



REVIEW ARTICLE

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Magnetic nanoparticles for diagnosis and treatment

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Abstract

Cancer is a complex disease in which certain cells in the body grow uncontrollably and spread to other parts of the body. Although there have been advances observed in the diagnosis and treatment of cancer, many studies are conducted to eliminate the side effects that occur during treatment. Magnetic nanoparticles (MNPs) are of great interest in the field of cancer diagnosis and treatment due to their magnetic features, biocompatibility, and stability. These features allow them to be used as a contrast agent for magnetic resonance (MR) imaging as a therapeutic system with a drug release system and hyperthermia. MNP-based imaging, drug release systems, and hyperthermia treatments have been studied by researchers and reported to be promising for the treatment of various types of cancer. Although the clinical applications of MNPs for cancer treatment are still controversial, researchers think that MNPs will play an important role in meeting health needs in the future. In this review, we present advances in in-vitro and in-vivo research for diagnosis and treatment, besides an overview of the basic technical principles of MNPs.

Keywords: Magnetic nanoparticle, cancer, hyperthermia, drug release systems, active and passive targeting

Introduction

Cancer is one of the most common diseases today and the treatment options available for the disease are very limited. It is a complex disease that is caused by genetic changes and is considered a public health problem due to its frequent occurrence and fatality. The World Health Organization reported that there were approximately 10 million deaths from cancer worldwide in 2020 [1]. Despite advances in clinical diagnosis and treatment, cancer-related death rates have increased in recent years [2].

While cancerous tissue in bone tumors, head and neck cancers, and breast cancer were treated by burning in 3000 BC [3], different treatment methods such as chemotherapy have been applied for the last 30 years. Chemotherapy treatment is one of the methods used for cancer treatment together with radiotherapy and surgery. The most important side effect of chemotherapy treatment is that when applied to the patient, it destroys not only

fast-growing cancer cells but also fast-growing healthy cells such as hair, mouth, and gastrointestinal cells. Low tumor selectivity can lead to cell damage and multi-drug resistance [4]. Therefore, it is very important to search for new treatment modalities that target only cancer cells and protect healthy cells. Cancer research substantially changed to overcome all these problems in the past ten years. For example, researchers showed that Melatonin could prevent tissue damage in breast cancer. Moreover, they reported that a combination of therapy with zinc and melatonin might help prevent tissue damage in breast cancer [5].

Today, traditional cancer treatment methods such as surgery, chemotherapy, radiotherapy, and additional treatment methods such as hormone therapy and immunotherapy are successful, but there are limitations such as adverse effects of drug treatment (for example nausea, vomiting, drug intoxication, etc.), poor response and individual-specific side effects [6-9]. Research continues in nanomedicine to overcome the present challenges in cancer treatment. For example, MNP-based therapeutic systems are among the recent methods used in drug release systems [10] and hyperthermia [11] applications.

MNPs are a class of nano-sized particles that can be manipulated

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under the influence of an external magnetic/electric field (alternating magnetic field (AMF), radio frequency (RF), microwave (MW) frequency). MNPs are generally composed of metal-polymer mixtures, pure metals (for example iron, cobalt, nickel), and their oxides. MNPs can be synthesized by many different methods from nano to micron size. The particles are coated with biocompatible materials to increase their stability during or after synthesis, and to stabilize them in physiological body fluids. The coating allows for increased chemical functionality and residence time in the body. Furthermore, this design provides MNPs to perform multiple functions simultaneously, such as real-time monitoring with drug release systems, multimodal imaging, and combined therapeutic approaches. MNPs are used in different fields, such as hyperthermia therapy, imaging of cancer cells with MR, controlled drug release systems owing to their physical features, and biological interaction capabilities at the cellular and molecular level [12-14]. Many forms of MNPs with different chemical combinations are suggested and evaluated.

Among different magnetic materials, superparamagnetic MNPs attract more attention due to their suspension features and U.S Food and Drug Administration (FDA) approvals in MR imaging applications [15]. Superparamagnetic MNP platforms with sizes of 10-100 nm, which can be designed according to the target, have high magnetic susceptibility, high biocompatibility, and stability [16]. The superparamagnetic features of MNPs allow them to be oriented in the desired direction by an external magnet. Thus, the anticancer drug can be released at a certain rate in the desired area.

