, which are dissipation-free, energy-efficient, and low-field on-demand tailored drug release. (12) Nevertheless, ME nanostructures may consist of inorganic-inorganic nano-composites and organic-metal oxide frameworks. ME-NCs introduce a novel ion-free dissipation mechanism for achieving a highly efficient externally

regulated drug release process at the subcellular level through the use of remote low-energy direct current and/or alternating current (a.c.).[8]

The intrinsic electric fields within the NPs can be efficiently controlled by applying an external magnetic field, resulting in a non-zero magnetic moment for ME-NCs. At the Center of Personalized Nanomedicine @FIU, our research group has investigated the potential of ME-NCs for the safe delivery and controlled release of anti-retroviral (ARV) drugs across the blood-brain barrier (BBB) using a low-energy a.m. magnetic field. This approach also holds promise for non-invasive stimulation of neural activity deep in the brain to address Parkinson's disease.[13]

In a groundbreaking collaboration between Dr. Nair's group and Dr. Khizroev, computational technology was employed to predict the artificial stimulation of neurons using ME-NCs within the brain. Yue et al. successfully demonstrated this concept, proposing a non-invasive technique that utilizes the magnetic dipoles of ME-NCs to couple with neuronal electric signals. This established protocol has the potential to stimulate the brains of Parkinson's disease patients noninvasively, bringing the pulsed sequences of the electric field to levels comparable to those of healthy individuals. Simulation results indicated that a concentration of 36 × 106 particles/cc, with a size of 20 nm, and an externally applied magnetic field frequency of 80 Hz (at 300 Oe) can achieve the desired. The field-controlled ME-NP drug formulation exhibited a unique capability for field-triggered release across the BBB, thanks to its intrinsic magnetoelectricity. By applying an external magnetic field, the electric forces within the drug-NCs bonds enable remotely controlled delivery through the coupling of ME properties.[13]

Principle of Magneto Electric:

The magnetoelectric (ME) effect refers to the alteration in the electric polarization P of a material when subjected to a magnetic field H (direct effect), or the modification in the magnetization M of a material when exposed to an electric field E.

Physical Properties of Magneto Electric Nanoparticles:

Magnetic nanoparticles (MENs) with a diameter of 30 nm were synthesized using a hydrothermal process. These MENs had a core shell composition of CoFe2O4@BaTiO3, consisting of a ferromagnetic spinel core (CoFe2O4) that enhanced the magnetic moment, and a perovskite shell (BaTiO3) that induced magnetoelectricity. This composition was observed in a transmission electron microscopy (TEM) image shown in Figure. The functionalization chemistry plays a crucial role in ensuring that the drug remains firmly attached to the nanoparticles until an external control command is given. This control command is applied through the use of an alternating current (a.c.) magnetic field, which releases the drug from the MENs. It is important to note that while the drug is attached to the nanoparticles, it does not exhibit significant bioactivity. Therefore, it is safe to transport the drug-loaded MENs through the circulatory system towards the desired target site without causing any toxicity effects. In line with this in vitro investigation, a thin layer of glycerol-monooleate (GMO) measuring 2-nm in thickness was applied as an intermediate coating on the surface of MENs. This coating served as a mediator between MENs and PTX, facilitating a specific a.c. release field of approximately 50 Oe (100 Hz). Figure 1b displays the hysteresis loops obtained through vibrating sample magnetometry (VSM) for 30-nm MENs and 30-nm CoFe2O4 ferromagnetic nanoparticles (FNs). The FNs were utilized as control nanoparticles, exhibiting a significantly higher saturation magnetization (approximately 40 times greater than that of MENs (~1 emu/g)), but they did not exhibit any ME effect. This disparity between MENs and the control FNs aids in comprehending the distinct roles played by electric and magnetic fields in the examined delivery mechanism. Figure 1c illustrates the magnetic field dependence of the measured Zeta Potential (ZP) for 0.5 mg of MENs in a 1-ml PBS buffer solution with a pH of 7.3 (similar to that of blood). It is worth noting that a variation in the d.c. magnetic field from 0 to +/−100 Oe resulted in a ZP increase of more than 30%. Furthermore, the value of ZP solely relied on the strength of the field and was independent of the field's orientation.The Zeta Potential (ZP) reflects the equilibrium surface charge of nanoparticles in a liquid solution, influenced by double-layer chemistry. This charge plays a role in interacting with electrically charged cell membranes, impacting the cellular uptake of nanoparticles. The discovery of a strong magnetic field dependence of ZP is crucial for facilitating externally-controlled targeted delivery. A Magnetic Force Microscopy (MFM) image in Fig. 1d displays naked MENs on a silicon oxide substrate, magnetized along an in-plane direction by an external biasing field H (of 100 Oe). The contrast in the MFM image reflects the dipole orientation along the field direction. In Fig. 1e, a Scanning Tunneling Spectroscopy (STS) I-V curve from a point contact between a tungsten nanoprobe and a MEN at different field values (-100, 0, and 100 Oe) shows that the nanoparticles' conductivity increases with a d.c. magnetic field. This effect is independent of the field orientation, similar to ZP measurements.[17]

