Review

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Basics of magnetic nanoparticles for their application in the field of magnetic fluid hyperthermia

Abstract: The use of non-invasive alternating magnetic field (AMF) on biocompatible, small sized iron oxide nanoparticles can be used for heat generation in magnetic hyperthermia or for contrast enhancement of biological tissue. However, the behavior of magnetic nanoparticle in the presence of magnetic field is restricted by their size, shape, surface defects, and coatings. Hence, it becomes imperative to closely monitor the magnetic properties of the nanoparticles as current novel formulations of nanoparticles being developed for tissue targeting involves conjugating a magnetic nanoparticle with a site specific ligand or a peptide. Thus, in this review article we have reviewed the effect of size, shape, doping, and surface coating on the magnetic properties of the nanoparticle. Finally we have concluded with the clinical status of magnetic nanoparticle in the field of magnetic fluid hyperthermia.

Keywords: iron oxide nanoparticles; magnetic fluid hyperthermia; magnetic nanoparticles.

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Introduction

Nanotechnology, a science which deals with design and applications of nanomaterials, can provide valuable information to differentiate abnormalities in various body structures and organs to determine the extent of disease, and evaluate the effectiveness of treatment rendered. Hence, controlling nanomaterials in vivo is desired for optimum diagnostic or therapeutic outcome. Among nanomaterials, magnetic nanoparticles (MNPs) have received significant attention in the field of biomedical engineering. This is due to the fact that the intrinsic properties of MNPs provide a non-invasive means to control their fate for a wide variety of applications such as biosensors, magnetic fluid hyperthermia (MFH), magnetic resonance imaging (MRI), magnetic drug and gene delivery, and magnetic separation (1–4). In general, MNPs includes the class of metallic, bimetallic, and superparamagnetic iron oxide nanoparticles (SPIOs). The latter has already been FDA approved for its application as an MRI contrast agent because of its inoffensive toxicity profile and biocompatibility. Besides, along with their tunable magnetic properties, MNPs also provide reactive surface that can be readily modified with biocompatible coatings for targeting tissues. Thus aided aggregation of magnetic nanoparticles in tumor tissues can be achieved by conjugating nanoparticles with tumor targeting peptides or antibodies (5, 6). However, these functionalization and modification of the MNPs, lead to change in the size, shape which greatly affect the magnetic properties such as coercivity (Hc) of these nanosphere which is of utmost importance for their application in the field of magnetic fluid hyperthermia (MFH). For example, the MFH requires a particle which behaves as a soft magnet so that it will retain some magnetization after the removal of the magnetic field. Of course, care has to be taken to retain its inertness while synthesizing a soft magnet with the highest possible saturation. These intrinsic properties are mainly affected by particles shape, size, surface defects, surface ligands, and temperature to name few (7–10). Hence, it is imperative to mention that the design of novel MNPs for biomedical application requires careful evaluation of surface modification, size, and shape, on its magnetic properties. A thorough consideration of each design parameter must be evaluated to produce MNPs that can overcome biological barriers and carry out its function. Even though it is impossible to consider all these effects in details for this review article, in the next section we have tried to outline the striking effects of the above mentioned factors on the magnetic properties of the MNPs. Furthermore, we have

also reviewed the basic of magnetism such as ferromagnetism (soft and hard magnets), and superparamagnetism along with various MNPs for their biological application followed by their current clinical status in the field of magnetic fluid hyperthermia.

Basics of magnetism: soft and hard magnets

Magnetic materials encompass a variety of materials which are used in a diverse range of applications. They can be classified in terms of their magnetic behavior. Most common types of magnetic behaviors are diagmagnetism and paramagnetism which account for the magnetic properties of elements at room temperature. Consequently, most elements in the periodic table are usually referred as non-magnetic, whereas, those which are cited as magnetic are classified as ferromagnetic (7). Most of magnetic materials of industrial interests are ferromagenetic materials.

In general, the magnetic effects are caused by movements of particles that have both mass and electric charge. These particles can be electrons, holes, protons and positive and negative ions. We are aware that a spinning electric charged particle creates a magnetic dipole, called magneton which are associated in groups in a ferromagnetic material (7). Furthermore, the bulk of ferromagnetic material consists of a number of small regions of magnetons which are called domains as shown in Figure 1. The boundaries between domains are called domain walls.

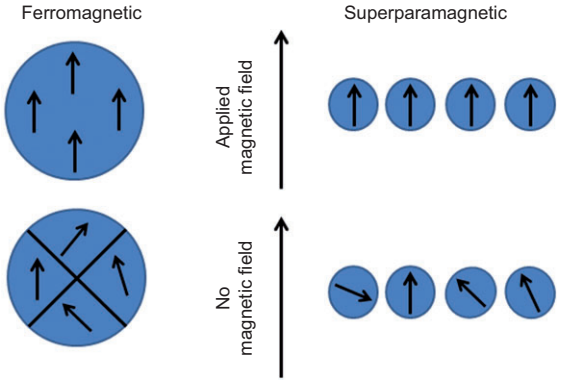

Figure 1 Magnetic moment in both ferromagnetic and superparamagnetic materials. On application of the magnetic field the domain walls in ferromagnetic materials are washed away and aligned to the direction of the magnetic field. Whereas, in superparamagnetic materials which are usually defined as single domain structures have no domain walls, but the magnetic moments align to the direction of the applied external magnetic field. The domain structure of the magnetic materials has been drawn for simplicity.

