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Magnetism for Drug Delivery, MRI and Hyperthermia Applications: a Review

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Abstract: Superparamagnetic nanoparticles contain unique magnetic properties that differ from the bulk materials and are able to function at a cellular level due to their size, shape, and surface characteristics. These features make them attractive candidates for drug delivery systems, thermal mediators in hyperthermia, and magnetic resonance imaging (MRI) contrast agents. This review provides an up-to-date overview of the application of iron oxide nanoparticles in cancer diagnosis, drug delivery, treatment, and safety concerns related to these materials are considered, as well. Furthermore, the general principles and challenges of the magnetic behavior of nanoparticles in the field of oncology are also discussed. Firstly, the basic requirements for magnetic nanoparticles for biomedical applications are outlined. The close link between structure, shape, size, and magnetic characterization are described, which is considered essential for non-invasive imaging modality, innovative magnetic-driven nanocarriers, and treatment based on the overheating. In conclusion, investigation of the toxicity profile of novel nanoparticles is provided, as well.
In the current review, the attention is focused on the role of magnetic nanoparticles, especially iron oxide nanoparticles in some bioapplications such as magnetic resonance imaging (MRI) contrast agents, targeted drug delivery, and magnetic hyperthermia systems.

Keywords: cancer; diagnosis; drug delivery; superparamagnetic iron oxide nanoparticles; MRI; biomedicine; toxicity; hyperthermia.

1. Introduction

Magnetic nanoparticles (MNPs) like nickel, cobalt, iron, and their chemical compounds are used in various medical applications [1, 120, 123, 124, 130-131]. Among these MNPs, iron oxide nanoparticles; magnetite (Fe_3O_4), maghemite and hematite (α-Fe_3O_4) are prevalent materials of common use [2, 100, 102, 104, 105]. It is conspicuous because of its large surface area to volume ratio, quantum confinement effect, remarkable magnetic properties, and poor toxicity [3, 4]. Typical magnetic characteristics of Fe_3O_4 nanoparticles include controlled orientation and arrangement through a strong magnetic field [128, 133] and according to these benefits, these materials could be used as objects of cancer diagnosis and treatment, drug delivery systems.

The diagnosis is a valuable issue in order to detect cancer disease in advance or/and imagination the smallest feasible amount of tumor cells. Currently, there are only several imaging modalities available in modern medicine: ultrasound (US) [6], computed tomography (CT) [5], magnetic resonance imaging (MRI) [7], single-photon emission computed

tomography (SPECT) [8], optical imaging [9], etc. A distinctive feature of MRI method is it is an extremely accurate method of disease detection. Additionally, the development of the synthesis and modification processes of MNPs has already guided to a variety of novel opportunities in the design of MRI contrast agents [10, 11]. The hydrodynamic size of MNPs, which is established as the overall size of the particle, assuming a hydration layer on it, is highly depended on the ability of particles to overcome the biological defense system, penetrate via the vascular barriers and get to the location of the lesion [12]. Accordingly, MNPs as drug vehicles for targeting drug delivery is an efficient approach that should not be neglected [13]. It is a highly promising approach that involves the use of non-ionizing radiation with no restriction on their penetration depth across biological tissues. In general, MNPs are used as drug carriers by binding antibodies [14-16] and chemotherapeutic drugs [17-19]. Furthermore, a number of nanoparticles and traditional/herbal medicines conjugates have been developed for targeted delivery purposes in order to increase its anticancer performance and to lessen side effects as well. As sub-class materials, MNPs are used in cancer therapy, as well. Recently, a number of techniques based on various designs of MNPs are applied in the realm of tumor therapy: magnetic hyperthermia (MHT) [22, 23], photodynamic therapy (PDT) [24, 25, 119], photothermal therapy [26], etc. In parallel to their increasing use for biomedical applications, safety concerns on human organisms have enhanced, as well [81]. Moreover, the accumulation of MNPs in cell cultures and *in vivo*, their effect on proliferation and viability, toxicity studying are the main research areas in terms of their clinical activity [82, 83].

The review includes advancements in the development of MNPs for targeted drug delivery systems, tumor diagnosis, and application in treatment issues. Moreover, several questions related to their toxicity, adverse effects, and acting mechanism on the living system were examined. Additionally, the physical principles of the magnetic behavior of nanoparticles applied in biomedical applications are also reviewed.

