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Magnetically Modulated Nanoparticles for Medical Application: Diagnosis, Drug Delivery, and Therapy

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Nanoparticles range in size from 1-100 nm although much larger nanoparticles i.e. up to 300 nm, are widely reported for medical application. Current trends in drug delivery research have shifted focus toward the designing of the "smart" drug delivery systems (DDS) for spacial and temporal control of the drug delivery. When a magnetic moiety is added to a DDS i.e. nanoparticle or liposome, it can be retained in a specific part of the body through localized magnetic field. These magnetically modulated drug delivery systems (MDDS) can also carry payload to deep lying tumor tissues which are difficult to target with other targeting modalities. MDDS are also used as hyperthermic agents under the influence of externally applied alternating magnetic field. Not only the magnetic hyperthermia can kill cancer cells but also causes phase-change in nanoparticles to induce abrupt drug release. Magnetic resonance imaging (MRI) is a diagnostic techniques used to image disease specific changes in tissues using contrast agents such as iron oxide nanoparticles. When iron oxide nanoparticles are loaded with drugs, they act as a contrast agent and carrier for targeted drug delivery which is revolutionizing medical field. In addition to drug delivery applications, magnetic nanoparticles are also being used in biosensors for identification and separation of target molecules/cells from complex mixture. However, challenges associated with optimized particle size, selection of biocompatible materials, and fate of MDDS after in vivo application need to be addressed. Emerging literature also points towards interaction of magnetic field with human body. Thus, carefully tailored magnetic modulated nanoparticles are expected to emerge as a key player in medical field due to their unique diagnostic, therapeutic, sensing and multifunctional application.

Keywords: MRI, Nanoparticles, Liposomes, Hyperthermia, Hydrogels, Thermoresponsive

INTRODUCTION

Current trends in the drug delivery research have shifted focus toward designing the "smart" drug delivery systems (DDS) that can provide spatial and temporal control of drug delivery[1]. Spatial control of drug delivery is important because many new therapeutic agents are non-specific i.e. they can affect both healthy and disease-affected cells[2]. This objective has been achieved by devising targeted drug delivery systems that can carry the drug exclusively to the disease-specific tissues. Temporal control of drug delivery systems is required in a situation where delayed or sequential drug release is desirable[3]. Novel DDS have been employed for diagnostic applications ranging from whole organ imaging to single-cell detection[4]. Recent developments of dual modalities ensure diagnosis, targeting, and treatment of challenging diseases in a single administration.

The curiosity to identify the medical benefits of the magnetic field started as soon as the discovery of the magnetic field. Although a lot of claims have been made of its potential benefits, scientific proof of such claims is limited or even absent in some cases. In pharmaceutical sciences, the magnetic field has shown promising applications to control the site and rate of release of potent therapeutic agents from DDS by externally applied magnetic field[5]. Magnetically modulated drug delivery systems (MDDS) have attracted vast interest in medical research due to the many important properties of the magnetic field. First, the magnetic field can easily pass through the body and the magnetic permeability of the human body is roughly the same as that of air[6]. This provides the opportunity to target MDDS to deep tissues which is a limitation of most other targeting strategies. Second, the magnetic field is generally considered safer than radiations and, currently, there are no clinically proven side effects after short-term application for diagnostic and therapeutic applications[7]. When a magnetic moiety is added in a DDS i.e. nanoparticle or liposome, it can be retained in a specific part of the body through a localized magnetic field. These MDDS can carry a payload to deep-lying tumor tissues which are difficult to target with other targeting modalities. Magnetic nanoparticles (MNP) are also used as hyperthermic agents under the influence of externally applied magnetic fields to induce drug release from DDS or as thermotherapy to kill cancer cells[8–9]. Diagnostic applications of MDDS ranges from MRI contrast agents to magnetic cell separation techniques. This review article discusses different applications of magnetically modulated drug delivery systems. Various medical applications that have been enhanced by a magnetic field are summarized in table 1. Magnetic field can be used at three different frequency ranges that are static, time-varying and radio frequency. Due to the phenomenon of coexistence of electrical and magnetic fields, reports have emerged on the unwanted health effects.

MAGNETISM IN DIAGNOSIS

A magnetic field has been largely used for imaging and cell separation due to lesser side effects than the use of hazardous radiations. It is also replacing surgical procedures to obtain biopsies which is a common method used for the diagnosis of many diseases.

Magnetic Resonance Imaging:

MRI is a non-invasive diagnostic technique that uses a magnetic field to produce a three-dimensional image of different body tissues and organs. MRI operation involves placing the patient in the strong magnetic field that will make protons in mobile water of the body, usually hydrogen nucleus, to align along with the applied field. Then, a radiofrequency pulse is passed through the body that will stimulate the protons to pull out of the applied field. When the radiofrequency source is removed, protons revert to realign to a normal state and release energy[10]. The time protons take to realign with the magnetic field and the amount of energy released are characteristic of the anatomical environment and chemical nature of tissues. Due to the absence of ionizing radiations, MRI is considered superior to CT scan and X-ray-based imaging techniques especially when repeated imaging is required[11]. MRI has also effectively replaced invasive procedures to obtain biopsies in many diagnostic applications. In addition, MRI is more suitable for soft tissue imaging than other imaging modalities[12]. Native contrast in MRI imaging is proton density, T_1 relaxation (recovery of longitudinal magnetization), and T_2 relaxation (recovery of transverse magnetization).[13] However, contrast-enhancing agents may be given to the patient before MRI to facilitate the faster realignment of protons and produce a brighter image.[14] These contrast agents may act at any sub-atomic event in the magnetic resonance mechanism. Iron oxide nanoparticles have emerged as excellent contrast agents in cancer detection with added benefits of their theranostic activity.[15]By controlling magnetic field and radiofrequency pulse, a wide variety of pathologies can be diagnosed due to changes occurring in proton density during the disease. The first step in MNP enhanced MRI is the systemic injection for site-specific accumulation by application of magnetic field or by attachment of targeting ligand[16]. Then, MRI is performed for high-quality imaging (figure 1). MNP coating with antifouling agents prevents surface attachment of proteins and other biological moieties that can limit contrast efficiency in the body[17]. MRI has also been used in combination with drug-loaded nanoparticles for image-guided drug delivery. Similarly, MRI has been used to induce hyperthermia from MNP which will be

Table 1. Diagnostic and treatment applications of magnetically modulated nanocarriers in different medical conditions.