These domain walls are not thin surfaces but should be visualized as zones of transition of finite thickness in which the magnetization gradually changes the direction from one side to another (Figure 1) (7, 11).

Thus, a magnetic domain in a ferromagnetic material refers to the volume of the material in which all magnetons are aligned in the same direction by the exchange forces. This concept of domains distinguishes ferromagnetism from paramagnetism. The ferromagnetic materials in a demagnetized state does not show any magnetization as the total magnetization is cancelled because of the random orientation of the magnetizations in magnetic domains. However, on the application of an external magnetic field, the magnetic domain walls are washed away and magnetic moments become aligned to the direction of the magnetic field and saturate the magnetization (Figure 1). This magnetization is called saturation magnetization (Ms) (Figure 2). On removal of the applied magnetic field, instead of retracing its original path, ferromagnets retain some memory of the applied field called as remanence (Point A in the curve, Figure 2). To reduce the magnetization of that material to zero, a coercive force (Pont B in the Curve, Figure 2) must be applied to a ferromagnetic material so as to close the loop. Thus coercivity measures the resistance of a ferromagnetic material to become demagnetized. This behavior of the ferromagnetic material is known as the hysteresis and the path which it follows is known as the hysteresis loop (Figure 2). The hysteresis depicts the behavior of ferromagnets under the influence of the magnetic field and differentiates them from paramagnets.

Due to its varied dependence on the magnetic field the ferromagnetic materials can be categorized into soft and hard magnetic materials (Figure 2) (11, 12). Soft magnetic materials are those which can be demagnetized at low magnetic fields and hence the coercivity (Hc) is low. On the other hand, soft magnetic materials can be easily magnetized and hence the permeability is high. Consequently, for a ferromagnetic material to be soft, their magnetocrystalline anisotropy must be low which can be responsible for the easy migration of the magnetic domains (7, 11, 12). Anisotropy can be defined as a difference in a material's physical or mechanical properties such as magnetic, absorbance, refractive index, conductivity, tensile strength, etc. when measured along different axes. However, when the domain wall is difficult to migrate a higher magnetic field is required for the alignment of the magnetic moments of the ferromagnetic material (7, 11, 12). These types of ferromagnetic materials are referred to as hard magnets (7, 11, 12). In other words, these types of ferromagnetic materials are difficult to magnetize, but once magnetized, they are

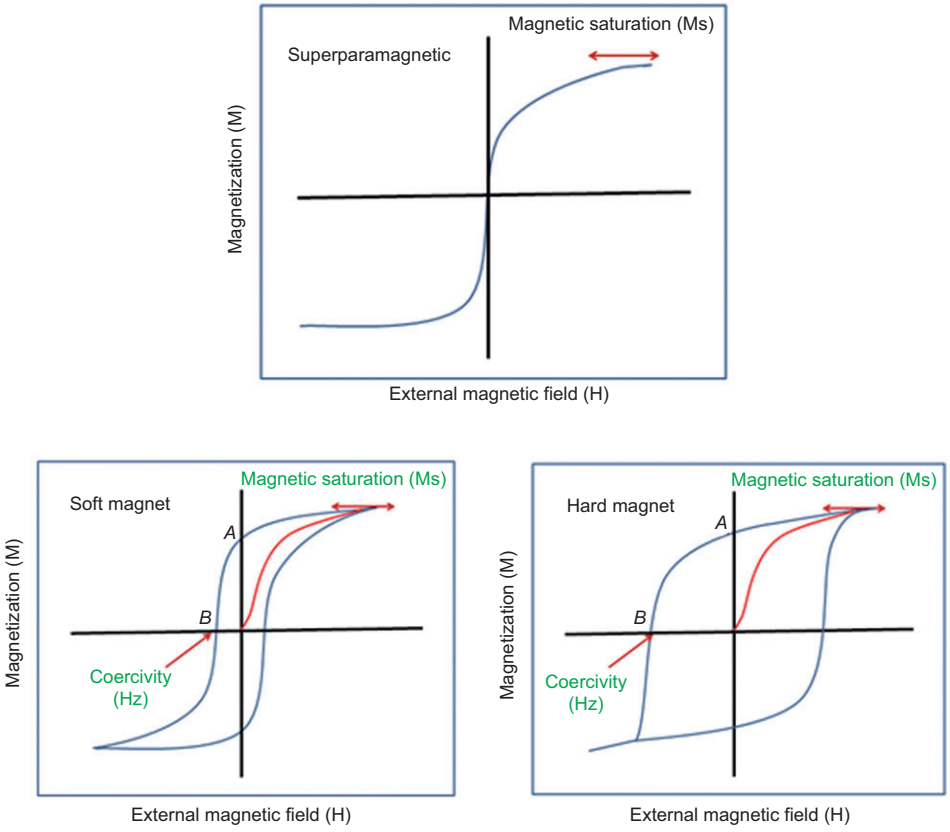

Figure 2 A typical hysteresis loop such as that obtained from superparamagnetic and ferromagnetic (soft and hard) materials.

difficult to demagnetize. Hence, it is an obvious fact that in contrast to the soft magnetic materials the hard magnetic materials have high magnetocrystalline anisotropy and coercivity (Hc) (12).