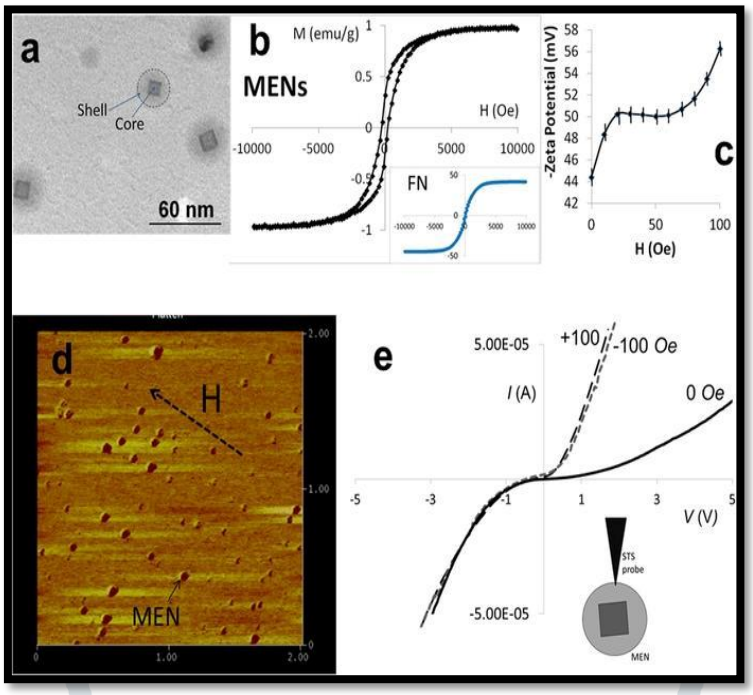

Fig: Transmission Electron Microscopy (TEM) image showing the core shell nanostructure of MENs.

Magneto Electric Composite Material:

The ability of magnetoelectric (ME) composites to either induce magnetization in reaction to an externally provided electric field or to polarize in response to an applied magnetic field allows for the ME effect to occur at room temperature. This property is crucial for the biomedical applications of ME composites. Furthermore, the coupling of ME composites' electric and magnetic characteristics offers remarkable chances to build charges in the absence of electrical connections, enabling less intrusive integration into wearable and implantable electrodes, energy harvesters, sensors, and other devices. Comprehensive summaries of electroactive materials and composites, specifically piezoelectric materials, have been given elsewhere. [14]

The combination of piezoelectric and magnetostrictive phases in composites, such as polyvinylidene fluoride (PVDF) and metglas or Terfenol-D, has led to significant magneto-electric (ME) properties. These strain-induced ME effects have resulted in the development of composites, both polymer-based and hydrogel-based, that exhibit ME coefficients of up to 370 V/(Oe cm) when subjected to an externally applied magnetic field at room temperature . This value is close to that of human body temperature, making these composites highly promising for a wide range of tissue engineering applications.[15]

ME materials in the form of core-shell nanoparticles have attracted significant attention for a range of drug delivery systems. They enable precise control over tissue regeneration processes through an external magnetic field, facilitate wireless powering of small implantable devices without causing harm to tissues, and help in avoiding the need for multiple surgeries and the associated risks of infection or other complications.[16]

Materials and Magnetoelectric Properties of Core–Shell Structured MENPs:

Core–shell structured MENPs are multiphase heterostructured ME composites at the nanoscale, as illustrated in Figure. In these composites, the ME property is achieved through elastic interfacial coupling between the magnetostrictive and piezoelectric phases under a magnetic field. The core of MENPs typically comprises ferromagnetic materials with a spinel structure (AB2O4) exhibiting magnetostrictive properties and a high magnetic moment. On the other hand, the shell is usually made up of ferroelectric materials with a perovskite structure (ABO3), demonstrating spontaneous electric polarization and piezoelectric properties. Examples of ferromagnetic materials for the magnetostrictive core include Fe3O4, NiFe2O4, and CoFe2O4, while perovskite materials for the piezoelectric shell consist of PbTiO3, BaTiO3, and BiFeO3. In cases where the core and shell of the core–shell MENP are the piezoelectric and magnetostrictive phases, respectively, the application of a magnetic field to the MENP results in the partial shielding of the transmission of the electric field generated by the piezoelectric core to the surrounding area by the shell. This leads to the transmission of electric energy to tissues or reactants in the vicinity of the MENP. The strategic selection of suitable materials is essential for achieving significant ME effects in MENPs. Furthermore, the interfacial coupling between the core and shell plays a crucial role in enhancing the mechanical transmission from the magnetostrictive core to the piezoelectric shell. To achieve this, clearly defined boundaries between different phases without interfacial chemical diffusion, facilitated by low synthesis temperatures, promote elastic interfacial coupling, thereby ensuring high ME effects while maintaining chemical, thermal, and mechanical stability.