Application	Magnetic system	Mechanism
Diagnosis	Magnetic Resonance Imaging (MRI)	MRI is an imaging technique which measures changes in proton density in target tissues that occur during course of disease.
	Magnetic cell separation	Target cells are tagged with magnetic nanoparticles and magnetic field is applied to separate the tagged cells.
	Immunoassays	Antibodies are conjugated to the magnetic nanoparticles and magnetic field is applied to collect nanoparticles bound antibody-target molecule (antigen) complexes.
Cancer treatment	Alternating magnetic field (AMF) for thermotherapy	Magnetic nanoparticles are given to patient that accumulate in cancer. Then, AMF is applied which produces hyperthermia to kill cancer cells.
	MRI for image guided therapy	This involves administration of magnetic nanoparticles for imaging of cancer using MRI. Then, high frequency AMF is applied to produce hyperthermia, as in thermotherapy, or to induce release of co-loaded drug for treatment.
Brain function study	MRI	Changes in blood flow during performance of different tasks shows which part of brain is associated with the function.
Drug delivery	Static magnetic field	Magnetic nanoparticles are attached to drug delivery systems and an externally applied magnetic field is used to guide their transport in the body.
	MRI	MRI of is used to produces hyperthermia to induce drug release from magnetic nanoparticles tagged drug delivery systems.
Psychic diseases	Transcranial magnetic stimulation (TMS)	AMF is applied over specific brain point to induce electric pulses as mean to induce or to synchronize neuron firing.
	Magnetic seizure therapy (MST)	AMF of higher frequency than used in TMS is used to cause seizure to control brain function.
Musculoskeletal diseases	Millimeter wave therapy	Uses AMF of extremely high frequency to treat pain and bone healing.
	Microwave diathermy	Induces localized hyperthermia to relieve pain and swelling, and to improve healing.
	Pulsed AMF	Pulses of electromagnetic field reduce degenerative pathways and induce regenerative and growth cells.
	Static magnetic field	Guides direction of growth of new cells in tissue engineering

discussed in the next headings.

Magnetic separation techniques:

The magnetic field's ability to control the movement of magnetic nanoparticles in time and space has innovated the field of separation techniques, as following:

Magnetic cell separation techniques: The separation of the magnetic and nonmagnetic components in a mixture is made possible by the application of a magnetic field as a driving force. However, biomedical applications have emerged in the last few decades[18]. The isolation and purification of different cells and biochemical molecules have been recognized as the most important application of MNP[19]. In magnetic cell separation, cell sorting is done through the attraction of labeled cells in a heterogeneous mixture towards magnetic flux. The first step is to label MNP with specific ligands for target cells to be separated. Labeled MNP is incubated with cell culture for a specified time to allow targeted binding on the cell surface. This can be facilitated by using a positively charged polymer matrix that can bind negatively charged cell membranes[20]. The interactions mediated by targeted ligands reduce the time for adsorption and enhance the separation efficiency of different components. Core-shell microspheres formed by using the modified silica and Fe_3O_4 as a magnetizing agent have also been used for application in the separation of cells and different biomolecules such as nucleic acid.[21] Aldehyde modified silica nanoparticles have demonstrated better adsorptive and targeting properties in in vitro experiments.[22]

Magnetic nanoparticles in immunoassay: The magnetic field can also be used to assist immunoassay-based separation techniques. This is done by attaching the antibody to MNP for the detection of target biological molecules. The magnetic field is used in these systems to aid in the detection and separation of bound molecules. Interestingly, MNP can be recovered after the experiment as reusable agents.[23–24]

Magnetic nanoparticles in biosensors: MNP has been engineered as biosensors for one-step detection of