Normally, hard ferromagnetic materials have memory because they remain magnetized after the external magnetic field has been removed. Whereas, soft ferromagnetic materials such as iron or silicon steel have very narrow magnetic hysteresis loops resulting in very small amounts of residual magnetism making them ideal for a variety of biological applications. Additionally, since a coercive force must be applied to overcome this residual magnetism, work must be done in closing the hysteresis loop. This magnetic hysteresis results in the dissipation of energy in the form of heat with the energy wasted being in proportion to the area of the magnetic hysteresis loop. Thus the amount of loss depends on the material's value of coercive force. To our advantage, the resulting heat can be used for the in-situ heating of the tumor cells. Since the heat loss is determined by the hysteresis loop which is in turn determined by the magnetic material, the type of magnetic material plays an important role in its biological application. For example, a soft magnet is usually preferred for its use in magnetic hyperthermia so as to achieve a temperature increase of ~5–10°C. Thus the coercivity (Hc) of the material usually defines the application of a particular magnet. In a broader sense, the magnetic properties of any ferromagnets depend on various factors such as particle size, shape, defects, surface effects, and temperature to name but a few. In the following section we have tried to discuss the dependence of coercivity on the particle size, shape, and surface coatings of the magnetic materials as these are the controlling factors in the engineering of nanoparticles for its biomedical applications.

Dependence of coercivity on the size of the nanoparticle

The domain structure of a ferromagnetic material determines the size dependence of its magnetic behavior (12). In fact, the two most studied finite-size effects in nanoparticles are the single domain limit and the superparamagnetic limit (11). As discussed earlier, a large magnetic particle is well known for its multidomain structure with regions of uniform magnetization which are separated by domain walls (Figure 1). This formation of the domain walls is energetically favorable if the energy consumption

for the formation of the domain walls is lower than the difference between the magnetostatic energy of the single domain and the multidomain states (7). As the dimensions of the particles are reduced, the relative contribution of the various energy terms to the total energy of the ferromagnetic material is changed. Thus, the surface energy of the domain walls becomes more important than the magnetostatic energy. Below the critical diameter it costs more energy to create a domain wall than to support the magnetostatic energy of the single-domain state (11). Hence, when the size of a ferromagnetic material is reduced below the critical diameter, it becomes a single domain. The configuration of the magnetization inside a single domain particle then depends strongly on the magnetic anisotropy and the particle's shape (7). As stated previously, the effect of ferromagnetic materials to an applied field is well described by the hysteresis loop, which is characterized by two main parameters *viz* remanence and coercivity (12). The latter is related to the 'thickness' of the curve. Dealing with fine particles, the coercivity is the single property of most interest and it is strongly size-dependent. It has been found that as the particle size is reduced, the coercivity increases to a maximum, and then decreases toward zero as shown in Figure 3. With a further decrease in particle size below the critical diameter, the coercivity becomes zero and such particles become superparamagnetic (Figure 3).

When considering only the dipolar interactions between magnetic particles, for smaller particles the simple magnetization reversal energy becomes equal to the energy at room temperature (7, 10, 13). Thus when typical ferromagnets obtain a critical diameter of <30 nm, the thermal fluctuations at room temperature are strong enough to spontaneously demagnetize a previously saturated assembly and hence these particles have zero coercivity and have no hysteresis (10). Therefore, superparamagnetic nanoparticles become magnetic in the presence of an external magnet, but revert to a non-magnetic state when the external magnet is removed. This avoids any 'active' behavior of the particles when there is no applied field. This behavior of superparamagnetic materials has led to its potential advantages for bio applications. Once in vivo these particles are 'magnetic' only in the presence of an external field, and give them the unique advantage in working in biological environments.

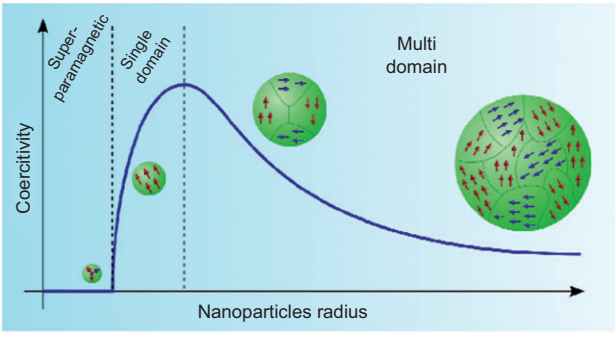

Figure 3 Schematic illustration of the coercivity-size relations of small particles. Copyrighted from reference (12).