Studies have shown that combined therapies with controlled drug release systems and hyperthermia may show promise for cancer diagnosis and treatment [17-19]. While the cancer cells are destroyed by this treatment method designed with the combined use of hyperthermia and drug release systems, which reduces toxicity in healthy tissues, has provided efficient and short-term chemotherapy sessions with targeted drug release. Several review articles have discussed the use of MNPs for cancer therapy [16, 20, 21]. However, we did not meet a detailed review of studies on MNP-based drug release systems and hyperthermia therapy. Here, we will review the features of MNPs, their target-dependent drug release system, and their application in hyperthermia.

Materials and Methods

Literature searches were performed using the Medline database and cross-referenced with identical search terms on PubMed and TRIP database (both web-based and open access). Two reviewers independently performed the search and identified articles for inclusion. Research studies conducted between 1998-2021 were included in this review.

Magnetic Features of MNPs

There are various forms of magnetism in nature, such as diamagnetism, ferromagnetism, and superparamagnetism. Superparamagnetism seems to be preferred for MNPs applied to problems in biomedical fields [22]. Superparamagnetism occurs when particles are small enough to cause their magnetic moments to randomly flip due to thermal effects. The size limits required to achieve superparamagnetism differ according to core material compositions. For iron oxide crystals the size is <30 nm [16].

Superparamagnetic MNPs contain magnetic moments in the same direction as the applied magnetic field. When the external magnetic field is absent, MNPs moments are random flipping due to thermal effects, and approximately zero magnetism is observed (Figure 1(a)). After an external magnetic field is applied, the MNPs' moments align in the direction of the magnetic field. (Figure 1(b)). The characteristic time from one moment-flip to the next is called the Neel relaxation time and is approximately determined by the Neel-Arrhenius equation: $\tau_0 \cdot \exp(KV/(k_B T))$. τ_0 is the time between flip attempts and is changed between 10^{-9} - 10^{-12} of range depending on the material. V is the particle volume, K is the magnetic anisotropy energy density, T is the temperature, and K_B is the Boltzmann constant [16].

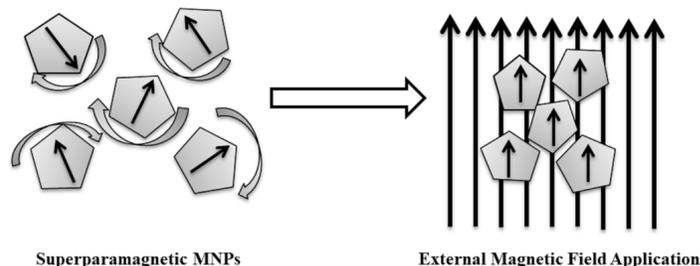


Figure 1. (a) Superparamagnetic MNPs flip because of temperature effects in the absence of a magnetic field. (b) MNPs respond to the applied magnetic field [16]

Superparamagnetic MNPs contain high magnetic susceptibility. Moreover, they do not show a permanent magnetization after the external magnetic field effect disappears. Therefore, they are appropriate for biomedical applications. The high magnetic susceptibility is the result of the reorientation of high-magnetization crystals responding to the applied field, as shown in Figure 1. The high magnetic susceptibility of MNPs is crucial for MNPs use in MR imaging, drug release systems, and hyperthermia applications.

Magnetic Nanoparticle Synthesis

MNPs can be synthesized by mechanical attrition or chemical methods. Thermal decomposition, solvent evaporation technique, polyol method, sol-gel reaction, co-precipitation electrochemical method, and sonolysis method are some chemical methods. All methods have advantages and disadvantages, but the co-precipitation method is the best-preferred method due to its ease of application [23]. Many studies have been carried out using magnetic cores such as cobalt, nickel, gold, and iron oxide in the synthesis of magnetic nanoparticles [24-26]. Iron oxide cores are found more successful in biomedical applications due to their biocompatibility and their use in clinical imaging. Ongoing research on iron oxides core forms includes magnetite (Fe_3O_4) and maghemite (Fe_2O_3) [27-29].