2. Basic requirements to MNPs for biomedical applications

There are some demands for biomedical applications of MNPs, such as high saturation magnetization (H_S) and good magnetic response (χ) [27-30]. It is known that diamagnets exhibit negative susceptibility (χ=-10^{-6} ÷ -10^{-3}). However, paramagnets show small positive susceptibility (χ=-10^{-1} ÷ -10^{-6}). But for biomedical applications ferromagnet materials, that exhibit a large, positive susceptibility are more effective[31]. It is clear that when the external magnetic field is removed, the diamagnets and paramagnets are not able to save their magnetic responsibility, while ferromagnetic materials pose stable magnetic properties. Furthermore, for biomedical applications, temperature dependency of the magnetic properties of the materials plays a significant role, as well. Ferromagnetic and ferromagnetic materials become paramagnetic only above Curie temperature (T_C), in which the change in the direction of the intrinsic magnetic moments can occur. In addition, magnetic anisotropy is also one of the most important properties of ferromagnets for health issues. It is the property that gives a preferred direction on the spin of materials that may not be aligned with an external magnetic field [32-34]. Whereas for a magnetically isotropic material (i.e., a superparamagnetic material) there is no preferential direction of the magnetic moment. In contrast, a magnetically anisotropic material will align its magnetic moment in one direction, which is called an easy axis [35, 125, 127, 129].

Brief information about the characteristic magnetic behavior of MNPs in diagnostic and therapeutic applications in the area of cancer issues will be discussed in the following sections.

3. Iron oxide nanoparticles in cancer diagnosis (Magnetic Resonance Imaging)

Diagnosis of cancer by using nanotechnology is a novel realm that allows us to visualize the tumor cells at an early stage. Moreover, detecting cancer noninvasively could eliminate the necessity for tissue sampling through a biopsy, which is characterized as a traumatic procedure, and consequently, the patient could benefit from it. In addition, MNPs have been proposed as a contrast agent for magnetic resonance imaging (MRI). Generally, the role of contrast agents in MRI is the determination of pathological tissues and clarifies their localization against the background of normal (unchanged) tissues. In other words, the effect of the contrast agent is based on the resonance features of the tissue, which directly depend on the changes of the local magnetic field that applied to the body. This change is coordinated by interactions among the protons of the tissue that can be characterized by two various types of relaxation time being longitudinal (T_1) and transverse (T_2), which are used to generate the magnetic resonance image [36, 37]. The relaxation is the process during which the protons that have been excited with radio-frequency pulse first align in one direction under the external magnetic field, and then return to the equilibrium state. The proton relaxation time depends on the surrounding molecules and atoms, and its value for healthy and tumor cells differ from each other. Generally, a contrast medium is required to improve the clarity of the images of genetically modified cells on the background of healthy ones. Most contrast agents with paramagnetic substances that are commercially available in MRI are characterized by many unpaired electrons and the higher magnetic moment [38, 107]. Moreover, the ability to produce an enhanced proton relaxation makes them valuable candidates for MRI assay with more diagnostic accuracy. In fact, iron oxide superparamagnetic nanoparticles that are characterized by the absence of residual magnetization are already in clinical use as T_2 contrast agents [39]. The face-centered cubic packing of oxygen in magnetite Fe_3O_4, allows the electrons to jump between iron ions occupying interstitial tetrahedral and octahedral sites, thus giving the molecules half-metallic properties that are suitable for MRI [40, 109, 110]. Moreover, iron oxide nanoparticles fulfill several prerequisites such as chemical stability and low toxicity in a physiological environment, and adequate high magnetic moments as well [41].