Recently, Kim et al. synthesized various nanocubes in the range of 20–160 nm and measured their coercivity at 300 K (Figure 4A). When the sizes of the nanoparticles were plotted against coercivity, the resulting single domain curve confirmed that a superparamagnetic character would be observed for the particle size of ~20 nm (Figure 4B) (14). Similarly, Krishnan and colleagues demonstrated that the 16 nm magnetic particles responded better to the alternating magnetic field as compared to the particles of larger diameter (15). However, Osaka and colleagues, recently, reported that the larger sized particle (44 nm) had better heating efficiency in vitro as compared to the smaller sized particle (13 nm) (16). In the same study, the authors reported that the magnetic properties of the particles synthesized with a 13 nm diameter were superparamagnetic in nature, whereas, those with a 44 nm diameter showed a ferromagnetic behavior (Figure 5). Finally, the heat treatment of these cells lines (MCF-7) internalized with these two nanoparticles (13 and 44 nm) revealed that the magnetic nanoparticles with a diameter of 44 nm demonstrated a higher increase in temperature in vitro as compared to the nanoparticles with a diameter of 13 nm (Figure 6). This difference in temperature rise can be attributed to the difference in the coercivity of both particles and hence their magnetic nature.

There are a number of crystalline materials of various sizes that exhibit ferromagnetism. Since ferrite oxide-magnetite (Fe_3O_4) is the most magnetic of all the naturally occurring minerals on the earth it is widely used in the form of superparamagnetic nanoparticles for all sorts of biological applications such as magnetic field hyperthermia (MFH) and magnetic resonance imaging (MRI) magnetic separation and magnetic drug and gene delivery. However, for its use in tissue specific applications such as tumors, a tumor specific ligand is usually conjugated onto the surface of these nanoparticles. This leads to the change in the surface of the magnetic nanoparticles, leading to the change in magnetic properties of these nanoparticles *via* the changes in surface anisotropy. These changes in the surface effects also have a pronounced effect on the shape of the nanoparticles due to formation of the defects and/or strain on the surface. Thus in addition to the size, the magnetic properties of the nanoparticles depend to a great extent on its surface and shape which are discussed in the next section.

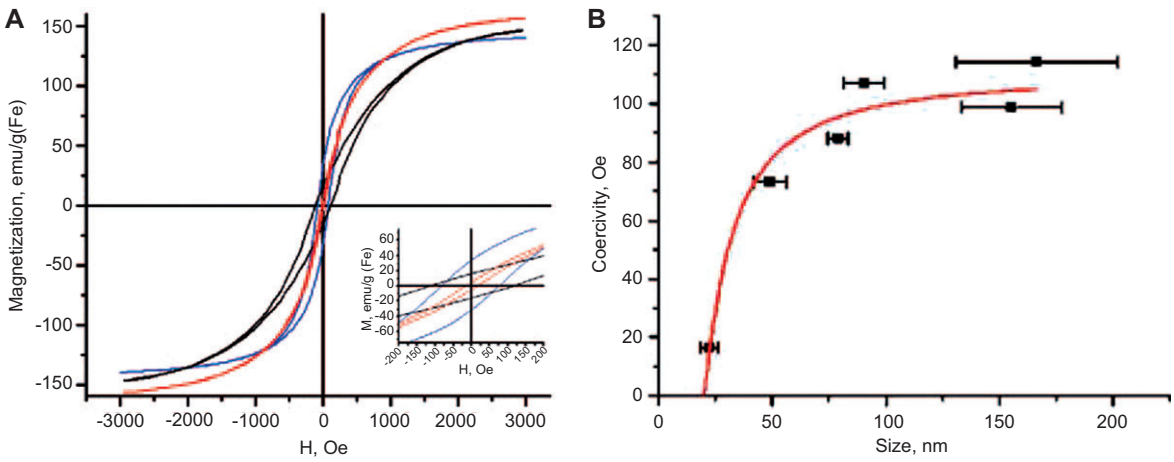

Figure 4 Magnetic behavior of the Fe_3O_4 nanocubes measured at 300 K: (A) M–H curves for 22-nm- (red), 80-nm- (blue), and 160-nm- (black) sized nanocubes; (B) size-dependent coercivity (error bar: size distribution). Copyrighted from reference (14).

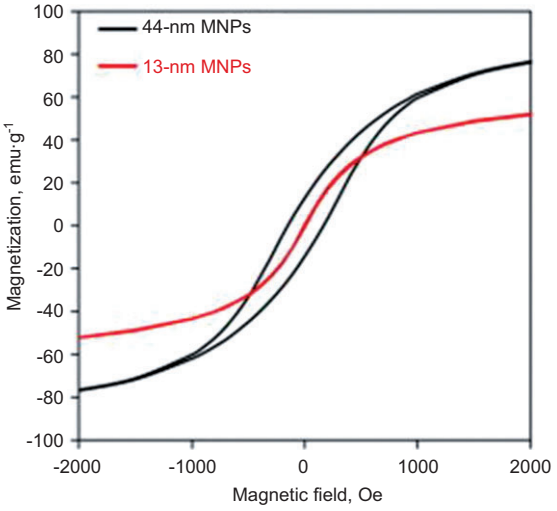

Figure 5 Shows the magnetization curves of 44 (black line) and 13 nm MNPs (red line). Copyrighted from reference (15).

