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Review Article

Magnetic nanoparticles - a promising tool for targeted drug delivery system

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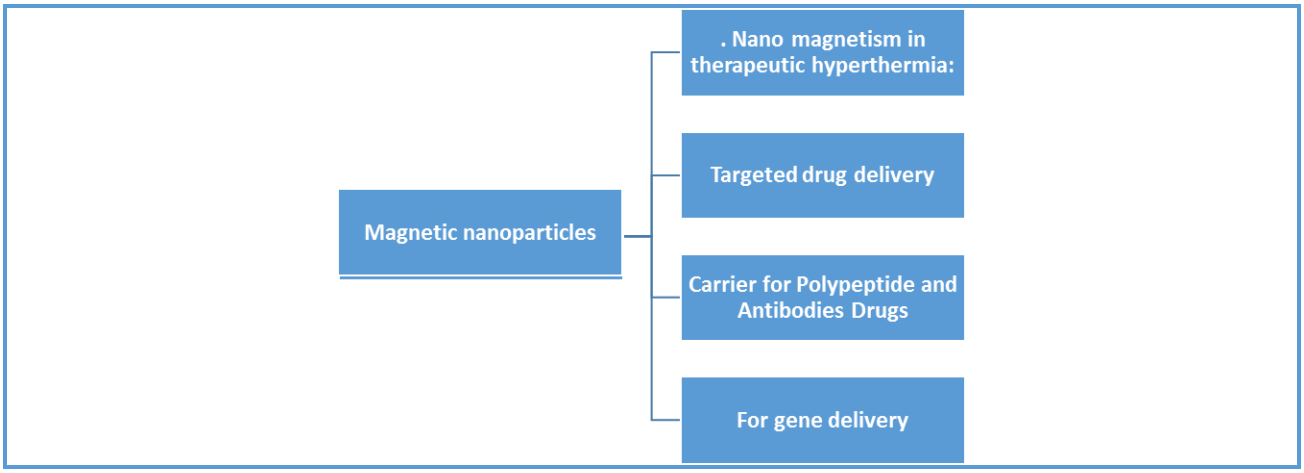
ABSTRACT

Over the last decade, nanotechnology has brought great development in the biomedical field. This study reviewed some physical and chemical characteristic of magnetic nanoparticles that are crucial for medical applications. Advances in preparation of magnetic nanoparticles have some superior applications in hyperthermia, magnetic drug delivery, gene delivery, and magnetic resonance imaging. It was found that, the bio-distribution, pharmacokinetic, and biocompatibility magnetic nanoparticles can be affected by their physicochemical properties, size, shape, and surface chemistry.

Graphical Abstract



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Introduction

As nanoscience has developed substantially over the last decades, the toolbox for preparing NPs has been amazingly broadened, which encouraged scientists to work at the molecular and cellular levels to produce essential advances in healthcare [1, 2].

Magnetic nanoparticles (MNP) are typically 1-100 nm in diameter and consist of iron, cobalt, nickel and their compounds [3]. As magnetic nanoparticles may respond to magnetic field, MNPs have various unique magnetic properties including superparamagnetic, high magnetic susceptibility, and low Curie temperature [4]. MNPs have been also used in various medical and environmental industries such as medical diagnosis and treatment magnetic fluids, biomedicine, catalysis, and magnetic energy storage [5, 6]. The most prominent applications of MNPs are including cancer treatment, drug delivery, magnetic resonance imaging (MRI) [7, 8], magnetic assays [8], and the diagnostics [9]. They have a unique ability to turn on and off their magnetic properties as temperature changes, which provides an excellent analytical tool for an effective cancer therapy.

Each potential application of the magnetic nanoparticles requires having different properties. For example, in data storage applications, the particles need to have a stable and switchable magnetic state to represent bits of information that are not affected by temperature fluctuations. In biology and medical diagnosis, MNPs should be stable in water at pH 7. The colloidal stability of this fluid depends on the surface chemistry (which give rise to both steric and coulombic repulsions) and particle size, which should be sufficiently small to suppress the precipitation effect [11, 12]. For biomedical uses, the application of particles that present superparamagnetic behavior at room temperature is preferred.