The combination of synthetic and biogenic polymers with inorganic nanoparticles is the basis for improving nanosystems that can be used simultaneously in diagnosis and therapy. Various natural and synthetic polymers including carbohydrate derivatives (for example polycaprolactone (PCL), polyethylene glycol (PEG), polylactic-co-glycolic acid (PLGA)), silica (SiO_2), dextran, and chitosan are approved by the FDA. Coating synthesized core forms with natural or synthetic polymers during or after synthesis causes an increase in their functionality. The formed form is called the "core-shell" structure. The coatings stabilize MNPs in physiological fluids

and increase their half-life in the body. Furthermore, the coating provides bonding to the surface for the therapeutics and target molecules [16] (Figure 2). Making additional modifications in the structure allows MNPs to be used simultaneously in treatment and imaging. MNPs coated with dextran and carbohydrate derivatives are used as MR contrast agents and marketed, for example, Ferrodex®, Resovist®, Combidex® for clinical applications, when these contrast agents increase the resolution in the imaging techniques and give more reliable results. Moreover, coatings on the magnetic core increase the biocompatibility of the particles.

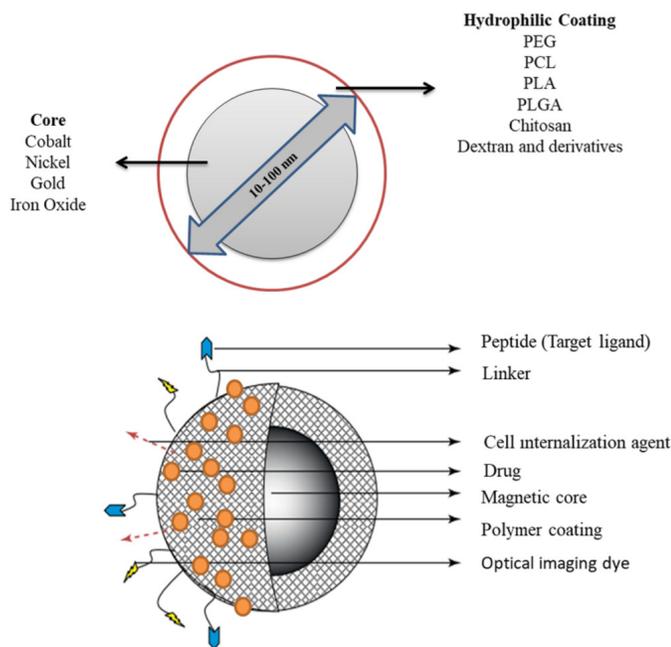


Figure 2. Core-shell structure [16]

Biocompatibility of MNPs

The use of MNPs is limited due to their biocompatibility. When nanoparticles are not biocompatible, they cause toxic effects by disrupting cellular and chemical tissue metabolism. MNPs behave differently in body conditions because blood is highly heterogeneous. When MNPs enter the bloodstream, they can stick together, react with intercellular substances and cells [30]. Therefore, the biocompatibility of MNPs is very important for their use in MR, drug release systems, hyperthermia fields in biomedicine.

Opsonization is one of the main factors determining the biocompatibility of MNPs and their circulation time in blood plasma. As shown in Figure 3, opsonin proteins in circulation adsorb to nanoparticle surfaces, flagging them as exogenous materials for plasma clearance. Reticuloendothelial system tissue macrophages recognize labeled MNPs and remove them from the circulation via phagocytosis. The interaction of MNPs with the reticuloendothelial system determines the lifetime of nanoparticles in blood plasma [16,30]. The hydrodynamic size of 10-100 nm is optimal for the intravenous application of MNPs. Nanoparticles >100 nm in size are filtered by phagocytosis in the spleen, while small nanoparticles <10 nm in size are rapidly cleared by renal filtration [16].

The coating of MNPs protects the magnetic core and increases biocompatibility [16]. Moreover, functionalization of MNPs with ligands prevents opsonization and increases circulation time in the blood. Studies show that opsonization and clearance of MNPs can be prevented by hydrophilic polymers such as PEG [31]. PEG chains attached to MNPs provide resistance to opsonization and macrophage recruitment, increasing the residence time of MNPs in plasma. In a study with PEG-modified MNPs with a hydrodynamic size of 170 nm, it was shown that the nanoparticle has a circulating half-life of approximately 12 hours in the rats and tumor imaging can be performed with MR for a period [32].