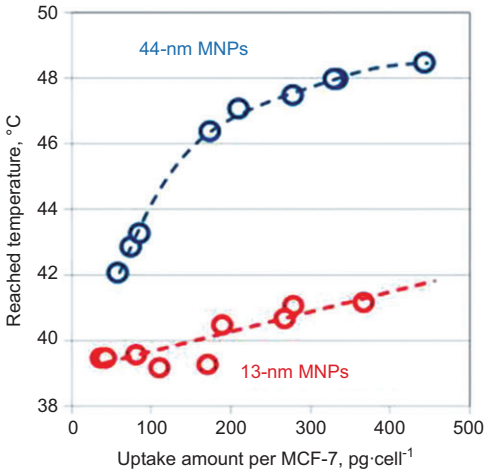

Figure 6 Shows the relation between uptake amount per MCF-7 versus temperature reached for 44 nm MNPs (blue) and 13 nm MNPs (red). Copyrighted from reference (15).

Dependence of coercivity on the shape and surface coating of nanoparticles

Another source for the change in the coercivity of magnetic nanoparticles is the shape anisotropy. The departure from sphericity for magnetic nanoparticles has significant influence on the coercivity as is shown in Table 1 which list the particles with different aspect ratios (17). As the aspect ratio changes, the shape of the particle changes and hence the coercivity changes. Moreover, the shape of nanoparticles can influence its magnetic properties in different ways. For example, classical electrodynamics teaches us that the homogenous magnetization is achievable only for ellipsoidal bodies. Hence, an ideal single-domain particle has to be ellipsoidal. Deviation from ellipsoidal shape and distortions in particle shape can induce additional anisotropy. These distortions can lead to small deviations from

Table 1 Effect of shape on coercivity for Fe nanoparticles.

Aspect ratio (c/a)[a]	Coercivity (kOe)
1.1	820
1.5	3300
2.0	5200
5.0	9000
10	10,100

Source: Ref. (11). [a]Aspect ratio is defined as the ratio of length/breath of the nanoparticle.

uniformity in the magnetization field within the nanoparticles and can play an essential role in determining its magnetic properties (18).

The shape of real magnetic nanoparticles can be cubic, triangular, parallelepiped, cylindrical, or a triangular prism (19, 20). These particles with different shapes show variation in the sensitivity of dipole-dipole (magnetostatic) interactions between particles to their shapes. Moreover, Bøder et al. reported that the magnetic anisotropy changes when the surfaces are adorned by different molecules (21). Thus the coating material is a common denominator in engineering a bio-sensitive magnetic nanomaterial and has a huge effect on the shape anisotropy of the magnet. The coating material can be an organic polymer or a thin layer of metal which can be magnetic or non-magnetic. The presence of these coating materials can greatly influence the magnetic properties of a nanomagnet with a varying effect. Generally, a polymer or other non-magnetic coating on the surface of magnetic nanoparticles can lead to a decrease of the magnetization with respect to the bulk value (11). This reduction has been mainly associated with the existence of a magnetically dead layer on the surface of particles (22). Organic ligands such as polyethylene glycol, dextran, aminosilanes which are used to stabilize the magnetic nanoparticles, thus modulate their magnetic properties by modifying the anisotropy and reducing surface magnetic moment of the metal atoms located at the surface of the particles (23, 24). This modulation in the magnetic properties has also been reported by Yuan et al. who demonstrated that the magnetic nanoparticles with different biocompatible coatings led to a reduction in the magnetic phase. They also concluded that the solvent in which the measurements are carried out also plays an important role (25). The effect in the reduction in magnetic moments is also observed in colloidal particles of cobalt stabilized with organic ligands (23). However, when nickel nanoparticles were tagged with electron withdrawing triphenylphosphine oxides the resulting magnetic particles showed a reduction in the magnetization but the use of donor ligands, such as amines, did not alter the surface magnetism (26). These contrasting magnetic properties make it difficult to engineer a nanoparticle to meet specific needs.

Similarly it is difficult to predict the influence of the metal coating on the magnetic nanoparticles of the nanoparticles. For example, gold-coated cobalt nanoparticles have a lower magnetic anisotropy than uncoated particles due to a complex interplay between a core and coating materials (23, 27). In contrast, the gold coating of iron particles enhances the anisotropy, an effect which was attributed to alloy formation with the gold (27). Yet, in some cases a clear correlation can be drawn between the surface coating and the magnetic properties of the engineered nanoparticle. For instance, a silica coating can be used to tune the magnetic properties of nanoparticles, as a thin silica layer will separate the adjacent nanoparticles, thereby preventing cooperative switching (28).

A magnetic coating on a magnetic nanoparticle also has a vivid effect on the magnetic properties as the combination of two different magnetic phases will lead to new magnetic nanocomposites. Numerous systems are been investigated such as ferromagnetic nanoparticles (Fe_3O_4) coated with their antiferromagnetic oxides (e.g., Co/CoO, Ni/NiO), nitrides (Fe-Fe_2N), and sulfides (Fe-FeS). The large difference in magnetic properties in these complexes can be assigned to the large additional angiotropy resulting from the coupling of the ferromagnetic particles with an antiferromagnetic matrix. In another study a bimagnetic core-shell structure have been studied, where both the core and the shell, are strongly magnetic (FePt/$CoFe_2O_4$) (29). These bimagnetic core-shell nanoparticles basically allow a precise control of the magnetic properties by tweaking the aspects of the core and shell.