For in vivo applications, basic premises is that therapeutic agents are attached to or encapsulated within MNPs to prevent changes from the original structure, formation of large aggregates, and biodegradation when exposed to the biological system. These particles may magnetic core with polymer or metal coating which can be functionalized or may consist of porous polymers that contain magnetic nanoparticle precipitated within pores [13]. The nanoparticle coated with polymer will also allow binding of drugs by entrapment on the particles, adsorption, or covalent attachment [14]. Once attached the particle therapeutic agent complex is injected into bloodstream often using catheter to position the injection site near the target. Magnetic field from a high position, high gradients is the focus over the target site and forces on the particles as they enter the field allow them to be captured and extravasated at the target. While this may be effective to the target (close to the body's surface), as magnetic field strength falls off rapidly with the distance site deeper within the body become more difficult to target. The major factors, which determine toxicity and the biocompatibility of these materials are the nature of the magnetically responsive components, such as magnetite, iron, nickel, cobalt, the final size of the particles, their core, and the coatings. Iron oxide nanoparticles such as magnetite (Fe_3O_4) or its oxidized form maghemite (g-Fe_2O_3) are by far the most commonly employed nanoparticles for biomedical applications [15]. The main components of MNP's are magnetite, iron, nickel, and cobalt. The major factors, which determine toxicity and the biocompatibility of these materials are the nature of the magnetically responsive components, and the final size of the particles, their core, and the coatings. Iron oxide nanoparticles such as magnetite (Fe_3O_4) or its oxidized form

maghemite (g-Fe_2O_3) are by far the most commonly used nanoparticles for biomedical applications. Highly magnetic materials such as cobalt and nickel are susceptible to oxidation and are toxic; hence, they are of little interest [16, 17]. Moreover, successful application of magnetic nanoparticles is highly dependent on stability of the particles under a band of different conditions. The significance of size for controlling the various properties is obvious because in most of the cases, characteristic of the magnetic nanoparticles depends on their dimension and morphology.

Therefore, synthesis of magnetic nanoparticles with their controlled size and exposed facets is of core importance [18]. In most of the applications, the particles with 5-10 nm size have unexpected excellent results. However, the size requirement entiredepends upon the material and applications in which they are supposed to be used. The main problem associated with magnetic particles is their agglomeration. Also, magnetic nanoparticles are highly chemically active. Therefore, it is of utmost important to protect them against oxidation, which may involve functionalization and coating with an individual protective layer to form core-shell structure which completely modifies the magnetic nanoparticles. Although modification is useful (as it provides unique properties to the core magnetic nanoparticle), it may reduce the magnetic properties. Thus precise control of these various factors (size, shape, composition, and structure) can control the magnetic characteristics of the material [19, 20].

The first part of this review is concerned with the advantages of MNP's physical and magnetometric properties. The second part deals with the different methods described in the bibliography that are capable of producing these magnetic nanoparticles with a very narrow particle size distribution. The third part deals with the possible use of magnetic nanoparticles in pharmaceutical and biomedical applications.

Advantages of magnetic nanoparticles

MNP's are considered to be the most favorable candidate for bio-applications as they have low toxicity, biocompatibility, and non-immunogenicity. Also, high effective surface areas and lower sedimentation rates [21, 22]. These particles should be small enough to maintain in the circulation and to transit via the capillary systems of tissues. To control the motion of MNPs in the blood vessels with an external magnetic field, the MNPs must have a high magnetization [4, 22]. The synthesis method of NPs can characterize the shape, the surface chemistry of the particles, the size distribution, the particle size as well as magnetic properties. Magnetic nanoparticles display the phenomenon of superparamagnetism, not keeping magnetized after the action of magnetic filed, offering the advantage of reducing the risk of particle aggregation they have sizes that place the mat dimensions comparable to those of a virus (20±500 nm), a protein (5±50 nm) oragene (2 nm wide and 10±100 nm long).The magnetic nanoparticles, which used inbio applications are usually made from biocompatible materials such as magnetite (Fe_3O_4) for which susceptibility is significant [23]. The effective use of MNPs for biomedical applications such as targeted drug delivery depends on size and magnetism. Parameters such as the physicochemical properties of the drug-loaded MNPs, field strength and geometry, depth of the target tissue, rate of blood flow, and vascular supply, all play a role in determining the effectiveness of this method of drug delivery [15]. Targeting of drugs by nanoparticles is intended to reduce drug wastage, the frequency of drug administration, side effects providing

prolonged, sustained drug delivery to desired targeted organ [24].