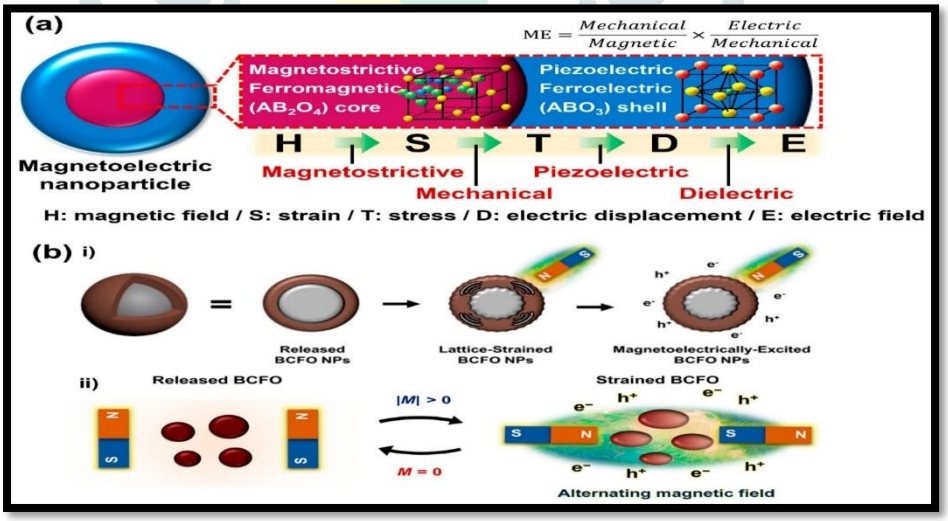

Fig: Magnetoelectric (ME) effect of MENPs.

The ME coupling In MENPs is illustrated in Figure . The dielectric asymmetry present in MENPs generates an electric field, which is then propagated to the surrounding area when subjected to alternating magnetic fields (Figure (i)). In most cases, the surface of MENPs experiences an induced electric potential due to alternating electrical

polarization. Initially, when an alternating magnetic field is applied, the magnetostrictive core undergoes vibrational lattice strain, which is subsequently transmitted to the piezoelectric shell as stress through the mechanical interface coupling between the different phases of the core and shell. This stress is then converted into electric polarization through the piezoelectric effect, resulting in the continuous generation of an electric field in the MENPs upon repetitive application and removal of the magnetic field, as depicted in Figure (ii). Consequently, an electric field is induced on the surface of MENPs, leading to the generation of charge carriers, namely electrons (e-) and holes (h+), within the tissue.[3]

Common Synthesis Strategies of Magneto Electric Nanoparticles:

Bottom-up methods, including hydrothermal, sol-gel, solvent evaporation, and solid-state reactions, can be employed to synthesize MENPs. The sol-gel and hydrothermal syntheses are particularly popular for producing magnetostrictive and piezoelectric phases in core-shell structured MENPs. The sol-gel method is advantageous in achieving the desired particle size as the synthesis conditions can be easily regulated by adjusting the pH, temperature, and concentration.[18] To achieve this, a uniform precursor solution is prepared by dissolving the initial material in a solvent with the appropriate pH and increasing the reaction temperature, causing ionization through hydrolysis. Once the precursor solution is evaporated, a dehydrated gel is formed through the polycondensation of alkoxides. Subsequently, the obtained gel is calcined at high temperatures, resulting in the formation of nanocrystalline materials. One notable study conducted by Song et al. utilized the sol-gel method to synthesize core-shell CoFe2O4@BaTiO3 (CFO@BTO) MENPs. These MENPs consist of magnetostrictive CoFe2O4 cores with piezoelectric BaTiO3 shells, as depicted in Figure . To coat the CFO cores with BTO shells, BaCO3 and Ti(OCH(CH3)2)4 were dissolved in a citric acid solution to generate Ba and Ti ions. The precursor solution containing Ba2+ and Ti4+ was then combined with the CFO nanoparticles, leading to gelation around the CFO cores upon evaporation. Finally, thermal annealing resulted in MENPs with a shell nanoarchitecture of BTO and a size of 50 nm.[19]