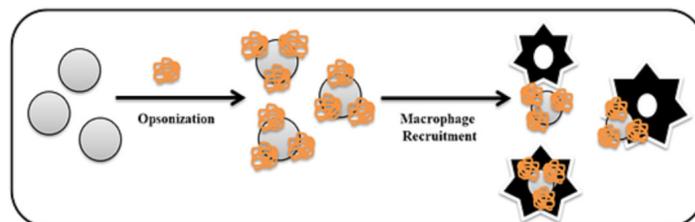


Figure 3. Illustration of the reticuloendothelial system plasma clearance of MNPs [16]

MNPs removed from the circulation by phagocytosis by the reticuloendothelial system accumulate in the liver, lung, spleen, or other non-target tissues. This raises toxicity concerns[30]. Functionalized MNPs should be evaluated toxicologically. Histopathological analysis, liver function tests, lipid hydroperoxide levels, cytokine detection, and complete blood counts are known to be useful in evaluating toxicity [16].

Targeting of MNPs to the Tumor Area

Passive Targeting with EPR Effect

MNPs can be delivered by direct injection in the tumor tissue. The direct injection method is the injection of magnetic fluid with a specific MNP concentration directly into the cancerous tissue. This is a simple approach as it does not require any additional intervention. Therefore, the direct injection method is often preferred in clinical studies. However, because MNPs tend to agglomerate after injection, this negatively affects their homogeneity within the tumor. With the direct injection method, only the MNP concentration in the tumor area can be controlled. Since this method is only effective in easily accessible tumors, this approach is limited for many types of cancer [33].

MNPs are injected intravenously for systematic practices. As shown in Figure 4 (a), the leaky vasculature of tumors facilitates the targeting of MNPs. Nanoparticles are transported to tumor cells by convection and passive diffusion from capillaries. Increased permeability and retention (EPR) effects of tumor tissues cause MNPs to penetrate the tumor site. This method is called passive targeting.

Passive targeting is the most widely used method in oncology clinics. Using passive targeting, anticancer drugs can be released around or inside the tumor tissue. Passive targeting of MNPs by intravenous application provides a more homogeneous distribution of particles than intratumoral injection. However, it is difficult to provide the required MNP dose for effective treatment with the intravenous

application. Moreover, MNPs can accumulate in some healthy tissues and cause toxic effects. Active targeting strategy is used to improve the localization of MNPs and provide specific targeting [34].

Active Targeting

Active targeting of MNPs to the tumor area is achieved through the decoration of the nanoparticle surfaces with ligands binding to receptors overexpressed onto the tumor cells. Targeting occurs through various ligands such as peptides or monoclonal antibodies that increase cellular uptake. As shown in Figure 4 (b), the addition of targeting ligands allows drug-encapsulated nanoparticles to be delivered into cells, thus reducing the undesirable systemic exposure of anticancer drugs. These receptor-ligand or antigen-antibody interactions, which are usually increased by the effect of EPR, are an effective method to increase the residence time of MNPs in tissues such as tumors.

Targeted ligands such as proteins [35], aptamers [36], peptides [37], and small molecules [38] were investigated for active targeting. Earlier, cationic peptides and synthetic polymers were considered instead of target ligands. Although cationic agents were effective in transporting MNPs, it was observed they did not perform specific targeting [39]. Moreover, MNPs functionalization with cationic agents may cause a shortening of their plasma life. Therefore, the cationic activity must be considered when functionalizing.

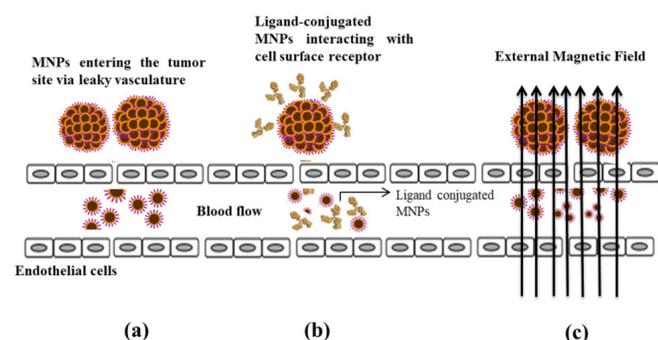


Figure 4. Illustration of MNPs targeting tumor cells by different mechanisms. (a) Passive targeting uses the nano size of MNPs and the EPR effect. (b) Active targeting with functionalized MNPs. (c) Actively targeted MNPs with the application of an external magnetic field [23]

Reddy and colleagues used the peptide F3 expressed in tumor endothelium and cancer cells to deliver MNPs to brain tumors. The researchers used MR to view the distribution and pharmacokinetics of nanoparticles within the tumor. They found that targeted nanoparticles in glioma-bearing rats significantly increased survival compared to untargeted nanoparticle treatment. The study showed the efficacy of the multifunctional nanoparticle for cancer diagnosis and treatment [40].