Physical and magnetic properties of magnetic nanoparticles

Magnetic effects are caused by movements of particles that have both mass and electric charges. These particles are electrons, holes, protons, positive and negative ions. A spinning electric-charged particle creates a magnetic dipole, so-called magneton. In ferromagnetic materials, magnetons are associated in groups. A magnetic domain (also called a Weiss domain) refers to a volume of ferromagnetic material in which all magnetons are aligned in the same direction by the exchange forces. This concept of domains distinguishes ferromagnetism from paramagnetism. The domain structure of a ferromagnetic material determines the size dependence of its magnetic behavior. When the size of a ferromagnetic material is reduced below a critical value, it becomes a single domain. Fine particle magnetism comes from size effects, which are based on the magnetic domain structure of ferromagnetic materials. It assumes that the state of lowest free energy of ferromagnetic particles has uniform magnetization for particles smaller than a certain critical size and has nonuniform magnetization for larger particles. The former ones are referred to as single domain particles, while the latter is called multidomain particles [25]. According to the magnetic domain theory, the critical size of the single domain is affected by several factors including the value of the magnetic saturation, the strength of the crystal anisotropy and exchange forces, surface or domain-wall energy, and the shape of the particles. The reaction of ferromagnetic materials on an applied field is well described by a hysteresis loop, which is characterized by two main parameters: remanence and coercivity. 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 (Figure 1).

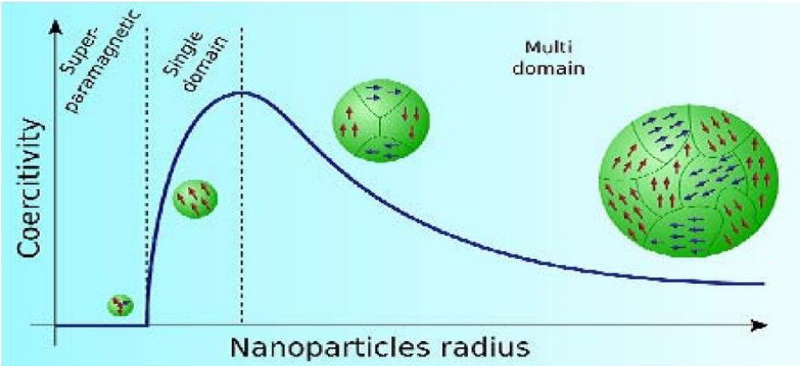


Figure 1. Schematic illustration of the coercivity-size relations of small particles

When the size of single-domain particles further decreases below a critical diameter, the coercivity becomes zero, and such particles become superparamagnetic. Superparamagnetism is caused by thermal effects. In superparamagnetic particles, thermal fluctuations are strong enough to spontaneously demagnetize a previously saturated assembly; therefore, these particles have zero coercivity and have no hysteresis. Nanoparticles become magnetic in the presence of an external magnet, but revert to a

nonmagnetic state when the external magnet is removed. This avoids an 'active' behavior of the particles when there is no applied field. Introduced in the living systems, particles are 'magnetic' only in the presence of an external field, which gives them a unique advantage in working in biological environments. There are some crystalline materials that exhibit ferromagnetism, among others Fe, Co, and Ni. Since ferrite oxide-magnetite (Fe_3O_4) is the most magnetic of all the naturally occurring minerals on earth, it is widely used in the form of superparamagnetic nanoparticles for all sorts of biological applications [23, 25].

Magnetic behavior

Materials are classified by their response to an externally applied magnetic field. Descriptions of orientations of the magnetic moments in a material help identify different forms of magnetism observed in nature. Five basic types of magnetism can be described: diamagnetism, paramagnetism, ferromagnetism, antiferromagnetism, and ferrimagnetism. In the presence of an externally applied magnetic field, the atomic current loops created by the orbital motion of electrons respond to oppose the applied field. All materials display this type of weak repulsion to a magnetic field known as diamagnetism. However, diamagnetism is very weak, and therefore, any other form of magnetic behavior that material may possess usually overpowers the effects of the current loops. Regarding the electronic configuration of the materials, diamagnetism is observed in materials with filled electronic subshells where the magnetic moments are paired and overall cancel each other. Diamagnetic materials have a negative susceptibility ($\chi < 0$) and weakly repel an applied magnetic field (quartz SiO_2). The effects of these atomic current loops are overcome if the material displays a net magnetic moment or has a long-range ordering of its magnetic moments [25, 26]. All other types of magnetic behaviors are observed in materials that are at least partially attributed to unpaired electrons in their atomic shells, often in the 3*d* or 4*f* shells of each atom. Materials whose atomic magnetic moments are uncoupled display paramagnetism; thus, paramagnetic materials have moments with no long-range order, and there is a small positive magnetic susceptibility ($\chi \approx 0$), e.g., pyrite [25, 26]. Materials that possess ferromagnetism have aligned atomic magnetic moments of equal magnitude, and their crystalline structures allow for direct coupling interactions between the moments, which may strongly enhance the flux density (such as Fe, Ni, and Co). Furthermore, the aligned moments in ferromagnetic materials can confer a spontaneous magnetization in the absence of an applied magnetic field. Materials that retain permanent magnetization in the absence of an applied field are known as hard magnets. Materials having atomic magnetic moments of equal magnitude that are arranged in an antiparallel fashion display antiferromagnetism (such as troilite FeS). The exchange interaction couples the moments in such a way that they are antiparallel, therefore, leaving a zero net magnetization. Above the Neel temperature, thermal energy is sufficient to cause the equal and oppositely aligned atomic moments to randomly fluctuate, leading to a disappearance of their long-range order. In this state, the materials exhibit paramagnetic behavior. Ferrimagnetism is a property exhibited by materials whose atoms or ions tend to assume an ordered, but nonparallel arrangement in a zero applied field below a certain characteristic temperature known as the Néel temperature (such as Fe_3O_4 and Fe_3S_4). In the usual case, within a magnetic domain, a substantial net magnetization results from the antiparallel alignment of neighboring non-