The hydrothermal technique offers the benefits of enhanced solubility and rapid reaction of starting materials at high temperatures and pressure within an autoclave, thereby decreasing the energy and cost needed for the process. Initially, the precursor solution, consisting of the raw materials, creates an amorphous layer with B-site ions in the perovskite structure (ABO3) through hydrolysis and aging. Subsequently, in the hydrothermal reaction within the autoclave, A-site ions are integrated into the amorphous layer near the supercritical point of water. Rongzheng et al. utilized Fe3O4@PbTiO3 core–shell particles to showcase the efficiency of the hydrothermal synthesis approach. To encapsulate Fe3O4 nanoparticles produced via the hydrothermal method with PbTiO3 shells, Ti4+ ions from the Ti(SO4)2 precursor developed a uniform layer on the Fe3O4 nanoparticles through an aging process. Following this, nanocrystalline PbTiO3 shells were created by incorporating A-site Pb2+ ions into the Ti hydroxide layer, at relatively low temperatures due to the high-pressure conditions in the autoclave. Furthermore, annealing was conducted to achieve more crystalline and compact core–shell Fe3O4@PbTiO3 particles.[20]

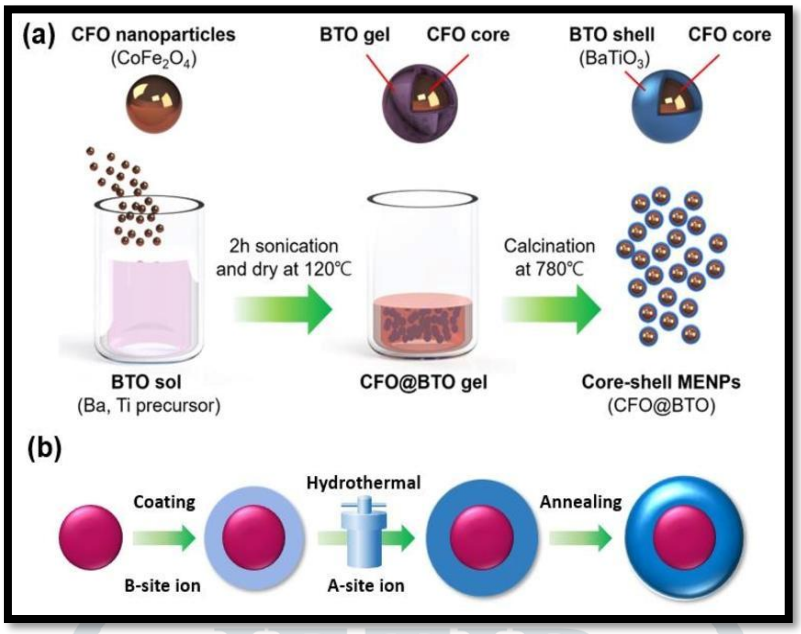

Fig: Widely adopted fabrication methods of MENPs with core–shell structure**.**

Furthermore, MENPs with an irregular structure were fabricated using the solid-state reaction method instead of a clear core-shell structure. In this process, piezoelectric BTO and magnetostrictive Ni0.5Co0.5Fe2O4 (NCF) were milled and combined to create BTO-NCF MENPs. The solid-state reaction involves mechanical mixing and ion diffusion at elevated temperatures. Moreover, single-grain BTO-(Mn0.5Zn0.5)Fe2O MENPs of different geometrical shapes were produced through the solid-state reaction technique.[21] Various methods have been utilized to create ferroelectric and ferromagnetic nanocrystals, including microemulsion-based, solvent evaporation, and sonochemical syntheses. In the microemulsion-based approach, nanocrystals are formed through the reaction of inorganic salts and the subsequent removal of water. This method has successfully produced MENPs containing CFO and BFO. Solvent evaporation is ideal for generating pure MENPs as impurities are easily eliminated during evaporation. For instance, BiFeO3 was synthesized by drying metal ions mixed with organic molecules followed by calcination. Sonochemical synthesis involves the agglomeration of nanoclusters due to the collapse of bubbles from acoustic cavitation, leading to the formation of perovskite nanocrystals like SrTiO3 nanoparticles after calcination.[3]

Application of Magneto Eclectric Nanoparticles:

1) Drug Delivery

2) Brain stimulation

3) Cell regeneration

4) Electrocatalyst

5) Imaging

1)Drug Delivery :

Traditional drug delivery techniques are effective in treating common illnesses, but they may not be sufficient for more complex diseases like ovarian cancer and AIDS, where traditional drug therapy methods fail to reach viral reservoirs. Therefore, there is a need for an improved and targeted drug delivery system. In this context, MENPs have the potential to revolutionize drug delivery systems due to their exceptional characteristics as nanocarriers. Their ability to generate electric fields internally is advantageous for biomedical applications, as living cells possess inherent electrical properties and rely on them for essential recovery functions. Additionally, the most remarkable and beneficial feature of MENPs is that their excitation can be wirelessly controlled by applying a low-frequency magnetic field.[(22)] MENPs serve as effective drug delivery nanocarriers, facilitating precise drug delivery in line with current research trends. While MNPs share similar traits like magnetic moments for targeted cell delivery, MENPs stand out due to their piezoelectric shell allowing controlled drug release through the electric field produced by the ME effect. Research indicates MENPs enhance drug efficacy compared to MNPs, with detailed examination of the bond-severing process between therapeutic agents and MENPs.