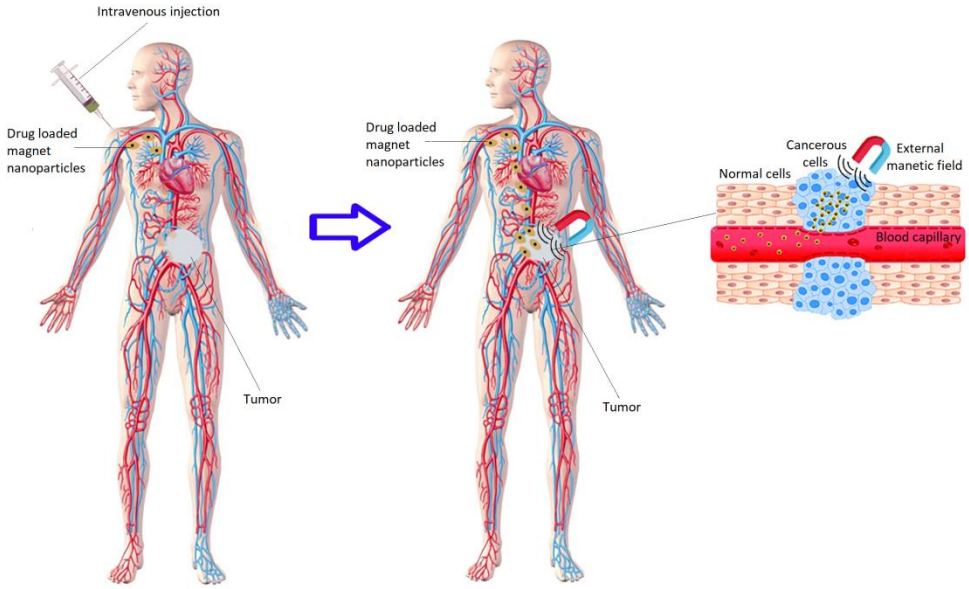
Kim *et al*. [42] synthesized superparamagnetic iron oxide nanoparticles by the sonochemical method for MRI contrast agents. Firstly, oleic acid was used as a coating agent for the spherical nanoparticles. In the next step, these particles were dispersed in chitosan (to make ferrofluids), which is considered as an appropriate carrier for bio-applications. Comparison of the MRI images received via ferrofluids and Resovists (a commercially available contrast agent for MRI) *in vitro* was carried out. It was realized that ferrofluids exposed improvement of the MRI contrasts compared to Resovists. In another study, Smolensky *et al*. [43] demonstrated that Fe_3O_4@organic@Au core-shell structure represented high magnetism and high relaxivity. This characteristic of plasmonic behavior makes these effective materials as effective agents for cell imaging. Another example [44], in which MNPs were used as a contrast agent in MRI were obtained by decoration the surface of them with mesoporous silica nanoparticles that were also medicated with dye. Silica that conjugated with magnetite nanocrystals through its surface area exhibited remarkable enhancement of MR

signal. This development is believed to be related to the synergistic magnetism, while the dye molecule of the system provided optical imaging modality.

4. Targeted drug delivery

Magnetic drug delivery is a rather efficient treatment method of delivering a drug to a disease location by exerting an external field, and it allows reducing the side effects of conventional chemotherapy. However, it decreases a significant amount of the medication in the non-target tissues [97, 101,103, 106, 111-118].

In a targeted magnetical drug delivery system, the drug can be either conjugated on the surface of the magnetic substance or encapsulated into a sphere. When the magnetic carrier is intravenously administered, it gathers in the areas that the magnetic field is applied (Scheme 1).



Scheme 1. Magnetically targeted drug delivery system using drug-loaded magnet nanoparticles.

The gathering process of the magnetic carrier at the target site allows them to deliver the drug locally. The efficiency of the accumulation of magnetic carrier, depends on several features such as particle size, its surface properties, applied field strength, and blood flow rate. It is worth noting that the targeted drug delivery system value of M_s is very important, and not only this variable, but also all magnetic properties (M_r, H_c, etc.) directly depend on the size of the particles [45-47]. However, after crossing the superparamagnetic value limit, the H_c and M_r increase as a result of growing particle size. According to some references, the d<70 nm limitation is given as a size range for the transition from a multi-domain to a single-domain state [48-50]. However, it is also known that the ferromagnetic nanoparticles smaller than this size limit demonstrate superparamagnetic features [126]. Above this critical size, the H_c and M_r values decrease with a further increase in the particle size. However, the values of M_s increases with increasing particle size. Thus, one of the main issues is to achieve a reduction in the size of nanoparticles without variation of the value of the saturation magnetization. Even though this should be the “ideal” expectation, in practice, the decrease of the saturation value is observed when the size is strongly reduced. Actually, for drug delivery applications, the nanoparticles should be steered from outside the body using magnetic fields [40, 51]. In order

to be managed by an external magnetic field, the value M_s should be correlated with the value of the magnetic field. That is why literature analysis shows that threshold or limitation value of M_s for successful targeting drug delivery is absent information [27-29, 35, 45, 52]. However, except for the value of the saturation magnetization (H_s), the saturation field (magnitude of the field needed to reach M_s) is a rather important parameter, as well [53, 98, 99].