equivalent sublattices. The macroscopic behavior is similar to ferromagnetism. Above the Néel temperature, the substance becomes paramagnetic (Figure 2) [27, 28].

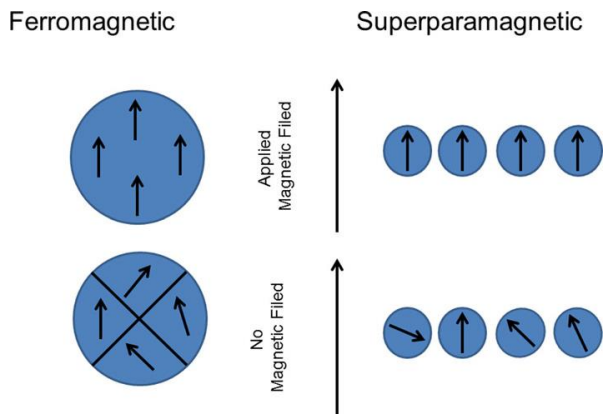


Figure 2. Magnetization behavior of ferromagnetic and superparamagnetic NPs under an external magnetic field

Under an external magnetic field, domains of a ferromagnetic NP align with the applied field. The magnetic moment of single domain superparamagnetic NPs aligns with the applied field. In the absence of an external field, ferromagnetic NPs will maintain a net magnetization, whereas superparamagnetic NPs will exhibit no net magnetization due to rapid reversal of the magnetic moment [15].

The core: materials for magnetic nanoparticle

All chemical elements or compounds of our planet show under certain conditions different magnetic effects. Following materials are used as core material for MNP's. Metals: The only metallic elements showing ferromagnetism at room temperature are iron, cobalt, and nickel. Alloys: The second group of ferromagnetic materials is the ferromagnetic alloys, such as CoPt, FePt, FeNi, or FeCo. Oxides: The group of magnetic oxide materials can be divided into mixed oxides with different crystal structures (e.g., the magnetic garnets and the ferrites) as well as the pure metallic oxides.

Synthesis of magnetic nanostructures

Numerous chemical methods can be used to synthesize magnetic nanoparticles such as chemical coprecipitation, template-directed microemulsions, sol-gel synthesis, sonochemical reactions, hydrothermal reactions, hydrolysis and thermolysis of precursors, flow injection syntheses, and electrospray syntheses. Physical and lithographic techniques have been extensively used for the synthesis of a wide variety of magnetic nanostructures including iron oxide, metal, metal alloys, and core-shell and composites structures. These methods have been used to prepare particles with homogeneous composition and narrow size distribution. Here we will give a short description of only those methods that offer excellent size and shape control.

Classical synthesis by coprecipitation

This method may be the most promising one because of its simplicity and productivity. It is widely used for biomedical applications because of ease of implementation and need for less hazardous materials and procedures.

The coprecipitation technique is probably the simplest and most efficient chemical pathway to obtain magnetic particles. Iron oxides (either Fe_3O_4 or γ-Fe_2O_3) are usually prepared by an aging stoichiometric mixture of ferrous and ferric salts in an aqueous medium. The chemical reaction of Fe_3O_4 formation may be written as eq Fe_2++2Fe_3++8OH-fFe_3O_4+4H_2O [1].

In this reaction, complete precipitation of Fe_3O_4 should be expected at a pH between 8 and 14; however, magnetite (Fe_3O_4) is not very stable and is sensitive to oxidation.