It was hypothesized that a symmetric ionic bond exists prior to the application of a magnetic field, resulting in the formation of an electric dipole moment. However, the introduction of a magnetic field disrupts this symmetry, causing a weakening of the bond where the dipole is induced, while strengthening the bond at the opposite end of the dipole. By precisely exciting the AC magnetic field, the direction of the dipole moment changes, leading to the uniform disruption of all bonds and the release of the agent. A carefully controlled electric field not only enables the controlled release of therapeutic agents but also triggers electroporation. This method has demonstrated superiority over other physical techniques for drug delivery, showcasing enhanced drug efficacy due to direct delivery into cells. In this approach, an electric field is utilized to enhance cell membrane permeability or open pores, thereby increasing the absorption of therapeutic agents. The main factors contributing to pore opening include electrostatic repulsion that alters the phospholipid bilayer and the continuous variation in membrane conductivity. Despite its benefits, the efficiency of electroporation heavily relies on the distribution and duration of voltage. Excessive excitation of high intensity and duration may result in unintended cell death. Nevertheless, electroporation using MENPs can target specific cells near a low-frequency, specific electric field generated by MENPs, known as nano electroporation. Due to the nanoscale of MENPs, the electric field produced is harmless to cells. Furthermore, nano electroporation significantly enhances the absorption of therapeutic agents, improves cell viability, and allows delivery across semipermeable barriers like the blood-brain barrier. Research indicates a five-fold increase in efficacy when MENPs are utilized as carriers compared to other carriers like HER-2 antibodies.

Magnetic iron oxide nanoparticles (MENPs) exhibit a strong attraction to various agents and medications that necessitate precise delivery methods, such as antiviral drugs for HIV treatment, CRISPR-Cas9/gRNA for latent HIV infection, and antiretroviral drug administration. The efficacy of drug delivery was demonstrated through the use of electroporation, cell targeting, and cell transport facilitated by MENPs. By subjecting human epithelial cells (HEP2)

to a 50 Oe AC magnetic field at 60 Hz, a single MENP was able to reduce its impedance, leading to cell permeation, intercellular communication, and electromechanical movement within the cells. Moreover, when a 40 Oe AC magnetic field at 30 Hz was applied, MENPs could navigate to the desired location without interacting with the cell membrane phospholipids. Continuous exposure to a 50 Oe DC magnetic field directed towards the microchannel outlet demonstrated that MENPs could manipulate live cells, guiding them to the target area by generating thrust. The outcomes of this in vitro investigation revealed predominantly positive effects of MENPs, with no significant toxicity reported. Biocompatibility assessments on HEP2 and NG-108 rat neuronal cells further confirmed the potential of MENPs as nanocarriers for improved targeted and controlled drug release without adverse effects.[3]

2) Brain stimulation:

Electric field brain stimulation has been shown to effectively alleviate symptoms of brain diseases, such as involuntary shaking in Parkinson's disease. Traditional methods involving electrodes can be invasive and lead to unwanted vibrations. Additionally, these methods may not provide uniform stimulation and could result in negative effects due to energy dissipation. Less invasive techniques like transcranial magnetic stimulation (TMS) face challenges with depth and focus, limiting their effectiveness in stimulating specific brain regions. Other devices using magnetic induction or optoelectronics may not penetrate deeply enough. MENPs offer a promising solution by providing precise and uniform brain stimulation wirelessly after an initial injection. The magnetic field can control the distribution of MENPs due to their magnetic moment, resulting in minimal energy dissipation and potential damage to brain cells. This approach may also help in understanding neural networks and improving imaging techniques. MENPs show great potential as a non-invasive and effective option for deep brain stimulation.