Overall, the magnetic behavior and hence the coercivity of an assembly of nanoparticles is a result of both the intrinsic properties of the particles and the interactions among them, whereas, the distribution of the sizes, shapes, surface ligands and defects are only a few of the parameters influencing the magnetic properties. Therefore, it must be concluded that the magnetic response of a nanoparticle to an inert coating is rather complex and system specific, so that no firm correlations can be established at present and in most of the cases, the effect of the coating is less clear and cannot be predetermined before the actual magnetic measurements have been performed. Even with limited information on the behavior of these systems various attempts have been made to bioengineer magnetic nanoparticles so as to potentially utilize them for magnetic hyperthermia. In the following section we have tried to outline a few of these applications of magnetic nanoparticles in the field of MFH followed by their current status in clinical trials.

Applications of MNPs for magnetic hyperthermia

As discussed earlier, whenever, a ferromagneitc material is placed under an alternating magnetic field the magnetic domain walls are washed away and magnetic moments become aligned to the direction of the magnetic field

(7, 11, 12). However, upon removal of the magnetic field, instead of regaining the magnetic domains a very small amount of residual magnetism is retained resulting in a hysteresis loop (Figure 2). Given that a coercive force must be applied to overcome this residual magnetism, work must be done in closing the hysteresis loop resulting in the release of energy which is dissipated as heat from the magnetic material. This heat is known as hysteresis loss and the amount of loss depends on the coercivity of the magnetic material and is proportional to the area of the magnetic hysteresis loop. This resulting heat has been used for the in-situ heating of the tumor cells by hyperthermia. In general, the field of oncology has shown the importance of the MFH in destroying specific tumor tissues by raising the temperature above the physiological level (40–45°C). This increase in temperature is usually triggered through the losses of sub-domain magnetic particles under the influence of an alternating magnetic field. In contrast to MFH, the other methods for increasing temperatures above the systemic values (i.e., 37.5°C) are based on the application of microwaves. However, the inability to control temperatures, and undesired collateral effects such as radiation and lack of selectiveness that affect the surrounding healthy tissues have been major issues which hamper the use of these high energy radiations. Moreover, MFH has an additional advantage over microwave hyperthermia where MFH uses the AC magnetic field with much lower frequency (10^5 Hz) as compared to microwave hyperthermia (Figure 7). An operating frequency of 10^5 Hz the heating effects of MFH an on living tissues are negligible.

Therefore, different from other hyperthermia methods, MFH needs a heating agent anchored on to operating tissue in order to produce a localized temperature increase. This difference is the main reason for the potential advantages of MFH over alternative strategies. Since MNPs can in principle be selectively targeted or even introduced into the cancer cells by conjugating them to a tumor specific peptide or a ligand, their concentration into the tumor cells can be increased on purpose. Once targeted onto the cancer cells, the ability of the soft magnetic nanoparticles to retain their magnetism and release them into the cancer environment in vivo in the form of heat under the influence of AC magnetic field makes them a perfect weapon against these cancer cells. Thus, the success of this approach depends critically on the ability to target a magnetic particle on the cancer cells that are to be killed and the softness of the magnetic particle. The use of soft magnetic nanoparticles will ensure that the process of heat release can take place under the influence of the minimum AC magnetic field which will provide us with an advantage to control the temperature at ~40°C. In contrast, the use of hard magnetic nanoparticles is usually discouraged as it incorporates permanent magnetism in the core of the nanoparticle thereby making the process of heat release extremely difficult. Additionally, placing a permanent magnet inside the body will increase the coagulation and accumulation of all biological magnetic particles towards this permanent nanomagnet and thus disturb all biological processes. Thus coercivity (Hc) plays an important role in deciding when to use a nanomagnet in the application of MFH.

The use of iron oxide nanoparticles for selective heating can be traced to when Medal and Coworkers in 1957 used a 0.02–0.1 µm (20–100 nm) sized Fe_2O_3 nanoparticles for selective heating of lymph nodes in dogs (30). No magnetic studies were carried out and the authors used a maximum magnetic field strength of ~200–240 Oe for about 3 min on the dissected samples of nodes. This high magnetic field strength increased the temperature of the system in vitro by 14°C (30). Two decades later in 1979, Gordon et al. used a 6 nm Fe_3O_4 in 70% sucrose solution

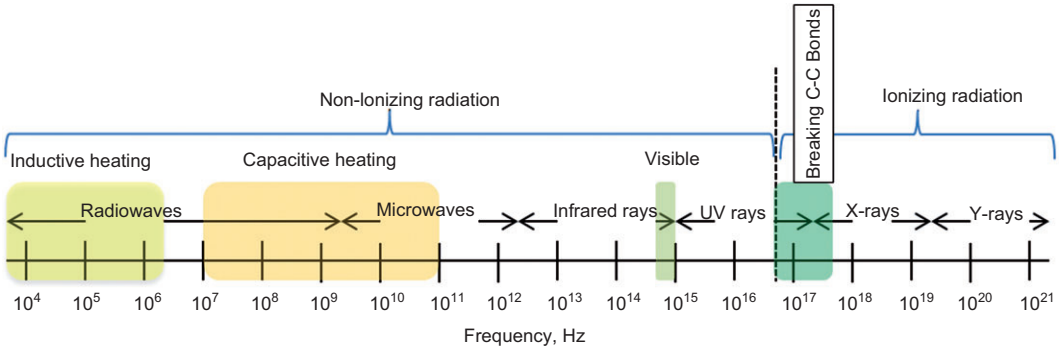

Figure 7 Schematic of frequencies (in Hz) used by various techniques; magnetic field hyperthermia (MFH), magnetic resonance imaging (MRI), computed tomography (CT).