Studies are carried out using the active targeting strategy. Active targeting of MNPs can reduce the risk of potential damage in the spleen, liver, or bone marrow and side effects caused by indiscriminate killing of non-tumor cells.

Targeting with External Magnetic Field Application

MNPs have an extra advantage over other nanocarriers in that they can be externally orientated, and the movement can be regulated by using an external magnetic field. As shown in Figure 4(c), MNPs

can be directed by applying an external magnetic field and drug release can be achieved in the desired area. Orientation of magnetic nanoparticles by the external magnetic field is achieved using their susceptibility to external magnetic fields. MNPs response to external magnetic field application allows the combined use of drug release systems and hyperthermia therapy.

Pala and colleagues developed dextran-coated iron oxide MNPs conjugated with specific anti-human epidermal growth factor receptor (HER2) aptamer and used them for the induction magnetic hyperthermia in cultured cells. Results showed that aptamer-labeled NPs were specific for HER2-expressing cells [41]. In summary, when the activity of MNPs increases with hyperthermia after active targeting, the particles can efficiently induce cell death.

The combination of MNP and external magnetic field application can overcome the diagnosis and treatment difficulties of many diseases such as cancer.

Application Fields of Magnetic Nanoparticles

Magnetic Nanoparticles Used in Imaging for Cancer Diagnosis

A general medical application for magnetic nanoparticles is used as a contrast agent for MR imaging [42]. MR is one of the most preferred non-invasive techniques for clinical imaging. It is a radiation-free imaging method based on radiofrequency waves that interact with protons in the body.

Magnetic Nanoparticles Imaging (MPI) is a technique with a high spatial and temporal resolution developed in the early 2000s. This method is based on MR monitoring of magnetic nanoparticles, which creates contrast differences between cellular structures. It is not a structural imaging technique unlike traditional imaging methods such as MR, X-ray, and CT. It is a viewer imaging technique like PET and SPECT. PET and SPECT tracers also have half-lives on the order of minutes to hours, while MPI tracers can last for days to weeks [43]. The new imaging method, which allows the noninvasive detection of cancer, produces positive results for the patient and reduces the physical charge on the patient by eliminating the need for biopsy with imaging.

During the imaging, there is a local difference in the proton density of the tissues that produce the MR images. MNPs provide contrast in MR by shortening the longitudinal (T1) and transverse (T2) relaxation times of the protons surrounding the tissue [23]. The ability of MNPs to enhance proton relaxation of specific tissues and be used as MR contrast agents is one of the most promising applications in the field of nanomedicine.

Among different magnetic materials, superparamagnetic nanoparticles (IOP) receive more attention in MPI [44]. Due to their nanoparticle suspension features, and their reproducible applications in biosystems FDA approved their utilization in MR applications. MNPs in this form have actively been studied as imaging contrast agents. IOP applications like commercially available bowel contrast agents (Gastromark® and Lumiren®) and liver/spleen imaging (Feridex® and Endorem®) have paved the way for clinical applications of MNPs [27]. MR evaluations of IOP showed that they are appropriate for being a clinical diagnostic tool as a theragnostic agent (Table 1).

Table 1. Commercially available and clinically used IOPs [20, 47]

MNPs	Hydrodynamic size (nm)	Coating	Application	Status at Clinical
Ferumoxide (Feridex®, Endorem™, AMI-25)	80-200	Dextran	Liver imaging	Used and discontinued
Ferumoxsil (Lumirem®, GastroMARK®, AMI-121, Oral-SPIO)	400	Poly [N-(2-aminoethyl)-3-aminopropyl] siloxane	Abdominal tissue and bowel imaging	Used and discontinued
Feruglose (Clariscan™, MION-46, NC100150)	20	PEGylated starch	Liver lesions and perfusion imaging	Clinical trial
Feruglose (Clariscan™, MION-46, NC100150)	3500	Polystyrene (sulfonated styrene-divinylbenzene copolymer)	Gastrointestinal, abdominal imaging	Approved and discontinued
Ferumoxytol (Feraheme®, Rienso®)	30	Polyglucose sorbitol carboxymethylether	Brain tumor imaging	Clinical trials
Ferucarbotran (Resovist®, Cliavist™, SHU 555A)	60	Carboxydextran	Liver, spleen imaging	Approved
Feraheme®	30	Polyglucose sorbitol carboxymethylether	Treatment of iron deficiency anemia in adult patients with chronic kidney disease	Approved and using
NanoTherm®	15	Aminosilane	Magnetic hyperthermia therapy for brain tumors	Approved and using
SPION-epirubicin	50-150	Anhydroglucose	Magnetic drug targeting	Clinical trials (terminated)