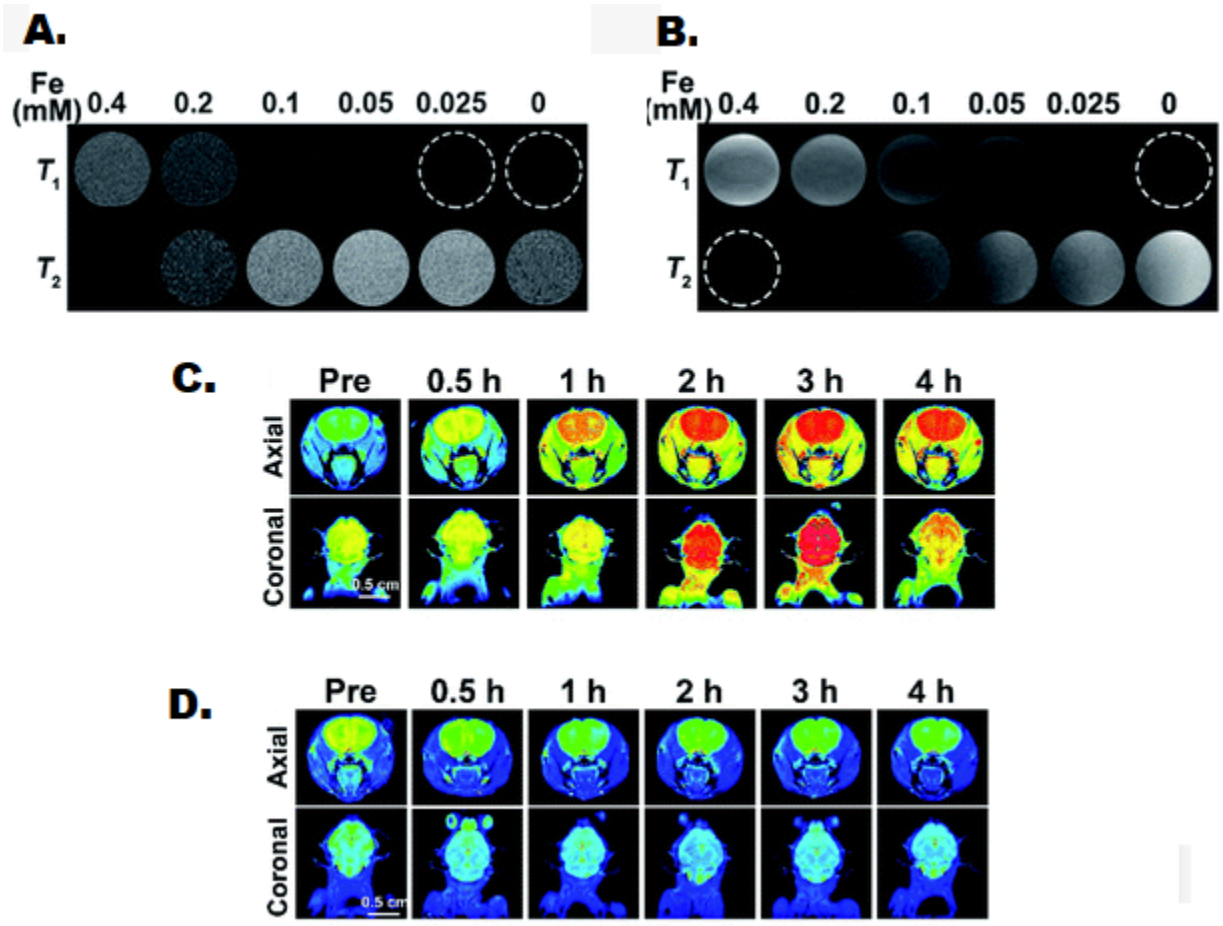

Figure 1. Presentation of small sized iron oxide nanoparticles as contrast for MRI imaging of brain. T_1 and T_2 weighted phantom imaging of iron oxide nanoparticles was acquired at 0.5 T (A) and 1.5 T (B) scanner. T_1 (C) and T_2 (D) weighted imaging of nude mice after intravenous injection of iron oxide nanoparticles at the dose of 2 mg iron per kg of body weight. Adapted from ref. 16. Copyright of Royal Society of Chemistry, 2021.

various analytes. These types of sensors can measure changes in signal, such as light reflectance and electrical resistance, due to the conjugation of MNP with the biological analyte. The MNP is paving the way for fabrications of highly sensitive, rapid, and economic biosensors for mobile applications.

MAGNETIC FIELD IN DRUG DELIVERY

Lack of selectivity and uneven distribution of different therapeutic agents has limited the use of many potent chemotherapeutic agents. Targeted DDS are designed to deliver drugs selectively to the desired site. The targeted delivery of DDS by conjugation with magnetic nanoparticles has opened a new era in drug delivery[25]. MDDS target loaded drugs or other therapeutic moieties to the desired site by an externally applied static magnetic field. On the other hand, MNP has been used to initiate drug release from colloidal DDS due to hyperthermia induced by an alternating magnetic field. Multiple systems, depending upon their size, functional capabilities, and structural composition, have been categorized under magnetic carriers including magnetic liposome, noisome, micro nanoparticles.

Magnetic microparticles and nanoparticles

Magnetic microparticles tend to respond to the static magnetic field by moving in direction of the field lines according to Coulomb's Law.[26] Magnetic microparticles can respond to alternating magnetic fields leading to the transition of energy from the field to the microparticles. The resulting heating may be used for hyperthermia therapy and to aid in the release of potent drugs from thermoresponsive DDS.[27] Magnetic particles can be prepared with the flexibility of size range from a few nanometers (usually >10 nm) to tens of micrometers which is comparable to the cell size of (10-20 μm), viruses (0.02-0.45 nm), proteins (5-50 nm), and gene products

(2 μm width and 0.1 nm length). So, the proximity with biological targets offers a variety of advantages in drug delivery.[28] Drug delivery to the central nervous system (CNS) via the blood-brain barrier provides limited access because of physiological differences of blood capillaries in CNS, less solubility, and poor bio-distribution of drug molecules.[29] Conventional delivery of chemotherapeutic agents had shown to be less effective, although the disruption of blood-brain barrier integrity has shown to increase the penetration of drugs during multiple disorders. The development of micro-sized drug carriers (microcapsules) coated with the drug molecule leads to enhanced drug delivery to brain tissues that is further strengthened by the use of magnetic resonance techniques.[30] The transport of magnetic microcapsules in the blood vessels was demonstrated by different biomimetic approaches. These studies elaborate on the effect of blood flow and particle size as well as other electrostatic and steric forces.[31] Furthermore, magnetically modulated targeting of microparticles to brain tissues does not induce an immune response which has been a limiting factor for many novel DDS.