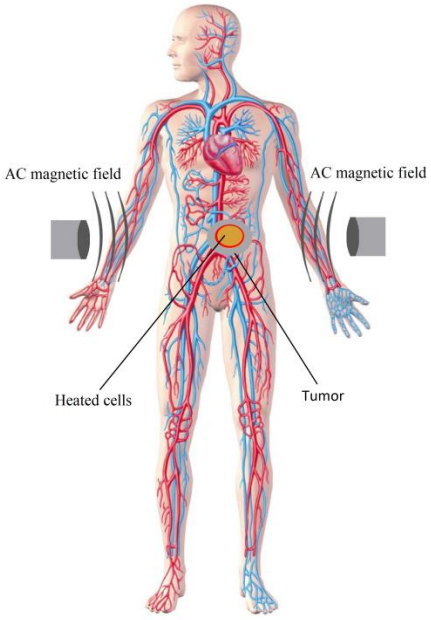
Ease of synthesis, superparamagnetic properties, and ability to readily respond to the external magnetic field makes iron oxides a more effective applicant compared to other magnetic nanoparticles [108]. On the other hand, such MNPs possess high surface energies, and consequently, the process of agglomeration is inevitable. Additionally, the naked iron oxide nanoparticles are characterized by high chemical activity and could readily oxidize in air. In turn, these aspects are provided with a loss of magnetism and dispersibility. Accordingly, providing suitable surface coating methods and developing effective protection strategies for ensuring the stability of MNPs are rather important issues. These strategies mostly contain coating using polymers such as silica [54], dextran [55]chitosan [56], or PVA [57], PEG [58], or metals such as gold [59] to which functional groups can be attached via cross-linkers. Moreover, the coating is also required to achieve effective medicine loading profiles and make these nanoparticles water-soluble in order to improve their circulation time [60, 61]. The drug loading is generally carried out in two various ways: drug could be dissolved in an organic phase (non-aqueous phase) and in an aqueous phase containing the MNPs [62, 63]. Furthermore, the drug cargo and the drug release pace are significant parameters that should be considered. Drugs in a low therapeutic dose but with a strong electrostatic affinity towards MNPs can be loaded just by adsorption onto the surface of nanoparticles. In contrast, drugs that are characterized with high therapeutic doses should be embodied in the organic/inorganic shell generated over the magnetic core [64, 65].

Gang *et al*. [66] via emulsion-diffusion method prepared superparamagnetic Fe_3O_4 poly ε-caprolactone core/shell nanoparticles with the size of approximately 160 nm that were conjugated with the gemcitabine (Gem). Under the influence of an external magnetic field, these magnetically guided nanoparticles showed significantly higher (15-fold) antitumor activity in human pancreatic adenocarcinoma cells compared to the free anticancer drug Gem *in vivo*. In another research, anticancer drug (DOX) incorporated in the cross-linked polymer coating layer of superparamagnetic iron oxide nanoparticles (SPIONs). Positively charged DOX and negatively charged polymer layers connected via electrostatic interactions [67]. The study discovered that despite the higher dose (8-fold) of free DOX than the DOX@polymer-superparamagnetic nanoparticle system, the free drug showed poor antitumor activity (38% and 63% respectively). Moreover, the toxicological investigation revealed that the therapeutically active dose of free anticancer drug DOX caused several health problems such as lymphatic damage, hepatic impairment, and reduced white blood cell amount, whereas the nano formulated system was founded to be harmless.

5. Magnetically induced hyperthermia for cancer treatment

Magnetic hyperthermia is an experimental treatment for cancer based on the overheating of cells at certain temperatures [68, 121, 122]. This treatment method is classified into three types, according to the temperature value: thermal ablation (tumor subjected to temperatures > 46ºC), moderate hyperthermia (41ºC<T<46ºC), and diathermia (T<41ºC) [69]. Accurate temperature control is presently impossible, so there is always the risk of overheating

the surrounding healthy tissue. Accordingly, the most prevalent strategy is ""moderate"" hyperthermia, carried out between 41ºC and 46ºC temperatures. In broad terms, the procedure involves dispersing magnetic particles throughout the target tissue and then applying an AC magnetic field of sufficient strength and frequency to cause the particles to heat, which causes the rapid death of tumor cells while surrounding normal tissues are stayed unaffected (Scheme 2). Regarding the physical principles of this process, it could be explained in the following way: the heat absorbed by the biological tissues is supplied by the dissipative oscillations of the nanoparticles' magnetic moments induced by an external oscillating magnetic field.