The size and surface features of MNPs affect MR imaging. The growing core size ensures high magnetic forces, but the interaction of MNPs with the target may be limited. Therefore, to reduce the particle size and increase the magnetic response, the core size of the nanoparticle was increased, and coating thickness was decreased. The study showed that the created nanoparticles function as a contrast enhancer for MR imaging of brain glioma [45]. Another study showed the impact of the different surface coating of MNPs in MR imaging. The researchers reported that hydrophilic surface coatings caused the highest proton relaxation [46]. The use of MNPs with MR increases the success of imaging, but this practice has not become a standard procedure in the clinic.

The non-standardization of IOP in clinical MR imaging is associated with various reasons. First is the unwillingness of healthcare providers to use IOP in regular practice because of toxicity concerns backed by the FDA [47,48]. Another issue is the unwillingness of pharmaceutical companies to produce IOP contrast agents [49].

MNP-based contrast agents provide long-time imaging at the tumor site due to enhanced cellular internalization and slow clearance from the tumor site. New-generation MPI systems have the potential to diagnose diseases and determine their localization. Thanks to MPI, cancer progression, reproduction, and spread can be prevented, and cancer-related death rates can be reduced. Researchers must develop IOPs have fewer toxicity concerns and higher contrast performance.

Role of Magnetic Nanoparticles in Treatment

Drug Release Systems: Since chemotherapeutic drugs usually target dividing cells, traditional chemotherapy drugs cannot

destroy cancer stem cells due to their high resistance. This causes cancer to recur. Moreover, since chemotherapeutic agents are non-specific, they damage both cancerous and healthy cells. Controlled drug release systems are modified release systems that release the active substance at a predetermined rate within a specific period. Drug release systems developed can target tumor cells with increased efficiency and minimized side effects. For example, the highly toxic drug doxorubicin (DOX) can be delivered directly to tumor cells using liposomes without affecting the heart or kidneys. Research showed that targeting can be done with the developed drug release systems [50].

The success of magnetic nanoparticles in imaging has led to their use in drug release systems. Coating the surfaces of MNPs with polymer provides points where drug molecules can connect to MNPs. Therapeutic drugs can be connected to nanoparticles [16]. In this way, the therapeutic effect of a cytotoxic drug can remain until it reaches the target site. Moreover, an external magnetic field can be applied to the tumor area to target and release anticancer drugs. MNP-based drug release systems are studied for tumor targeting. Thanks to drug release systems based on MNPs, the side effects of chemotherapy drugs decreased, and drug levels were provided at the concentration required for treatment. In 2008, Sun and colleagues showed that their magnetic drug release system increased the effectiveness of drugs which showed limited efficiency in conventional therapy and reduced their side effects on healthy tissues [27,51]. In 2010, Hao-Li Liu and colleagues showed that using focused ultrasound (FUS), and magnetic targeting (MT), large molecules can be transported to the brain. The targeted particles were monitored with MR simultaneously at the time of the treatment. Researchers showed that particles could target the brain by crossing the blood-brain barrier (BBB), and the

anticancer drug epirubicin, which cannot penetrate the BBB, can be connected by conjugation to particles [52]. In 2014, Halupka-Bryl and colleagues synthesized iron oxide nanoparticles coated with DOX-containing PEG. The study confirmed the efficient release of the PEG-PIONs/DOX anticancer drug to the tumor site. PEG-PIONs/DOX received by murine colon cancer cells reduced the tumor cell viability [53]. In another study conducted in 2015, researchers showed that PLGA nanocapsules loaded with the anticancer drug 5-fluorouracil excellent anti-tumor activity against colon cancer [54]. There are advances in issues such as the prevention of the uptake of MNPs by the reticuloendothelial system and their accumulation at the target. However, further studies are needed for the clinical use of drug release systems based on MNPs. Magnetic drug release systems that combine molecular imaging and therapy have the potential for effective diagnosis and treatment for cancer.