MNP is a class of magnetic particles in the size range of 1-100 nm. Advancement in the availability of different biodegradable, as well as non-biodegradable materials and developmental technologies, facilitate the production of these particles with different physical, chemical, and functional modalities. MNP decorated with different functional modalities has been utilized to address the above-mentioned challenges of diagnosis and treatment of the different diseases in spatiotemporal mode[32]. MNP can be retained at localized tissue due to externally applied magnetic fields. One example of these systems is the high retention of nanoparticles at inflamed tissues of the skin and the underlying musculoskeletal system. After the drug is released, the magnetic field can be switched off leading to the elimination of nanoparticles from the body.[33] Another targeting application of magnetic field is locoregional chemotherapy. This involves intra-arterial administration of nanoparticles that are directed to and localized in tumor tissue by an externally applied static magnetic field. This increases drug accumulation in targeted tissue leading to improve efficacy.[34] Recently, magnetosomes have gained interest in the medical field due to their biocompatible nature. These are intracellular nanoparticles chain used by magnetotactic bacteria to navigate in the direction of the earth's magnetic field. Due to their homogenous size and vesicular structure, they have been used for the delivery of large drug molecules. Gareev et al. has written a review article that comprehensively discusses magnetosome applications in the medical field.[35] MNP has also been used to induce drug release from other drug delivery systems. This goal is achieved usually by bonding a magnetic moiety to a polymer resulting in an amphiphilic structure of polymer that can form nanoparticles by self-assembly in vitro or in vivo. Conversely, MNP can be loaded in as-formed polymeric nanoparticles to cause thermoresponsive drug release at the target site 32b [36,37]. The advantages in two ways i.e.amount disease-affected target tissuesirpharmacological effect normal drugtoxic Thegelatin capsule to GIT, thus, releasing the encapsulated drug at the target site In another study, functionalized montmorillonite (MMT) materials were used as unique porous structures(FePt)FePt@MMT contract enhancer FePt@MMT-MIT, in addition to MRI imaging and MFH, chemotherapy[38]. Similarly, hybrid systems have been prepared for simultaneous delivery of chemotherapeutic agents, gene products, and SPION, a strategy that may enable complete eradication of tumor and associated stem cells. Another recent innovation in magnetically modulated drug delivery is nanomotors, sometimes referred to as nano-swimmers that can swim in the blood to deliver encapsulated drugs to the target site. These nanomotors rotate under the influence of the applied magnetic field and move toward the target, thus no build-in fuel reservoir is needed. Another benefit of nanomotors is their ease to cross biological barriers by disrupting the target membrane or extracellular matrix.

Magnetic liposome

Liposomes consist of a phospholipid bilayer and an internal aqueous core which enable them to encapsulate both hydrophobic and hydrophilic drugs, respectively. Advances in liposomal drug delivery involve targeting and "clickable" drug release by the inclusion of magnetic or paramagnetic particles[39−41]. The magnetic particles can be incorporated in the central core of vesicles, lipid bilayer, or make complexes on the surface of the liposome (figure 3). In addition, phospholipids tagged with magnetic or paramagnetic materials such as gadolinium can be used to form liposomes. The presence of magnetic materials tends to align the movement of liposomes along the lines of the magnetic field and enhance the penetrability and penetration of liposomes at the target site. Drug release from liposomes is mediated by magnetically induced hyperthermia. When magnetic liposomes are exposed to an alternating magnetic field, hyperthermia is produced which destabilizes lipid bilayer leading to the release of encapsulated drug. Consequently, the drug release rate can be controlled by varying patterns or strength of applied magnetic field[42]. Fabrication of magnetic liposomes with targeting ligands, functional groups, fluorescent compounds, and contrasting agents enables multi-modal applications in diagnosis, imaging, and delivery of multiple therapeutic compounds to the target cell and tissues.[1, 43] The most important application of magnetic liposomes is the delivery of gene products due to their intrinsically high penetration in cells