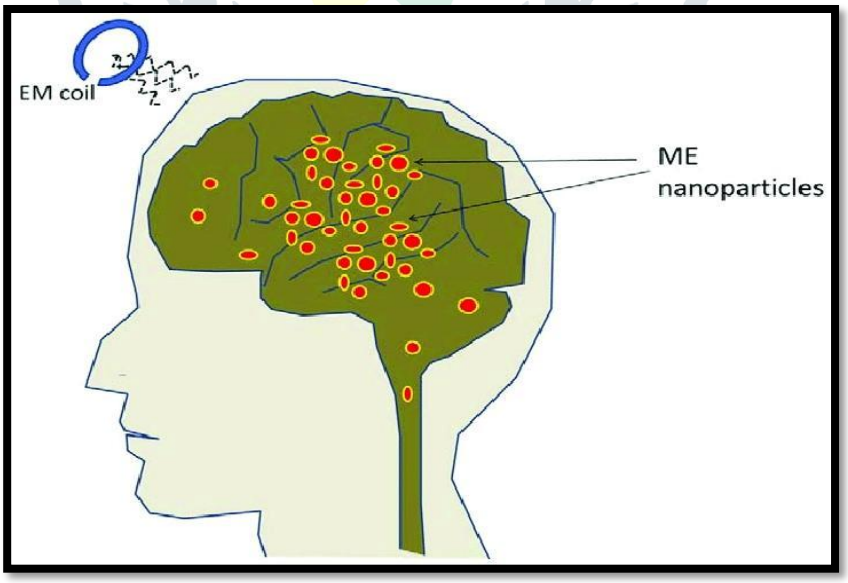

Fig:Illustration of human brain stimulation using MENPs.

Numerous studies have verified that the utilization of MENPs poses no harm to living organisms. However, in order to ascertain their efficacy and safety as brain stimulants, thorough investigations are necessary. A groundbreaking

computational study has proposed that the use of MENPs surpasses established techniques like DBS with implanted electrodes. This study compared the typical electric field signals of a Parkinson's disease patient's brain when exposed to different treatments. The findings indicate that after being stimulated with MENPs, the electric field signals of the diseased brain resembled those of a healthy brain more closely compared to conventional therapies. Subsequent to this initial computational study, various effects and phenomena of MENPs for DBS have been observed and extensively examined. An in vitro study confirmed an increase in neuronal cell activity by measuring intracellular Ca2+ when MENPs were activated using AC and DC magnetic fields. Additionally, the number of c-Fos-positive cells in mice significantly increased, which is a common indicator of neurons firing action potentials. The postmortem examination of the mice's brain cells confirmed the elevated number of c-Fos-positive cells in the nonmotor thalamic region and the absence of neuroinflammation. Due to their numerous advantages and superior characteristics, MENPs can be considered an alternative to conventional brain stimulation methods as they allow for stimulation of the inaccessible subthalamic region.[13,26]

3)Cell regeneration:

Furthermore, MENPs have the potential to be beneficial in various medical applications apart from those related to the brain. These nanoparticles have the ability to stimulate cell differentiation, a crucial process in cell regeneration. A study conducted in a laboratory setting. It is widely recognized that electrical stimulation not only triggers differentiation but also influences cell proliferation and protein secretion, among other effects. However, current methods of electrical stimulation rely on invasive electrodes. In contrast, electrostimulation using MENPs would be non-invasive and could enhance the distribution and efficiency of stimulation. Although piezoelectric materials can also be used for non-invasive electrical stimulation in certain cases, they are limited by the requirement for specific movements that may harm cells. MENPs offer a simple solution to this issue due to their unique and convenient characteristics for wireless electric stimulation. This was confirmed by an in vivo study involving a patient with a spinal cord injury, where a combination of MENPs and biocompatible polymeric materials successfully stimulated and facilitated the regeneration of functional axons. Additionally, the ME effect of MENPs can be utilized to stimulate the brain and potentially eliminate specific Alzheimer's β-amyloid aggregates, which are believed to contribute to the gradual degradation of cells. This stimulation may also enhance the function of brain cells.

Magnetic nanoparticles (MENPs) can be integrated with a biocompatible scaffold to promote bone cell growth . Scaffolds are commonly utilized to enhance the diffusion of oxygen, nutrients, and waste products, which are crucial during the initial stages prior to vasculogenesis or angiogenesis. Current research on bone regeneration focuses on developing scaffolds that can be combined with specific biochemical molecules to facilitate tissue growth. Due to the beneficial impact of MENPs on cell regeneration, they can be included in scaffolds to boost the cell growth process. Consequently, a notable 134% increase in cell proliferation was observed when scaffolds were combined with magnetically stimulated MENPs. Furthermore, fluorescent images revealed that MG63 cells adhered effectively

to the scaffold, demonstrating successful bone cell growth and underscoring the significance of MENP-induced electrical stimulation in enhancing cell viability.[3]

4) Electro catalyst:

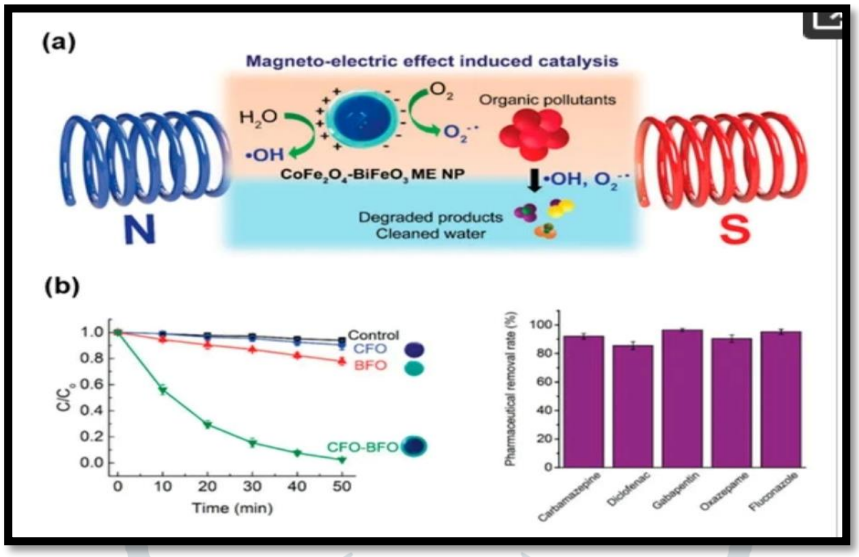

Fig: Applications of MENPs as degradation catalysts for wastewater purification.

Proper water treatment is essential for ensuring and preserving the future supply of safe drinking water, especially as industrialization continues to expand. Magnetic and electrically active nanoparticles (MENPs) have emerged as a promising solution for wastewater treatment, specifically in the degradation of organic pollutants. While current technology primarily focuses on the use of photocatalysts and magnetic nanostructures as recoverable carriers for catalytic materials, the potential of nanoparticles with magnetoelectric properties has been overlooked. Research has shown that MENPs can initiate a redox reaction, leading to the formation of hydroxyl and superoxide radicals. This unique characteristic significantly enhances the efficiency of degrading organic water pollutants, with degradation rates reaching up to 97% within a short period of less than an hour (as depicted in Figure a). In comparison, other nanoparticles, such as magnetic nanoparticles, do not exhibit the same level of efficiency within the same timeframe. Furthermore, MENPs have also demonstrated the ability to remove common pharmaceuticals from water with an efficiency of up to 85% (Figure). These impressive results highlight the potential of MENPs as catalysts in wastewater purification. Despite the promising findings, the number of studies exploring the application of MENPs in water treatment remains limited. However, considering the escalating pollution levels and ongoing climate changes, this approach is expected to play a crucial role in the future. By harnessing the unique properties of MENPs, we can address the pressing need for effective wastewater purification and contribute to the preservation of our environment and public health. [24]

5) Imaging:

Magnetic resonance imaging (MRI) is commonly used for the non-invasive examination of the brain and internal organs, providing high-resolution images that are essential for healthcare in hospitals. MRI allows for the detection and diagnosis of various diseases, particularly in the brain. Magnetic nanoparticles (MNPs) can be utilized as a contrast agent to enhance imaging quality. On the other hand, magnetic particle imaging (MPI) is a developing magnetic-based imaging technology that differs from MRI in its approach. MPI does not detect signals from magnetically aligned atoms, but instead traces MNPs and detects voltage changes due to magnetization. This method is more sensitive and can not only produce images but also quantify changes. The ability to map neural activities in more detail makes MPI a promising imaging technique. By utilizing MNPs with magnetic effects, MPI has the potential to further enhance the imaging process.

Numerical simulation studies have revealed that MENPs are capable of producing small magnetic moments during the propagation of action potentials along neural axons, as illustrated in Figure .