In the coprecipitation process, two stages are involved: 35-40 a short burst of nucleation occurs when the concentration of the species reaches critical supersaturation, and then, there is a slow growth of the nuclei by diffusion of the solutes to the surface of the crystal. To produce monodisperse iron oxide nanoparticles, these two stages should be separated; i.e., nucleation should be avoided during the period of growth. The size and shape of the nanoparticles can be tailored with relative success by adjusting pH, ionic strength, temperature, nature of the salts (perchlorates, chlorides, sulfates, and nitrates), or the concentration ratio. The main advantage of the coprecipitation process is that a large number of nanoparticles can be synthesized. However, the control of particle size distribution is limited, because only kinetic factors are controlling the growth of the crystal.

The difficulty in preparing Fe_3O_4 magnetic nanoparticles by chemical coprecipitation is the tendency of agglomeration of particles because of extremely small particle size leading to great specific surface area and high surface energy consideration [24].

Thermal decomposition

This method of synthesis involves the chemical decomposition of the substance at an elevated temperature. During this method the breaking of the chemical bond takes place. This method of synthesis for magnetic nanostructures mostly use organometallic compounds such as acetylacetonates in organic solvents (benzyl ether, Ethylenediamine, and carbonyls) with surfactants such as oleic acid, oleylamine, polyvinyl pyrrolidone (PVP), cetyltrimethyl ammonium bromide (CTAB) and hexadecylamine [20].

By variation of the proportion of precursors to the starting agents (surfactants and solvents), the size and morphology of the resulting particles can be controlled. Using these methods nanocrystals with very narrow-sized distribution (4-45 nm) could be synthesized along with the excellent control of morphology (spherical particles, cubes) [29].

Microemulsion

Synthesis is a two-phase method for the production of nearly monodisperse MNP. For this purpose, a water-in-oil microemulsion is prepared by dispersion of nanosized water droplets (10–50 nm) in an oil phase, stabilized by surfactant molecules at the water/oil interface [29]. Since these droplets are used as micro-reaction vessels, the distance for diffusion and thus the nucleation and growth of particles is limited, which results in very uniform particles [30]. Due to their narrow size distribution, MNPs from the microemulsion synthesis shows magnetic properties promising for medical applications. The chitosan-coated magnetic nanoparticles (CsMNP's) prepared as a carrier of 5-Flurouracil (CS-5-FuMNP's) through a reverse microemulsion method where spherical with an average size of 100+20 nm, low aggregation, and good magnetic responsibility [31].

Hydrothermal synthesis

Another important chemical synthesis technique that involves the use of liquid-solid–solution (LSS) reaction and gives excellent control over the size and shape of the magnetic nano particles is the hydrothermal synthesis. This method performed in aqueous media at temperatures above 200 ˚C is realized in autoclaves at pressures above 2000 psi. This route exploits the ability of water to hydrolyze and dehydrate metal salts at high temperatures. Due to the low solubility of the obtained metal oxide particles in water at such temperatures, precipitation takes place, and by variation of concentration, temperature, and autoclaving time, particle size and morphology can be controlled [29].

Polyol synthesis

Bases on the oxidative alkaline hydrolysis of Fe^{2+} and Fe^{3+} salts in a polyol mixture (such as polyethylene glycol) (PEG)/diethylene glycol or N-methyldiethanolamine). Size and structure of the resulting MNP can be tuned by either reaction conditions or the employed solvents [24, 29].

Fictionalization of MNP's for drug delivery

Functionalization of MNPs with an amino group, silica, polymer, various surfactants or other organic compounds is usually provided to achieve better physical and chemical properties. Moreover, the core/shell structure of MNPs has the advantages of good dispersion, high stability against oxidation and an appreciable amount of drug can be loaded to the polymer shell [32]. Furthermore, lots of functional groups from polymers on the surface can be used for further functionalization to get various properties [33]. It is favored that MNPs retain sufficient hydrophilicity and, with a coating, do not exceed 100 nm in size to avoid rapid clearance by reticuloendothelial system (RES) [34].

(*I*) Polymer Coating

Nanoparticles are more reactive than bulk materials due to their high surface to volume ratio [35]**.** As a result, these magnetic core nanomaterials need to be protected against corrosion. This coating also prevents the leaching of potentially toxic components into the body during in *vivo* applications. The coating also solves the stability of nanoparticles against oxidation. Coating magnetic nanoparticles with natural polymers such as carbohydrates and proteins are common. Many natural polymers are biocompatible and therefore suitable for coating nanoparticles for biomedical applications. Carbohydrates are particularly popular as coating materials for magnetic nanoparticles because of their biocompatibility. For example, dextran-coated magnetic nanoparticles have been used in many biomedical applications, and they are commercially available. To diversify the surface properties, dextran has also been used as a blend with other polymers (including chitosan, poly-L-lactic acid, and silica) to form blended coatings for magnetic nanoparticles (*Grüttner* et al. 2001) [35]. But there are some disadvantages of these natural polymers such as water solubility and lack mechanical strength. Cross-linking is needed to prevent them from breaking down in water. Also, these coatings tend to be porous and sometimes show non-selective adsorption Since many natural polymers lack mechanical strength while others, synthetic polymers may provide a solution to this problem. Synthetic polymers such as poly(ethylene glycol) (PEG) [14, 36], polyvinyl alcohol (PVA) and poly-L-lactic acid (PLA)) are some examples or coatings for magnetic nanoparticles. The choice of synthetic polymer coating depends on the required surface properties for particular applications