Hyperthermia: Another significant application of MNPs is to provide therapeutic effects through hyperthermia. Hyperthermia is an abnormally high body temperature. In the classical hyperthermia method, the temperature of the tumor area is increased above the physiological temperature (37 °C). Tumor cells are selectively destroyed by raising the temperature to ~41-46°C. Irregular vascular networks and low blood flow within the cancerous tissue reduce the rate of convective cooling of the tumor and cause the tumor to overheat. Cancerous cells undergo apoptosis while healthy cells can resist these temperatures for some time. However, healthy tissue can spread heat to neighboring tissue by conduction and convection [55]. Therefore, between 41-46 °C, the viability of cells in cancerous tissue is significantly reduced, while healthy tissues can successfully dissipate heat and survive. Standard hyperthermia treatment uses the laser beam, focused ultrasound waves, microwave radiation, and radiofrequency [56]. Moreover, hyperthermia treatment can be applied as systemic hyperthermia, external hyperthermia, regional hyperthermia, interstitial hyperthermia, luminal hyperthermia, or nanoparticles-based hyperthermia. The main reason why hyperthermia is not widely used and accepted in clinics is that it cannot provide localized tumor heating. Although significant advances have been made in the clinical application of hyperthermia techniques, they have several side effects such as burns, blisters, pain, and irregular tissue growth [57].

Hyperthermia application with MNPs is called magnetic nanofluid hyperthermia (MSH)[58]. This method is relatively non-toxic compared to other tumor treatment methods. MSH can specifically heat tumor cells without damaging the surrounding tissues. It has been investigated for many years as a new in-vivo treatment method to eliminate the side effects caused by traditional treatment methods such as chemotherapy and radiotherapy. MSH has recently been approved in Europe for the treatment of glioblastoma multiforme in a procedure that requires direct delivery of MNPs to the cancer site [59].

There are several types of materials used as MNP cores for hyperthermia treatment such as cobalt, nickel, iron, zinc, and their oxides. Pure metal applications have high saturation and magnetization. However, their biomedical applications are limited due to their instability and toxicity in the human body. Metal oxides have higher stability and biocompatibility in the body than

metals. Thus, they are more preferred for biomedical applications. Magnetite (Fe_3O_4) and Maghemite (Fe_2O_3) are well-known metal oxide materials that can be stabilized with different ligands such as cationic liposomes, dextran, hydrogel, and polyvinyl alcohol. The other MNP group is based on ferrites such as manganese ferrite (ZnFe_2O_4), cobalt ferrite (CoFe_2O_4), and nickel ferrite (NiFe_2O_4). Ferromagnetic MNPs such as Au doped Fe and iron oxides doped with Zn/Mn ($\text{Zn}_x\text{Mn}_{(1-x)}\text{Fe}_3\text{O}_4$) are known utilized in hyperthermia applications [21]. Studies show that this technique can improve therapeutic outcomes for cancer patients, either as a stand-alone treatment or in combination with chemotherapy and radiotherapy.

MSH can be applied either by intravenous routes or intratumorally injection of a colloidal suspension of MNPs. MNPs deposited in the tumor area are exposed to an external magnetic field (AMF, RF, MW) as shown in Figure 5. Superparamagnetic MNPs absorb this energy and transform it into heat energy through the relaxation of magnetic moments. MNPs can generate different degrees of heat depending on their formulation and magnetic field parameters [60].