for their potential application in magnetic fluid hyperthermia after systemic application. The temperature rise of ~8–9°C was reported but no information was provided on the magnetic field strength and the coercivity of magnetic iron oxide nanoparticles (Fe_3O_4) (31). Subsequently, in 1982, Rand et al. injected a ferromagnetic particles into renal carcinomas of rabbits for its application in MFH. During these study they made a novel conclusion that the periodic on and off heating to 55°C for short period of time is not effective in the necrosis of the tumors as compared to the sustained long-term heating for about 50°C (32).

Lately, Theisen and colleagues reported the direct injection of dextran-coated magnetite nanoparticles with a core size of approximately 3 nm in tumors for its application in the field of MFH in 1997 (32, 33). Similarly, Balivada and colleagues, evaluated the influence of bimagnetic Fe/Fe_3O_4 core/shell nanoparticles (MNPs) coated with dopamine-oligoethylene glycol ligands which were further conjugated to TCPP (4-tetracarboxyphenyl porphyrin) (34). These bimagnetic core/shell nanoparticles were then influenced with a short external alternating magnetic field to examine the effect on growth of subcutaneous mouse melanomas (B16-F10). The results indicated that micromolar concentrations of iron given within the modified core-shell Fe/Fe_3O_4 nanoparticles caused a significant anti-tumor effect on murine B16-F10 melanoma with three short 10-min AMF exposures (34). In another study, by Prasad and colleagues, who used Mn doped magnetic nanoparticles $\gamma\text{-}Mn_xFe_{2-x}O_3$ ($0 \leq x \leq 1.3$) with coercivity of 20 kOe to study the effect of hyperthermia induced by the application of an AC magnetic field on HeLa cells (35). The results showed the death of the HeLa cells and mortality was found to be proportional to the quantity of the particles and the duration of application of the AC magnetic field (35).

Another independent study was conducted by Tang and colleagues to evaluate the potential and therapeutic effect of MFH on the rabbit VX2 liver tumor model (36). They concluded that on direct intratumoral injection of uncoated Fe_3O_4 magnetic fluid nanoparticles the nanoparticles were selectively accumulated on to the tumor as imaged by CT-scan (Figure 8)

Subsequent treatment of the targeted magnetic nanoparticles with AC magnetic field satisfactorily demonstrated the necrosis of tumor after 28 days. Moreover, they also reported that the heat treatment had no effect on normal tissues. Microscopic examination of the tumor revealed that coagulation necrosis was observed in the heated area, with a clear boundary line surrounding the tissues as shown in Figure 9 (36).

The field of MFH has also been extended to clinical studies to evaluate the feasibility, toxicity, and quality of life during MFH trials in patients. In March 2003, the first clinical study on the application of MFH was conducted on 14 patients who were suffering from glioblastoma multiforme (37). The patients responded well to the thermotherapy with minor side effects. The maximum intratumoral temperatures observed during these studies were in the range of 42.4–49.5°C. In February of 2004 another clinical study was carried out on 22 patients with recurrent and non-resectable pre-treated tumors (38). The studies reported that the patients responded well to the heat treatments with only minor feelings of heat, superficial skin burns, increased pulse rate, and rise in blood pressure.

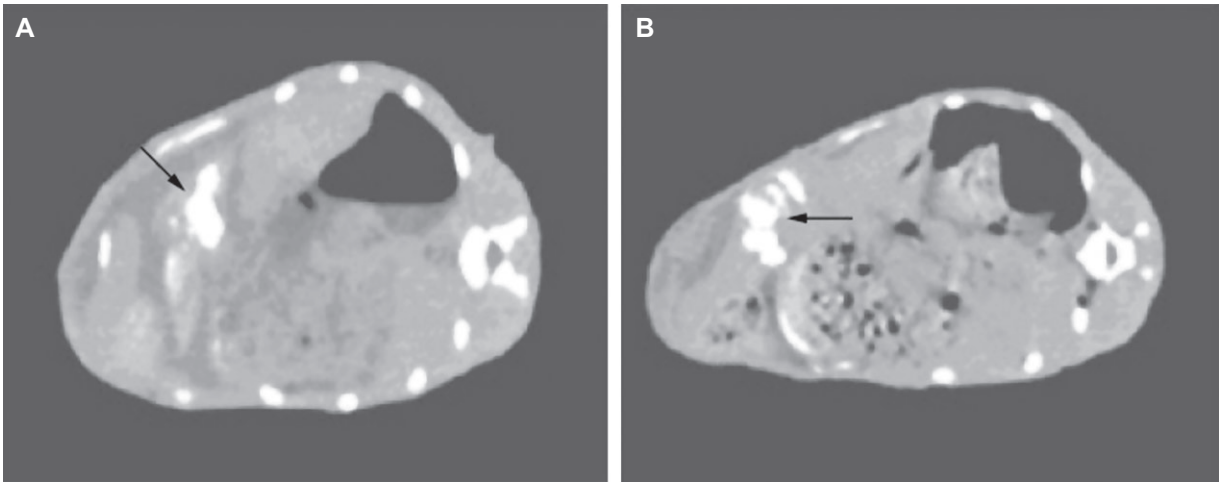

Figure 8 CT image of a rabbit abdomen after the injection of the magnetic fluid (A) day 1 and (B) day 14. Accumlation of magnetic nanoparticles onto the tumors are shown by the arrows. Source: Ref. (36).