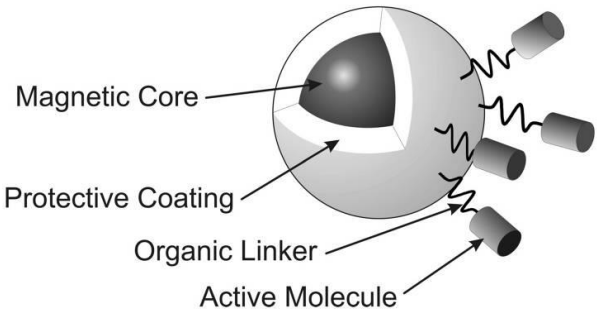
[14, 36]. Although synthetic polymers have better mechanical strength they have some limitations coatings formed from synthetic polymers are still porous on molecular scales, which means that corrosion of the magnetic core is still possible. Also, some of these polymers are difficult to further functionalize.

(*I*) Protein coating: Natural proteins such as albumin, lipids are also used to functionalized magnetic nanoparticles for biomedical and other industrial applications.

(*II*) Silane coating: Magnetite nanoparticles can be modified also with oleic acid, silane, or organosilane. Silanes are commercially available with many amine groups, so forming an ideal system to tune the surface functionality of the Fe_3O_4 nanoparticles for protein conjugation [37] .

(*III*) SiO_2 coating: Silica is an amorphous material with high mechanical strength. It carries negative charges at pH <3 because of the silanol groups (–Si–OH)on the surface. Superparamagnetic nanoparticles of Fe_3O_4 coated with SiO_2 layer were synthesized via conventional microemulsion and sol–gel technology. To control overall particle size and shape, silica coating is carried out as the hydrolysis of tetraethyl orthosilicate (TEOS, also known as tetraethoxysilane) at a certain pH (8–10) or the neutralization of silic acid [14].

4. Other coating material: In some studies, other organic compounds and commercial products were applied for MNPs functionalization. Without surface modification, biomolecules may not bind to the magnetic nanoparticles. Even if they do, it can be very weak, resulting in the instant release of these molecules during the delivery with little control. As a result, surface modification is necessary to create strong interactions to enhance the binding process of biomolecules and also to control the release mechanism. Modification through organic linkers is commonly used, as organic linkers provide a wide range of surface properties to suit various biomolecules in many conditions. Common organic linkers are an amine, carboxylic acid aldehyde, and thiol.



Applications of nanoparticulate delivery systems

Magnetic solids either of micro- or nano-size found many applications in the field of chemistry, biology, and medicine. In the field of therapy, magnetic particles possess several applications-hyperthermia, drug and DNA delivery exploiting magnetic field guiding and MRI [38].

One of the most primary requirements before designing therapeutic nanoparticles is the rapid clearance during systemic delivery. After entering the blood stream nanoparticles surface may experience nonspecifi c protein adsorption called as opsonization. This process makes them more visible to phagocytic cells.

These opsonized nanoparticles could be easily cleared from the bloodstream through phagocytosis by the mononuclear phagocyte system (MPS) in the liver and by spleen filtration. Factors that govern the clearance and biodistribution of nanoparticles are as follows

(*I*) Nanoparticle size plays an important role in controlling the circulation and biodistribution of nanoparticles during its journey through physiological parameters such as hepatic filtration, tissue extravasation/diffusion, and kidney excretion. Nanoparticles size range <10 nm can be rapidly cleared by the kidneys or through extravasation.

(*II*) The second factor that could affect nanoparticles uptake by the MPS cells is their surface charge. Positively charged nanoparticles generate a higher immune response compared to neutral or negatively charged nanoparticle formulations. Similarly, neutrally charged particles have demonstrated much lower opsonization rates than charged particles.

(*III*) Third factor, PEGylation, referred to the surface modifi cation of nanoparticles with PEG, which has favorable intrinsic physicochemical properties which were found to reduce nanoparticle accumulation in of target organs. Could improve the cell- or tissue-specifi c delivery of nanoparticles.