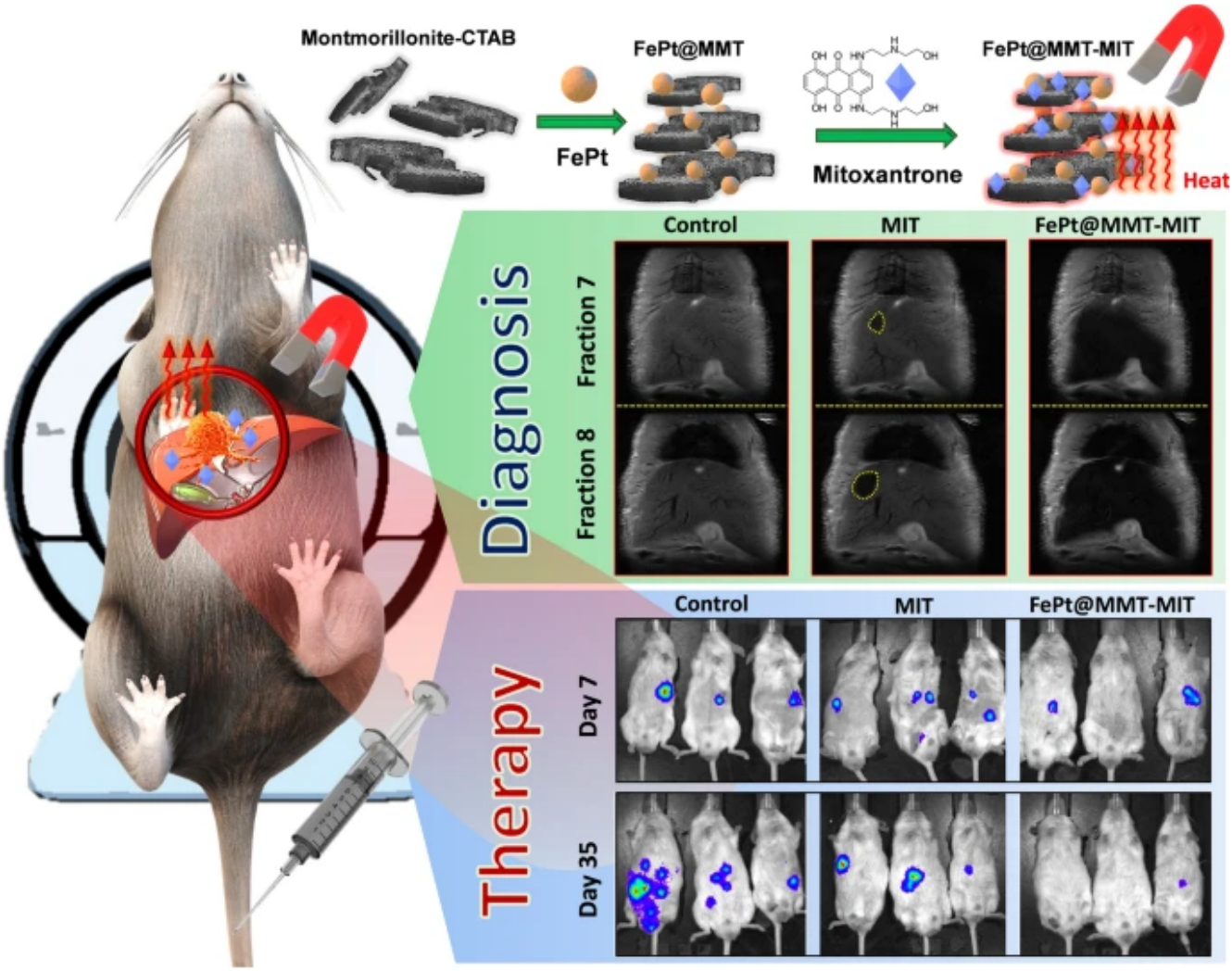

Figure 2. Mitoxantrone loaded FePt nanoparticles for diagnosis, magnetic hyperthermia (thermotherapy), and targeted chemotherapy of cancer in mice. Adopted from ref. 38. Copyright of Springer, 2021.

and transfection efficiency. Cationic lipids are generally used for these applications because they can strongly bind negatively charged nucleic acid.[44]

Magnetic Hydrogels

Hydrogels are a three-dimensional network of cross-linked polymers with tunable characteristics such as versatile chemical nature and biocompatibility.[45] The hydrogels can be loaded with different therapeutic and diagnostic modalities including microparticles, nanoparticles, liposomes, fluorescent and contrasting agents that have been discussed previously (figure 4). Different methods have been employed for the fabrication of these formulations but grafting-onto method[46], in situ precipitation method[47], and blending methods[48] are of prime importance. The incorporation of magnetic particles in the matrix of conventional hydrogels permits greater control over the release profile of different macromolecular therapeutic moieties including peptides, proteins, and hormones. The therapeutic payload, either drug or drug-loaded DDS, is loaded into hydrogel-MNP composite and magnetic hyperthermia is used to induce the release of payload. Hydrogels were also prepared with micron-sized pores for drug loading and subsequent release in a three-dimensional intracellular environment[49]. Interestingly, pulsatile release of payload can also be achieved by repetitive on and off application of the magnetic field application.[50]

MAGNETIC FIELD HYPERTHERMIA FOR TREATMENT OF CANCER

Hyperthermia has been used historically to cure illnesses and was a commendable point of interest. It has been

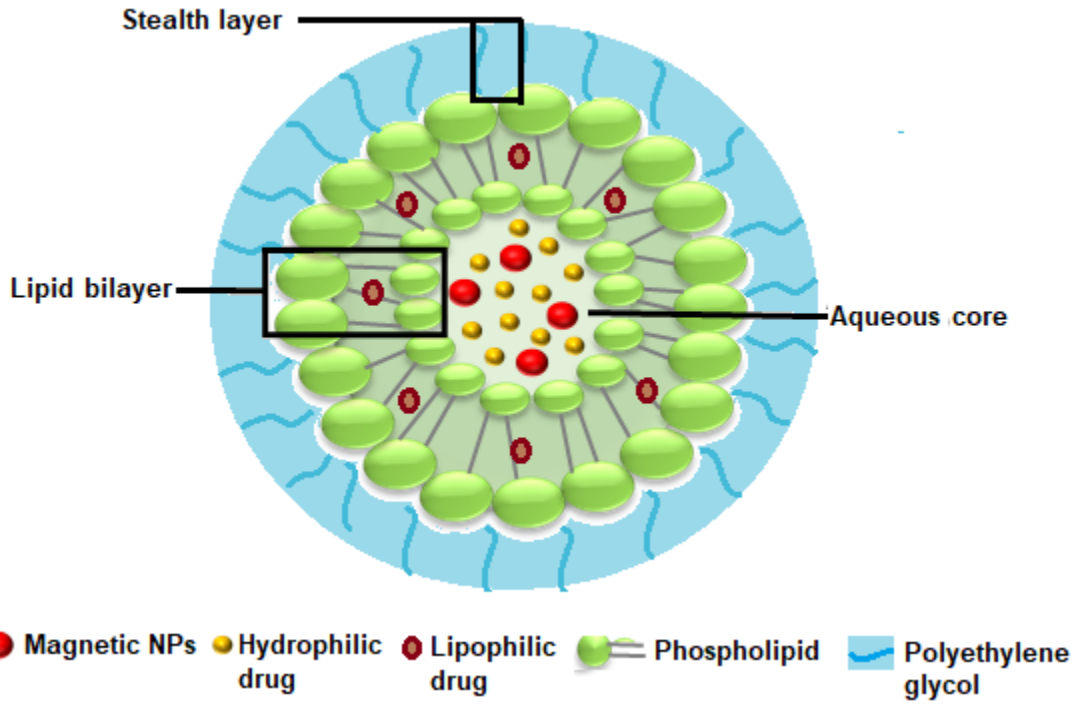

Figure 3. Structure of magnetic liposome consisting of a phospholipid bilayer coating an aqueous core containing magnetic NPs and drug payload.