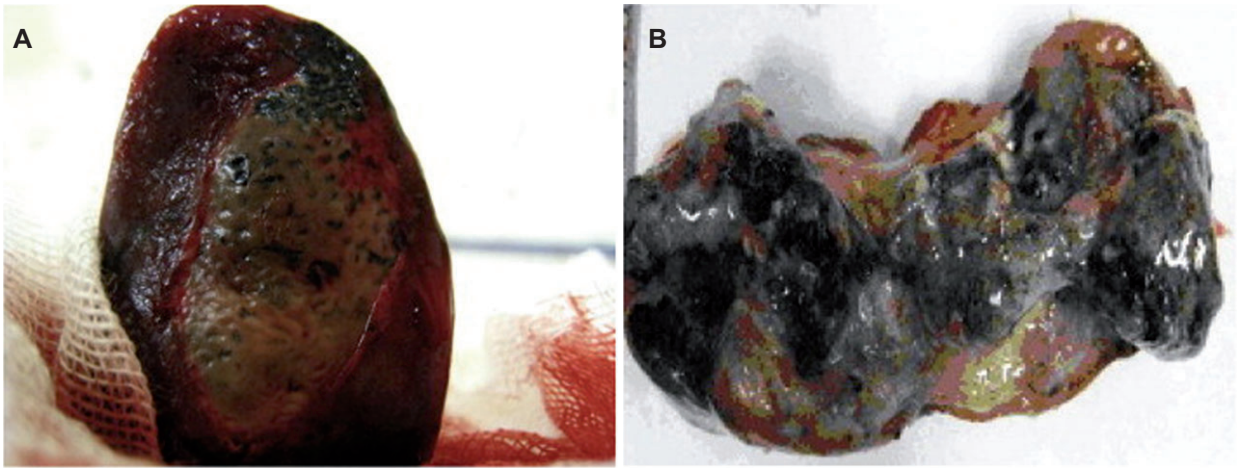

Figure 9 (A) A photograph of the liver tumor immediately before repeated hyperthermia. Local coagulation necrosis with a clear boundary line and magnetic fluid (black) infiltrating into the tumor surface was observed. (B) In the cross-section of the same tumor, almost complete necrosis of the tumor tissue and magnetic fluid that filled the tumor was observed macroscopically. Source: Ref. (36).

On similar lines, Johannsen and colleagues conducted clinical studies in patients with biopsy-proven local recurrence of prostate cancer (39). On injection of the nanoparticle and application of an AC magnetic field into the targeted nanoparticles the maximum and minimum intraprostatic temperatures measured were 48.5°C and 40.0°C during the 1st treatment and 42.5°C and 39.4°C during the 6th treatment. Authors also concluded that the interstitial deposition of nanoparticles was stable for several weeks, making sequential hyperthermia treatments possible without the need for additional injections. More importantly, they reported that the maximum intraprostatic clinical hyperthermia of prostate cancer temperatures achieved are in the thermoablative range (39).

Thus the biocompatible formulations of iron oxide nanoparticles can be targeted to tumors and subsequently heated in an externally applied AC magnetic field. The highly reliable heat distribution of these magnetic bioformulations provides an additional advantage particularly suitable for selective interstitial heating of tumors (40). Additionally, targeting magnetic nanoparticles by selectively conjugating them to tumor specific ligands will deliver the magnetic material directly into the tumor tissue leading to high concentrations of the magnetic material and onto a particular target and thus uniform heat distribution throughout the tumor environment. This addresses the major requirement for hyperthermia, namely that the heat is selectively targeted to the tumor region while sparing neighboring healthy tissue (40). Nevertheless, the potential application of this technique is still at the infancy stage and so far only three clinical studies has evaluated the safety and the feasibility of the technique (37, 39). Moreover, the use of magnetic fields is limited by local discomfort in the pelvic region and skin reactions. Additionally, the use of this technique is not suitable for patients with metallic implants such as artificial hip joints, cardiac pacemakers, and implanted defibrillators (40).

Conclusion

It seems that the use of nanoparticles without vectors is already fading and the synthesis of better magnetic nanoparticles with the integration of multifunctional ligands is being continuously investigated. Indeed, the production of nanoparticles has been fast-tracked in past decade and has led to the development of various magnetic nanoformulations such as liposomes, metallic/non-metallic, and polymeric nanoparticles. Consequently, the effect of size, shape, surface effects, and surface coatings on the coercivity and biocompatibility of magnetic nanoparticles have to be carefully evaluated to expand it from the lab to the clinic (41). The field of magnetic hyperthermia is already at the clinical stage, hopefully in years to come, the treatment of tumors using hyperthermia can become an outpatient surgery conducted within few minutes, supplemented by minimal side effects.

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