Scheme 2. Therapy process via hyperthermia using magnet nanoparticles.

In other words, in this case, either magnetic moment of nanoparticle or nanoparticle itself rotates in an external magnetic field. In the superparamagnetic particles, the heat is induced by susceptibility losses having Néel relaxation (τ_N) and Brownian rotation (τ_B) times. It is worth noting that the relaxation process is accompanied by heat dissipation. The identical size particles' susceptibility loss at low frequencies of the variable magnetic field caused by the Brownian rotation that is higher compared to Néel relaxation [70-73]. Hysteresis loss that occurs for larger magnetic nanoparticles is addressed to magnetic anisotropy. Thus, the produced heat is the function not only of the size, shape, and composition of nanoparticles but also their interactions, surface/interface effects as well. Moreover, in this case, the amplitude and frequency of the applied magnetic field also play a significant role. [70, 74-77]. So particle size is an essential argument in hyperthermia since the application of a magnetic field (AC) will conduct a heating process that emerges from either Neel or Brownian relaxation processes or hysteresis losses.

The cancer cells are destroyed if the temperature of 42ºC is maintained for 30 minutes. Therefore, the intensity and frequency properties of the external AC magnetic field should be appropriate to generate enough energy for reaching the required temperature. However, there is also another issue that, according to the international standards, maximum field-frequency products applied to live organisms should not exceed the upper limit of the Atkinson-Brezovich criterion [17] which is, $H \times f \leq 4.85 \times 10^8 A\ m^{-1}s^{-1}$. Thus, the appropriate frequency that applied should be between 30 kHz–300 kHz, while the permissible limit of the magnetic field should be $H \leq 15$ kA/m that is accepted as a rather low field. The majority of ferromagnetic materials

require a high field for magnetization, while superparamagnetic nanoparticles have the ability to magnetize at mentioned low fields. Since the superparamagnetic particles can generate large amounts of heat at the lower fields, the specific absorption rate (SAR) for them, which characterizes the efficiency of heating for magnetic materials will be high [70-73, 76, 77].

As it is mentioned in previous sections, iron oxide nanoparticles, as one of the most outstanding materials with unique magnetic properties, are being investigated in various branches of medicine almost in hyperthermia. Jin H. *et al*. [78] discovered the potential benefit of iron oxide nanoparticles in human breast cancer cells. Study results have shown that the particles coated with gold and having the sizes of 10-30 nm are heated comparatively well. In other research, the treatment process of rabbit liver tumors was carried out through hyperthermia at ~42ºC for 20 minutes. [79]. It was discovered that the growth of liver tumors was completely stopped after 2 weeks, compared to controls that grew in size about 20 times over the same time period. In another study, Kossatz *et al*. [80] provided the magnetic hyperthermia experiments *in vivo*. The superparamagnetic iron oxide nanoparticles were functionalized with either peptide and doxorubicin (DOX) or both via electrostatic binding. All samples showed an excellent heating potential in the alternating magnetic field. Moreover, a considerable tumor growth reduction was noticed after *in vivo* injection of the magnetic nanoparticles

6. Parameters of iron oxide NPs leading to toxicity

Iron oxide 'nanoparticles' (NPs) biocompatibility with the target organ is the first premise for clinical transfer, and these particles have long been believed to have low toxicity, and they are biocompatible with the human body. However, recently a great deal of works has been done to develop superparamagnetic iron oxide nanoparticles for applications in biomedicine, and due to this fact, there is an extreme necessity to carry out researches regarding their toxicity issue. Toxic effects caused by these ultra-fine particles have been reported *in vitro* and *in vivo* studies and still remain as a controversial issue [84-86]. Factors inherent to nanosystems, including iron oxide nanoparticles such as size, charge, surface functionalities, hydrophobicity, and other properties, tend to directly influence their toxicity [87]. Holding structure–performance relationship studies for iron oxide nanoparticles, however, is challenged by the fact that a change in one parameter (e.g., particle size) frequently leads to a variation in other parameters (e.g., magnetic properties), that in its turn intricates results. Moreover, the challenge to realize the interconnection of toxicity and structure–performance issues of iron oxide nanoparticles is the shortage of systematic approaches. Since the majority of implemented researches focus on short-dated approaches. In this case, toxicity in several cell lines is not able to display a potential variation in the living system's function and viability accurately.