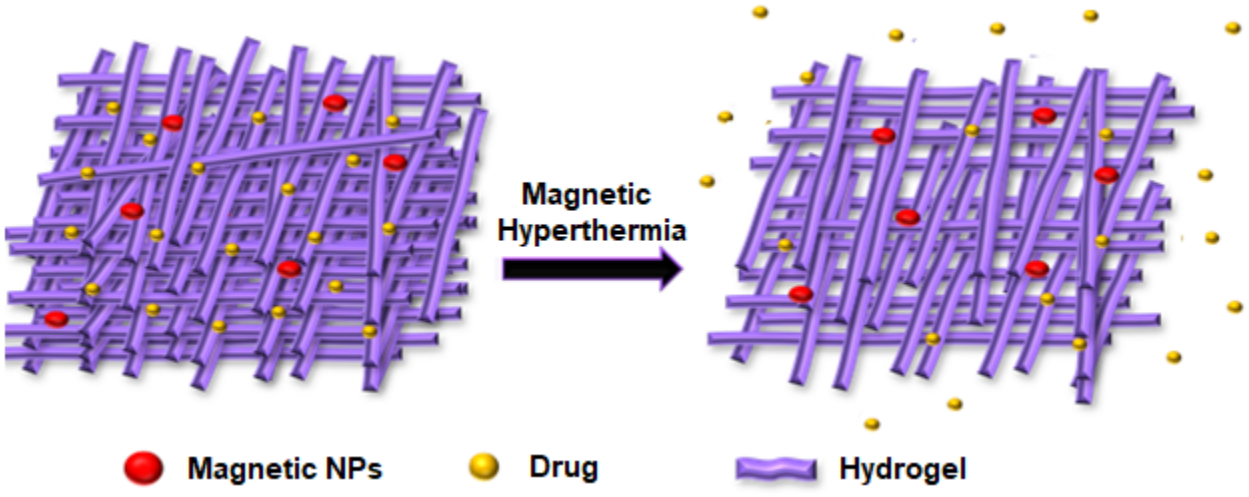

Figure 4. Schematic illustration of drug and magnetic NPs loaded magnetic hydrogel's network and induction ofdrug release upon magnetic hyperthermia.

assumed that cancer can be treated as well as its growth can be suppressed by fever[51]. In accordance with this assumption, scientists began to utilize this concept of fever induction to cure cancer[52] or using external sources to provide hyperthermia[53]. To achieve this aim, hyperthermia was induced by many tactics inside the body as well as from outside means via infrared radiation, alternating magnetic fields and ultrasound waves. The primary focus of this review are magnetic field related techniques which utilize heat to cure cancer. Owing to non-toxic character of iron oxide nanoparticles (magnetite Fe_3O_4 as well as maghemite γ-Fe_2O_3) have been majorly employed (Figure 5) [54]. Type of MNP, magnetosomes, are products of magneto-tactic bacteria inside bacterial cell wall via mineralization of oxides or sulfides of iron, which produce superior results as compared to iron oxide nanoparticles. Every magneto-tactic specie give its peculiar crystals.[55] Majority of studies have revealed undesirable experience upon MNP injection into tumor site directly. Currently, tumor-specific ligands have been employed to deliver MNP via IV route. For instance, attempts have been made to target intravenously administered MNP to tumors using tumor-specific ligands. For example, single-core magnetic nanoparticles were covalently conjugated with a fluorochrome and either ant-α-tubulin or anti-β-catenin antibodies for intracellular targeting in mice. Binding of antibodies did not alter the magnetic properties of the MNP. The antibodies retained their immunochemical properties, target specificity, the ability to visualize the protein distribution.[56] In case of magnetic field hyperthermia (MFH), there is external application of alternating magnetic field to heat up accumulated MNP inside tumor. The prominent disadvantage of hyperthermia is immediate buildup of heat shock proteins (HSP) upon MFH application. HSP belongs to those kind of proteins that hinder protein aggregation originated by heat heading to thermotolerance.[57] Hence, thermotolerance not only has put MFH status at risk as an antitumor therapeutic tool but also restrict its use to once or twice in a week. MFH heating range determines killing pattern of tumor cells such as autophagy, necrosis, and apoptosis.[58] Hyperthermia can be applied both locally as well as to the whole body. Higher temperature is required for local hyperthermia rather than whole-body hyperthermia which needs mild rise in body temperature. Classical or sub-lethal MFH has been generated from 41-46°C does not destroy cancer cells.[59] Classical MFH gives dose dependent effects which are reversible. Though its unambiguous target is unclear, but it is attributed to impair various intracellular enzymes, receptors, and proteins. Hence it is utilized along with radiotherapy[60] as well as chemotherapy.[61] Synergism of magnetic field is seen with other modes as well, but it is dependent on application time. Thermo-ablation or lethal MFH has been generated at 55°C, which destroys cancer cells directly.[62] This process burns cells due to temperature and results in necrosis at a broad spectrum. One research showed that patients incompliant to traditional chemotherapy, responded well to 43°C hyperthermia without significant adverse effects.[63−68] Additionally, it helps to measure extent of tumor mass reduction after MFH application. MFH can regulate flow of blood towards tumor for enhancing approach of immune elements to tumor.

According to recent research it has been seen that against tumors, MFH can produce and enhance the effect of Immune system. It is believed that the initiation of MFH is performed by none other than the HSP family members such as HSP-96 AND HSP-70.[68] The HSP-96 Vaccine, which is tumor derived, has been tested previously and it showed good results as in case of antitumor activity.[69] Anyhow, the synthesis produced by MSH and HSP release appeared to be an easy option because of its low cost and unavailability of surgical extraction. The altered immune response in sub-lethal MFH was observed due to higher level of HSP expression which were usually found in suppressed form in the tumors. In case of lethal MFH, release of stored HSP in tumor cell is the reason. Immune response seems appealing for three prominent reasons. First of all, it can upgrade the tumor killing mechanism of body naturally which also lowers the demand of the chemotherapeutic agents.[68] Secondly, the modulations in immune system has been seen to kill metastasized tumors that are distant and far away from hyperthermia exposure.[65]Third, the recurrent tumor risk decreases as MFH induced immune response lasts for a longer time frame.70 Modified tumor microenvironment and immunosuppressive cells determine HSPs vaccination effect. MFH application to eliminate tumors also counteract casual working of various immune system components in a complicated way. Previously, MFH has also been employed along with MRI as role of contrast agents was played by MNP in MRI.[71] This modality opens door to visualize tumor after injecting MNP inside patient body followed by MFH killing of tumor.