(*IV*) Ligand functionalization is the conjugation of targeting ligands to the surface of PEGylated nanoparticles which has also been proven to affect their biodistribution [39] .

Targeted drug delivery

Magnetic nanoparticles are used widely for drug targeting applications owing to its suitability. They can effectively and safely transfer the drug (with maximum loading) to a specific site. The rationale of using nanoparticles for tumor targeting is based on one of the most efficiency of nanoparticles is delivering the drug in the area of the tumor targets via the enhanced permeability and retention effect. This can also be achieved by active targeting by ligands on the surface of nanoparticles. Transportation of drugs to a specific site can eliminate side effects and also reduce the dosage required. The surfaces of these particles are generally modified with organic polymers and inorganic metals or oxides to make them biocompatible and suitable for further functionalization by the attachment of various bioactive molecules [2]. The process of drug localization using magnetic delivery systems is based on the competition between the forces exerted on the particles by the blood compartment and the magnetic forces generated from the magnet. Nanoparticles limits the drug distribution to the target organ hence reduces the drug exposure against healthy tissues.

The following Figure 3 shows the mechanism of targeted delivery of drug by magnetic nano particles to the tumor cell by receptor-mediated endocytosis. In this process, the drug-carrying magnetic nano particles are carried by the blood stream to the specific tumor cells where they enter by the formation of the endosome. Then endosome swells as a result of an increase in osmotic pressure and finally ruptures to release the drug in the tumor cells.

Nanomagnetism in therapeutic hyperthermia

Hyperthermia is one of the promising biomedical applications of magnetic nanoparticles for cancer treatment. In modern medicine, the local increase of tumor tissue temperature (hyperthermia) is widely accepted as an effective adjunctive cancer therapy. Hyperthermia is based on the fact that cells heated to a temperature >42 °C show sign of apoptosis and cells heated above 50 ◦C necrosis [38].

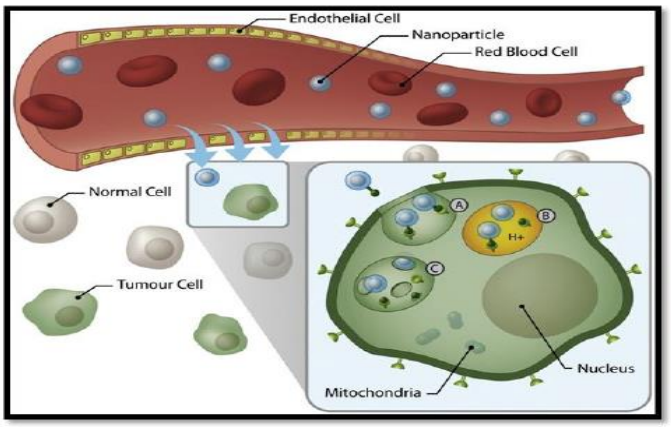


Figure 3. Illustration of tissue-specific delivery of MNPs through active targeting facilitated by "leaky" vasculature. A) Internalization of nanoparticles by A) receptor-mediated endocytosis and formation of an endosome. B) Endosomal acidification by proton pumps results in elevated osmotic pressure, swelling, and C) rupture of the endosome allowing for the release of the nanoparticle and conjugated therapeutic agents [40]

The cancer cells are considered more susceptible to heat than normal cells due to their higher rate of metabolism [39]. On a tissue level, tumors possess a disorganized vascular system and their ability to dissipate heat stress is decreased. Elevated temperatures also increase cell sensitivity to other treatments like radiation therapy or chemotherapy. In comparison with other methods, magnetic particle hyperthermia enables local heating of the target tissue by embedding magnetic particles to the target tissue and by using an external alternating magnetic field to heat it. Magnetic particles are directly injected within the tumor body or in the artery supplying the tumor. Further, magnetic particles can be visualized using MRI so a combination of therapy and diagnosis is possible. Magnetic iron oxide (γ-Fe_2O_3 and Fe_3O_4) particles are the most used materials for this reason due to higher biocompatibility than other materials (Ni and Co) [38]. A convenient example is magnetic particles where drug delivery combined with hyperthermia or MRI is common (Figure 4).