Nanoparticle size issue was discovered to play an essential role in cell toxicity. However, investigation of a harmful impact on DNA and other cells in the Ames test demonstrated that small (~10 nm) iron oxide nanoparticles coated with polyethylene glycol have stronger mutagenic potential compared to their larger (~30 nm) counterparts [88]. L. Yang and others [89] studied the size subject *in vivo* distribution, toxicity, and gene term changes of carboxyl coated iron oxide nanoparticles with various diameters in the range of 10-40 nm. It was discovered that on the first day of post-injection, iron oxide nanoparticles with different sizes mainly accumulated in the organs like liver and spleen. Moreover, it was observed that

the small iron oxide nanoparticles (10 nm) exhibited the highest uptake by the liver, whereas the largest ones showed the highest accumulation primarily in the spleen. In addition, blood biochemistry, hematological, and histological analyses revealed that obvious severe toxicity related to the iron oxide nanoparticles was absent. However, iron oxide nanoparticles with the size 10 and 20 nm demonstrated a significant influence on the metabolic process and apoptosis.

J.H. Lee [90] and others discovered that along with the size of iron oxide nanoparticles, the shape issue is also a major factor that promotes the particle toxicity. It was investigated that the degree of tumor necrosis that is correlated with a great degree of membrane damage was higher for the rod-shaped Fe_2O_3 nanoparticles compared to the spherical ones. Obtained results could be accompanied by the growth of surface area because this feature for spherical particles differs from particles with other shapes.

The utilization of nanoparticles in medicine requires their controlled interactions with biosystems [91]. In this case, for instance, surface structures of nanoparticles are able to transmit increased cellular internalization ability, non-cytotoxicity, and developed payload binding capacity necessary for effective intracellular delivery. The role of the surface functionalities for magnetic nanoparticles is essential due to the ability to reduce 'nanoparticles' aggregation tendency that, in its turn, can improve these materials' dispersibility, colloidal stability, and protect their surface from oxidation, as well. Polyethylene glycol (PEG) is one of the most commonly used shielding material because it is cheap and presently is considered as a safe substance. Moreover, PEGylation [93] is able to increase the blood circulation time by avoiding clearance by the reticuloendothelial system. It also modifies nanoparticles by giving them biocompatibility and reduces their adverse interactions, thus lessens their toxicity [92, 94], albeit some studies indicate opposite statements on the issue regarding the toxicity of this coating material. Genotoxicity of magnetite iron oxide nanoparticles with the identical diameter and various surface chemical structures such as poly (ethylene glycol) and poly (ethylene imine) were estimated using assays like Salmonella typhimurium reverse mutation assay, the *in vitro* mammalian chromosome aberration test, and the *in vivo* micronucleus assay [88]. It was revealed that iron oxide nanoparticles coated with poly (ethylene glycol) showed a mutagenic performance that was supposed to be related to the dose value in all samples, while coated particles exhibited toxicity characteristics only in metabolic activation. In another study [95], the effect of genotoxicity of functionalized superparamagnetic nanoparticles with three various coating materials such as chitosan, poly (ethylene imine), and aminopropyl-triethoxysilane on human endothelial and keratinocytes cells were assessed through the DNA damage. The results showed that in endothelial cells, with the exception of poly (ethylene imine)-superparamagnetic iron oxide nanoparticles, all iron oxide nanoparticles caused significant DNA damage.

7. Conclusions

MNPs that are characterized by unique properties could play an important role in biomedical applications. In this review, the centers of interest are cancer diagnoses, such as MRI, cancer therapy, the magnetic delivery of drugs, and treatment, such as magnetic hyperthermia.

Despite the fact that investigation for novel routes of applications in the biomedical realm of MNPs has been done and many achievements have been obtained, there is a lack of general guidelines for their assessment. First of all, the new synthesis methods or approaches are still needed to be improved to prepare novel MNPs with appropriate colloidal stability and

biocompatibility. Secondly, the toxicity issue of MNPs should not be ignored, either. The benefit-to-risk ratio balance needs further evolution according to the intended application character. Thirdly, more *in vivo* experiments are necessary to realize despite numerous studies have carried out in cell culture and/or small models, a significant part of MNPs formulations cannot satisfy the clinical requirement.

Although huge achievements have been implemented, there is still a long way to go not only for a more profound understanding of the properties of MNPs but also using them as a tool that could dramatically impact the challenges related to the cancer diagnosis and treatment.

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Conflicts of Interest

The authors declare no conflict of interest.

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