MNP has been traditionally used along with horseradish peroxidase (HRP), an enzyme commonly used for peroxidase activity. In these applications, catalytic activity is carried out by HRP, and MNP is used for magnetically modulated separation of a conjugated system for renewable applications. They can enhance efficiency at different processing steps and biological activity in complex mixture by the application of the magnetic field. However, Vallabani et al. found that MNP, such as magnetite (Fe_3O_4), possess intrinsic peroxidase-like-activity i.e. catalyze the oxidation of biological materials in the mixture.[72] This allows catalysis with Fe_3O_4 nanopar-

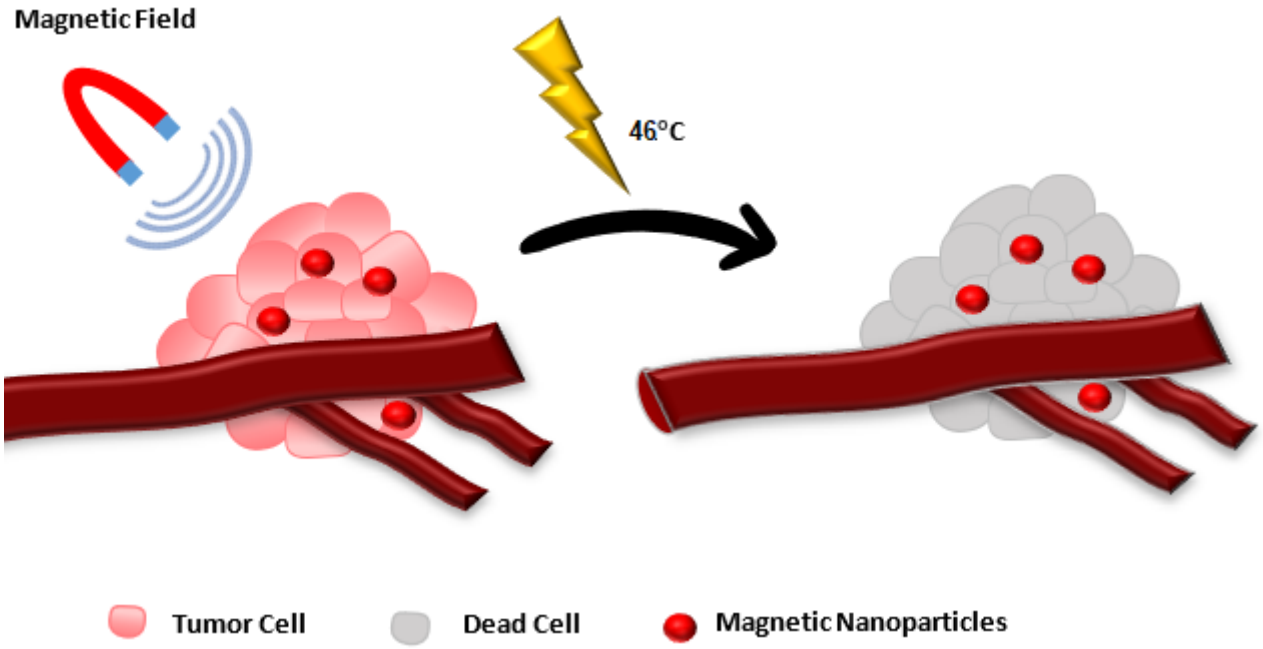

Figure 5. MNP mediated tumor cell destruction under application of alternating magnetic field (AMF). First, nanoparticles are targeted to tumor by application of AMF. Then, frequency of AMF is changed to induce localized tumor ablation

ticles where catalyst can be recovered by a magnetic field at the end or predetermined point. Since then, many inorganic nanoparticles have been tested for enzyme-like activities.[72,73] The mechanism of the peroxidase-like activity of MNP is similar to HRP but offers many advantages. The catalytic activity of MNP is directly proportional to the amount of Fe^{2+} ions on the surface. The presence of a large number of Fe^{2+} ions on the MNP surface leads to a much higher catalysis rate as compared to HRP which has only one Fe^{2+} ion. Optimum catalysis activity of MNP, just like HRP, is achieved in a range of H_2O_2 concentrations above or below which decreases the catalysis rate. Similarly, MNP activity is dependent upon the pH and temperature of the reaction mixture although they have a broader range of these working conditions. Due to their inorganic nature, MNP is much more stable and robust in biological systems. Interestingly, MNP show enzyme activity over a broad size range which makes them preferred candidates for immunoassays, biosensors, and nanodevices.[74–75]

Most researchers have prepared biosensors and biocatalyst of Fe_3O_4 in conjugation with other materials. Fe_3O_4 is conjugated to reduced graphene oxide (rGO) to combine the properties of both materials. rGO is a single atom thick layer of carbon and possesses excellent mechanical strength and flexibility. It has shown mild peroxidase-like activity of its own and can bind almost all materials due to its functionalized surface. Fe_3O_4-rGO shows higher enzyme activity than Fe_3O_4 or go alone and can be recovered under magnetic field.[72] In this way, it is also possible to stop the catalytic reaction at a certain time to obtain a product of desired composition or associated properties. Together with the physical properties of rGO, the Fe_3O_4-rGO has emerged as a first-choice inorganic catalyst for economic, robust, reusable, and high sensitivity devices. The Fe_3O_4 based composites have been successfully evaluated for the detection of various biological compounds such as glucose[76], dopamine[77] glycoproteins[78], etc.