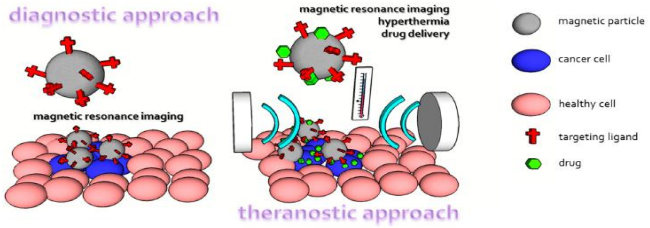


Figure 4. Comparison of magnetic particles utilization as a diagnostic and theranostic tool

Magnetic nanoparticles for gene delivery

Magnetic nanoparticle technology also offers the potential to achieve selective and efficient delivery of therapeutic genes by using external magnetic fields. As compared to traditional gene delivery strategies, magnetic drug delivery system has been shown to significantly increase

gene delivery to human xenograft tumors models. This implies that they, therefore, have the potential to turn the challenge of gene therapy in vivo into a new frontier for cancer treatment. Gene delivery via magnetic particles is predominantly used to reduce the time needed for transfection or minimize the dose of vector. Work is also being conducted on improving the overall transfection efficiency of this technique by using dynamic magnetic fields produced from oscillating arrays of permanent rare earth magnets [15]. It has been found that gene therapy with β galactosidase marker gene nanotubes showed greater expression compared to transfer of naked DNA. This assures the advantage of nonimmunogenicity in contrast to viral vectors used for gene transfer [41].

Carrier for polypeptide and antibodies drugs

The mechanism of polypeptide and antibody drug applications is to stimulate or inhibit the expression of cells in order to achieve perfect therapeutic efficacy. The MIONPs can be acted as the biotherapeutic carrier for peptides, and they also have the positive impact on therapy as therapeutic agents for themselves. More importantly, the internalization of many biological pathways is getting more efficient because of the existence of MIONPs [42].

The main problem here is that oral delivery of peptides and proteins is hampered by their degradation in gastrointestinal acid, low absorption, first-pass metabolism by the liver, and a significant initial increase in drug concentration.

In summary, for magnetic targeting, a drug or therapeutic radionuclide is bound to a magnetic compound, introduced in the body, and then concentrated in the target area by means of a magnetic field (using an internally implanted permanent magnet or an externally applied field). Depending on the application, the particles then release the drug or give rise to a local effect (irradiation from radioactive microspheres or hyperthermia with magnetic NPs) [33]. Drug release can proceed by simple diffusion or take place through mechanisms requiring enzymatic activity or changes in physiological conditions such as pH, osmolality, or temperature; drug release can also be magnetically triggered from the drug-conjugated MNP's [43].

Other applications

Biomedical applications include cellular labeling bioseparation, detoxification of biological fluids, tissue repair, magnetic resonance imaging any many more.

Magnetic resonance imaging. At the boundary between nanomaterials and medical diagnostics, superparamagnetic iron oxide NPs are proving to be a class of novel probes useful for in vitro and in vivo cellular and molecular imaging. Superparamagnetic contrast agents have an advantage of producing an enhanced proton relaxation in magnetic resonance imaging [MRI] in comparison with paramagnetic ones. Consequently, fewer amounts of a SPIO agent are needed to dose the human body than a paramagnetic one. To apply the magnetic fluids to a MRI contrast agent, a SPIO should be dispersed into a biocompatible and biodegradable carrier.

Bioseparation. In a biomedical study, separation of specific biological entities (such as DNAs, proteins, and cells) from their native environment is often required for analysis. Superparamagnetic colloids are ideal for this application because of their on-off nature of magnetization with and without an external magnetic field, enabling the transportation of biomaterials with a magnetic field.

Limitations of magnetic drug delivery

Since the magnetic gradient decreases with the distance to the target, the main limitation of magnetic drug delivery relates to the strength of the external field that can be applied to obtain the necessary magnetic gradient to control the residence time of NPs in the desired area or which triggers the drug desorption.

Another limitation relates to the small size of NPs, a requisite for super-paramagnetism, which is in turn needed to avoid magnetic agglomeration once the magnetic field is removed.

Conclusion

Magnetic nanoparticles possess powerful potential in medicine, covering both, diagnostics and nano-based drug delivery as attracted a great deal of attention from scientists in recent years. The preparative technique of MNPs is a mature technology at present. These novel drug delivery systems have increased the ability to deliver drugs for which conventional therapy has shown limited efficacy. This review discussed some physical and magnetic properties of magnetic nanoparticles that are crucial for biological applications. The significance of size for controlling the various properties is obvious because, in most of the cases, the properties of the magnetic nano particles are dependent on their dimension and morphology. Advances in preparation of MNPs with control of their properties have introduced new particles for diagnostic applications such as utilization of MNPs in hyperthermia, magnetic drug delivery, gene delivery, and magnetic resonance imaging. To take advantage of these applications, one of the most primary requirements before designing therapeutic nanoparticles is the rapid clearance during systemic delivery. In order to synthesize new MNPs and comprehensively study their behavior in the body, developing and using more advanced technologies is of prime significance.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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