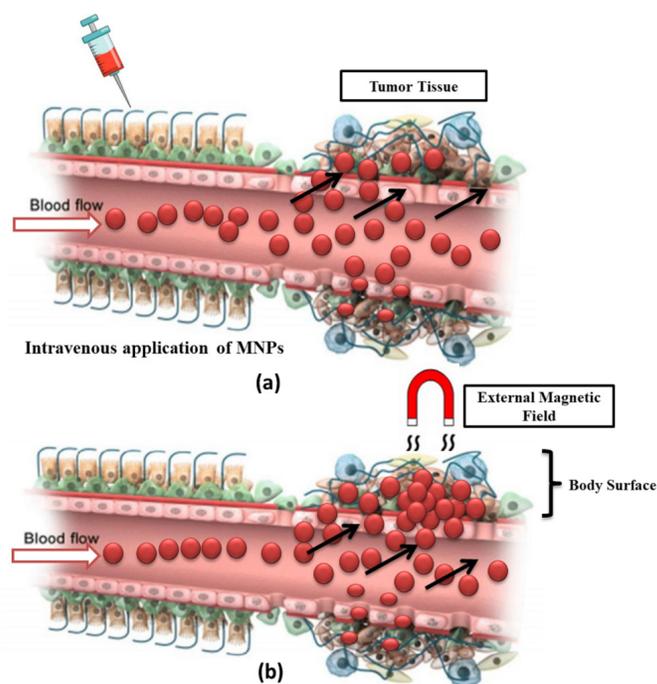


Figure 5. Magnetic Hyperthermia Therapy (a) Intravenous application of MNPs into the body. (b) Application of external magnetic field [12]

In 2005, Manfred and colleagues conducted a study by inducing MatLy Luv cells in the prostates of male Copenhagen rats. Tumor volume was measured at regular intervals in all rats after MNP has injected into the tumor site. Hyperthermia treatment was conducted using an AMF applicator system operating at 100 kHz frequency and variable field strength on the 10th and 12th days. In this study, researchers showed that magnetic hyperthermia inhibits tumor growth in the range of 44-51% [61]. In 2012, Basel and colleagues loaded iron/iron oxide nanoparticles into RAW264.7 cells and created a murine model of pancreatic cancer with peritoneal spread. Monocyte/macrophage-like cells loaded with iron/iron oxide nanoparticles were injected intraperitoneally after tumor growth had taken place. Three days after injection, mice were exposed to an alternating magnetic field for 20 minutes

for hyperthermia treatment, and this procedure was repeated three times in a group of mice. MNPs produced heat under AMF stimulation. The study showed that this system increased the survival rate by 31% in a murine model of pancreatic cancer [62]. In 2013, Jae-Hyun Lee and colleagues formed polyamide dopamine dendrimers (Ad-PAMAM) by coating the Adamantine core PEG. Later, they uploaded it with DOX to create DOX-SMNP. They evaluated the hyperthermia treatment potential of the developed MNPs and presented a protocol and showed that drug release and hyperthermia treatment were achieved with the designed DOX-SMNP. Moreover, they showed in the study that the highest decrease in tumor growth reached in animals treated with hyperthermia twice. Researchers concluded that controllable drug release systems can be used clinically by reducing side effects of drug candidates that have unsuccessful results in the toxicology test but have high therapeutic efficacy [63]. In their study in 2017, Mondol and colleagues synthesized hydroxyapatite-coated iron oxide nanoparticles and tried them for cancer treatment with magnetic hyperthermia. Hydroxyapatite-coated IOPs showed a hyperthermic effect on MG-63 osteosarcoma cells. Moreover, in vitro hyperthermia temperature of 45 °C was reached in 3 minutes [64]. Studies showed positive outcomes of hyperthermia treatment in reducing the volume of cancer tissue when MNPs are injected into the tumor and later exposed to AMF. We believe that targeted hyperthermia using magnetic nanoparticles has the potential to selectively destroy cancer cells in the body.

Conclusion

MNP platforms that combine imaging and therapeutic activities showed the potential to increase the effectiveness of cancer treatments such as drug release systems and hyperthermia by providing simultaneous diagnosis and treatment. The progress related to clinical applications of magnetic drug release is slow. However, there has a high potential due to the therapeutic application that will enable the emergence of personalized medicine. Achievement in MR imaging provides hope towards translation of MNP-based theragnostic into the clinics. Although the discussion about the clinical use of MNPs in cancer treatment continues, MNPs are powerful tools that reduce patients' pain, increase life expectancy and quality of life, and raise the success of cancer treatments. Researchers should continue to investigate methods to improve the stability and biocompatibility of multifunctional MNPs. In the case of cell imaging and tracking, new methods must be developed for particles to recognize the cell membrane receptor and provide long-term in-vivo monitoring. There is limited information on the effects of MNPs on human health. Since the use of MNPs in biomedical applications is significantly increased, further research is needed on their long-term side effects. New magnetic nanoparticle procedures developed for diagnosis and treatment can then be translated into clinical protocols.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

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