SAFETY OF MAGNETIC FIELD

Magnetic field application in the biomedical field is generally regarded as safe. As scientists believe that MF can be used for the treatment of diseases, they should expect the opposite too. Just like chemotherapeutic drugs, uncontrolled exposure to otherwise beneficial magnetic fields may be harmful. An increasing number of studies support the notion that magnetic fields can produce many unwanted effects at frequency and amplitude being used for different biomedical applications. Although systematic reviews and meta-analysis studies have rejected some of these studies based on improper design or lack of statistically significant results, all of these findings cannot be ignored. In the case of MRI, many problems were reported including attraction of metallic objects in the room, interference with electromagnetic or metallic medical devices used by the patient, and unwanted side effects especially in patients with previous history.[79] During the initial

years of MRI, a few accidental injuries and even deaths were reported due to metallic objects, such as oxygen cylinders or chairs, being attracted by the strong magnetic field and hitting the patient in MRI machine.[80] MRI interaction with metallic devices or implants used by the patients is two-tier. First, the static magnetic field can strongly attract metallic devices. Second, alternating AMF can generate current in these devices which may lead to fatal consequences. These effects can be hazardous to patients and may also distort image quality. However, current clinical practices have introduced various precautions and safety measures to reduce such complications. Usually, prior counseling of patients about the basics safety and efficacy of MRI is a useful step to prepare them for MRI and feel comfortable during the examination. Electromagnetic fields have been studied widely in animals and humans for their carcinogenic and genotoxic effects. The international agency of cancer research has categorized extremely low-frequency magnetic fields (ELF) (3-300 Hz) as possible carcinogens (class 2B). Currently, childhood leukemia is the only type of carcinogenicity whose association with occupational exposure to ELF is supported by scientific evidence.[81] Direct damage to genes is not supported by well-designed studies, however, such effects may be observed in the presence of genotoxic agents.[82] Similarly, various studies conducted to evaluate the effect of the static magnetic field indicated an increased risk of genotoxic effect. The genotoxic effects appeared in a dose-dependent fashion and tend to disappear after the removal of the magnetic field.[83] On the other hand, Gunes et al. reported that genotoxic effects are negligible even at the stronger magnetic fields used in clinical settings.[84]

Association between behavioral changes and radiofrequency field has been reported by patients for a long time and termed as electromagnetic hypersensitivity syndrome EHS). However, only a few studies have supported this assumption. Domotor et al. observed that patients who report EHS have a higher score of somatic and psychic traits which is an indicator of lower mental well-being.[85] Studies evaluating behavioral aspects showed that ELF improve the memory of participants in one study and impaired it in another study. In a study, sham versus static magnetic field settings was tested on rats to assess behavioral changes. The rats were trained to climb up the hole of the MRI machine to get the food. They found that rats stopped getting food from the hole whenever a magnetic field was applied to it. Nevertheless, this behavior was abolished when sensory parts of the brain were surgically removed.[86] Although most studies utilized exposure to random or occupational exposure, the risk may persist with deliberate exposure to medical ELF and static magnetic field (SMF). As discussed in the previous headings, magnetic fields of similar amplitudes or frequencies are being investigated for biomedical applications. Towards the end of the 20th century, emerging literature showed that conscious experience of brain function was related to the synchronization of neurons and not the number of neurons firing. Recently, the conscious electromagnetic information (CEMI) theory of McFadden and Peckett proposed that information from neurons is integrated to form an amplified electromagnetic field which influences the brain's overall AMF more effectively than would be possible by unsynchronized firing.[87]Moreover, some studies have suggested that the heart also produces a magnetic field due to electrical pulses of Purkinje fibers which may interact with different body tissues including the brain.[88] These magnetic fields may provide a clue of various biological effects of the magnetic field that are still unexplained. Biomedical application of the magnetic field may tend to interact with such fields and lead to an altered response, which can be either positive or negative.

As a safety measure, it is customary to question the patients about implants, metallic object, condition of vital organs, and gender-specific aspects of health to ensure before MRI examination.[89] The same principal should be extended to any medical applications involving magnetic field. In addition to questions mentioned above, the patients should also be inquired about his mental health and cognition if head region is under investigation, to avoid unnecessary negative effects on health. Therefore, the authors stress that well-designed studies are needed to establish the safety of such paradigms both in vitro and in vivo. Precautions and safety measures should also be adopted to ensure the safety of patients and healthcare workers in clinical settings.

CONCLUSIONS

Magnetic nanocarriers have found diverse applications in the medical field ranging from drug delivery to drug-free treatment and diagnostic applications. The ability of the MNPs to align with the applied magnetic field has enabled researchers to control the transport of a variety of nanoparticles filled with chemotherapeutics which enhances therapeutic effects and reduces side effects. Under an AMF, MNP produce hyperthermia either to cause ablation or to cause subcellular damage leading to apoptosis. MFH also increases blood flow in tumor and enhances MNPs accumulation. At the same time, MNPs can be loaded in liposomes and hydrogels to degrade the carrier matrix under MFH ad release the payload at targeted site. MNP are conjugated with targeting ligands for site-specific accumulation in the body.

Ligand conjugated magnetic nanoparticles are also used for the separation of cells from a heterogeneous mixture of biological macromolecules in an immunoassay. Similarly, magnetic nanoparticles conjugated to a cat-

alytic enzyme and allow the removal of the enzyme at any stage of the reaction. In addition to contrast enhancement in MRI, the flexibility to control pattern and frequency of MRI has provided an opportunity to target magnetic nanoparticles to target tissue, do diagnostic imaging and to induce hyperthermia after a single administration of magnetic nanoparticles.

Although generally regarded as safe for the human body, emerging literature pointed out the risk of cancer and a behavioral disease after application of magnetic field. Extremely low frequency AMF has been associated with childhood leukemia. Therefore, care must be taken to restrict future research to the range of the magnetic field which is safe for the body. Indeed, the future of medical applications of the magnetic field lies in the engineering of multifarious nanocarriers that will allow simultaneous diagnosis, thermotherapy, targeted drug delivery, or image-guided surgery of diseases.

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