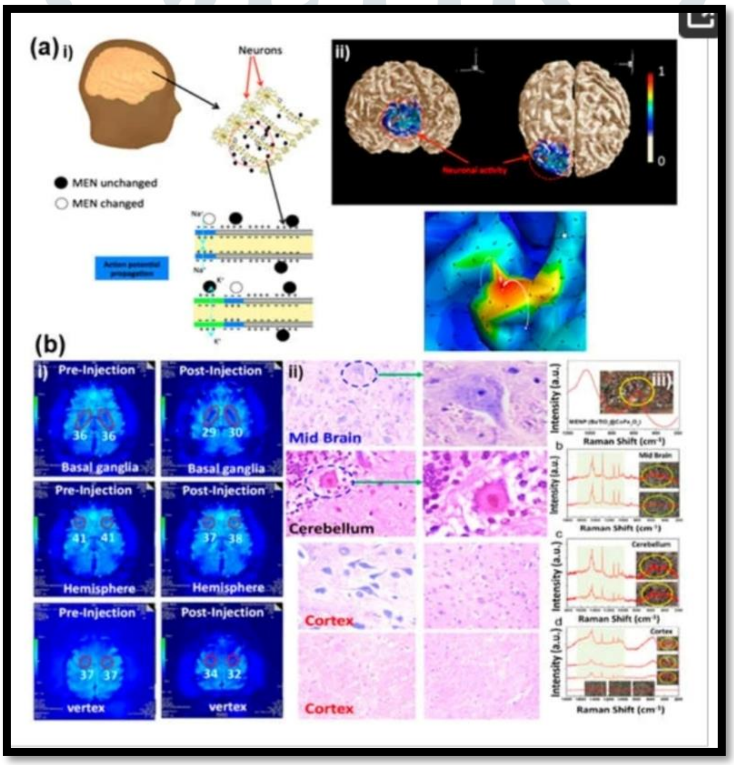

Fig: Brain mapping by detecting magnetic signals induced by MENPs located on the targeted brain or other tissues.

This phenomenon occurs as a result of the magnetic moments of MENPs aligning near the axons in response to a reversed local electric field, leading to a discernible change in magnetic image contrast. Consequently, this approach offers a means to observe the intricate neural activities of cells. Moreover, the alteration in the action potential of the excitatory postsynaptic potential originating from the neuron's apical dendritic tree exhibits a longer duration and is

theoretically more detectable than action potentials. A study has showcased the potential for enhancing brain imaging with MENPs through MPI. The benefits of MPI, including rapid temporal resolution and heightened sensitivity, facilitate the identification of potential alterations and, consequently, the detailed mapping of brain activity, as depicted in Figure b. While there is currently a lack of in vivo studies confirming the efficacy of MENPs in enhancing brain imaging, computational investigations suggest promising prospects, and other research indicates the safety and complete excretion of MENPs within 8 weeks. Further comprehensive research in the field of biomedical imaging is imperative to advance our comprehension of the brain and other bodily tissue.[3]

Future challenges:

The extensive utilization of ME nanoparticles has been a significant focus in the field of bone tissue engineering, as it plays a crucial role in enhancing bone healing, rejuvenation, and integration with artificial implants. While various bone formation strategies have been previously developed, the creation of new intelligent materials for artificial implants remains challenging. This is because implantable materials for bone tissue engineering must fulfill specific requirements such as bioactivity, biocompatibility, mechanical strength, durability, microstructure, porosity, and rapid response to the surrounding environment after implantation. Numerous ME composites have been developed and investigated for tissue engineering applications. For instance, the combination of poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) with cobalt ferrite nanoparticles has shown promise in magneto- and electroactive tissue engineering. However, the release of cytotoxic cobalt ferrite nanoparticles during magnetoactive operations poses a concern. Therefore, it is necessary to explore the use of biocompatible ferrites like Fe3O4 or non-toxic alternatives such as MnFe2O4 to replace cobalt ferrite. By using non-toxic materials, the released particles will not have any detrimental effects on cells. Additionally, Fe3O4 nanoparticles are the only oxide nanoparticles approved by the FDA for clinical use, making FDA approval a challenge that needs to be addressed. Furthermore, the mechanical properties of the ME composites, such as compressive strength and Young's modulus, can be affected by the rigid reinforcement effect of the ME nanoparticles.[4]

Conclusion:

Various MNP platforms are currently in existence and are undergoing rapid development. These MNPs can be utilized for diagnostic purposes (such as MR imaging contrast agents) and therapeutic treatments for various conditions, including both early-stage and advanced forms of cancer. By employing surface modifications (such as silica, gold, or biocompatible polymers like PEG or dextran), stable MNP systems can be created with minimal aggregation or opsonization, resulting in reduced systemic response and enhanced ability to pass through biological barriers (reticuloendothelial, vascular endothelium, or blood-brain barrier). The primary goals include achieving improved biocompatibility, precise targeting, and increased accumulation of target cells to elicit the desired biological response. Multifunctional MNPs have the potential to provide diverse therapeutic strategies for healthcare professionals. Furthermore, a recent research direction focuses on utilizing innovative (nano) particle imaging (MPI) for personalized imaging and targeted treatment approaches, effectively linking imaging contrast and efficacy to

therapeutic mechanisms while emphasizing a favorable safety profile. With no loss of signal intensity, MPI based on innovative nano tracers, typically SPIONs, could offer superior imaging contrast, spatial and temporal resolution, and an excellent signal-to-noise ratio. The emerging field of MPI heavily relies on the successful implementation of innovative tracers, which can benefit from the ongoing advancements in MNPs utilized for drug delivery applications.

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