



Historical perspective

Magnetic nanocarriers: Evolution of spinel ferrites for medical applications

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ABSTRACT

A valuable site-directed application in the field of nanomedicine is targeted drug delivery using magnetic metal oxide nanoparticles by applying an external magnetic field at the target tissue. The magnetic property of these structures allows controlling the orientation and location of particles by changing the direction of the applied external magnetic field. Pharmaceutical design and research in the field of nanotechnology offer novel solutions for diagnosis and therapies. This review summarizes magnetic nanoparticles and magnetic spinel ferrite's properties, remarkable approaches in magnetic liposomes, magnetic polymeric nanoparticles, MRI, hyperthermia and especially magnetic drug delivery systems, which have recently developed in the field of magnetic nanoparticles and their medicinal applications. Here, we discuss spinel ferrite (SF) as magnetic materials that are a significant class of composite metal oxides. They contain ferric ions and have the general structural formula $M^{2+}Fe_3^{3+}O_4$ (where $M = Co, Ni, Zn, etc.$). This structure indicates unique multifunctional properties, such as excellent magnetic characteristics, high specific surface area, surface active sites, high chemical stability, tuneable shape and size, and options for functionalization. The review assesses the current efforts on synthesis, properties and medical application of magnetic spinel ferrites nanoparticles based on cobalt, nickel and zinc. Based on this review, it can be concluded that MNPs and SFNPs have unlimited ability in biomedical applications. However, the practical application of SFNPs on a huge scale still needs to be considered and evaluated.

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Abbreviations: NPs, Nanoparticles; SF, Spinel ferrite; MNPs, Magnetic nanoparticles; AMF, Alternating magnetic field; M_s , Saturation magnetization; MRI, Magnetic resonance imaging; SPM, Superparamagnetic; MMONPs, Magnetic metal oxide nanoparticles; SFNPs, Spinel ferrite nanoparticles; CFO NPs, $CoFe_2O_4$ NPs; NFO NPs, $NiFe_2O_4$ NPs; ZFO NPs, $ZnFe_2O_4$ NPs; MRI, Magnetic resonance imaging; SMF, STATIC magnetic field; PMFs, Pulsed magnetic fields; AC, Alternating current; EGFR, Epidermal growth factor receptor; DI, Deionized; RFA, Radio frequency ablation; MFH, Magnetic fluid hyperthermia; EPR, Enhanced permeability and retention effect; RF, Radiofrequency; MPS, Mononuclear phagocyte system; DDSs, Drug delivery systems; GUVs, Giant unilamellar vesicles; SUV, Small unilamellar vesicles.

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Purpose of this review

In the past decade, there have been a number of excellent reviews on magnetic nanoparticles and magnetic spinel ferrite nanostructures that most of them have focused on synthesis and properties of these materials. The utilization of these nanostructures and their composites for biomedical applications has been notably increased in the past few years. Our aim with this review is to recap relevant issues such as: (i) features of spinel ferrites and their composites, (ii) application of MNPs and SFs, (iii) biomedical applications of MNPs and SFs (iv), classification of drug targeting (v) magnetic theranostic agents (vi), the toxicity of MNPs. In the conclusion, we outline the advantages of magnetic MNPs and SFs and discuss further developments in this interesting research area.

1. Introduction

Nanotechnology is considered as the leading technology of the 21st century. The science and engineering of nanometer-sized materials is currently employed for the development of numerous scientific, industrial, ecological, and technological fields. Biology, medicine, chemistry, pharmacy, agriculture, food industry, and materials science are the main fields which have benefited from the great technological progress developed in nanoscience. In recent years, remarkable growth has been observed in the biomedical application of nanostructured biomaterials [1]. Magnetic nanoparticles can be applied in biomedicine because of their small size, stability, easy functionalization and optical properties. They can be utilized in various applications such as drug delivery, diagnosis, magnetic resonance imaging and radiotherapy [2] as well as in noninvasive tumor imaging and early malignant growth detection, due to their optical and magnetic properties [3]. There are some limitations including high toxicity, poor aqueous solubility and unfavorable pharmacokinetics. Magnetic nanocarriers have the potential of generating a significant impact on drugs in cancer therapy via the following approaches: 1. Pharmacokinetic improvement of drugs; 2. Increasing the aqueous solubility; 3. Advancement of pharmacodynamics profiles of the drugs; 4. Increasing drug stability by reduced degradation in the circulation; 5. Enhancement of accumulation in tumor tissues through passive and active magnetic targeting; 6. Reduction of the drug concentration in nontargeted normal tissues; 7. Reduced toxic side effects [4]. Moreover, linking an organic/inorganic shell to the surface of MNPs allows a special bonding to a specific location. Protecting the MNPs, increases not only their biocompatibility, but also their nontoxicity properties [5]. The perfect drug-targeting delivery systems are systems which retain their loaded drugs in the circulating systems, however, release the loaded contents only after exposure to some internal triggers like enzymes, pH, or external triggers like magnetic field, ultrasound, temperature, and light at the targeted tissues. By applying the stimulus, nanocarriers display various responses like variations in volume, shape, permeation rates, structure disruption, collapsing/swelling, hydrophobic/hydrophilic surfaces, hydration state or conformational changes. Many cancer therapeutic deliveries with conventional vehicles indicate several limitations for a successful treatment. Chemical mechanisms of external stimuli factors developed to release the drug when its effect is necessary, represent a significant improvement in treatment [6].

Spinel ferrites (SFs), with a general formula of MFe_2O_4 , where M represents a metal cation, are chemically and thermally stable magnetic materials that have been used for numerous applications [7]. Since their discovery, there has been an exponential increase of interest in ferrites, which is still growing. Their magnetic properties make them beneficial in magnetic resonance imaging (MRI), electronic devices, information storage, and drug delivery [8]. There has been a number of excellent reviews on SFs published in the past decade, but most of them are focused on investigations of ferrites' synthesis and their properties [9]. In the past few years, the interest shifted toward the application of SFs and their derivative composites (SFCs). In this review, the interest is focused upon spinel ferrite magnetic nanostructures containing nickel, zinc, and cobalt as divalent cations. These systems indicate broad applications, especially in biomedicine.

2. Spinel ferrites

Ferrites, transition metal oxides with spinel structures, are one of the most important MNPs. Ferrites are classified based on their crystal structures and magnetic properties, as spinel (MFe_2O_4 , where M = Mn, Fe, Co, Ni, Co, Zn, etc.), garnet ($M_3Fe_5O_{12}$, where M = rare earth cations), hexaferrite ($SrFe_{12}O_{19}$ and $BaFe_{12}O_{19}$), and orthoferrite ($MFeO_3$, M = rare earth cations) [10]. Among these groups, special attention has been given to spinel ferrite nanoparticles (SFNPs). Spinel ferrites are homogeneous materials with a general chemical formula of AB_2O_4 , where A and B are metallic cations positioned at two different crystallographic sites, tetrahedral (A sites) and octahedral (B sites), composed of Fe (III) as one of the main elements in their structure. In the formula MFe_2O_4 , depending on the position of M(II) and Fe(III) site preference, three possible spinel ferrite structures are known called normal, inverse, and mixed structure. In a normal spinel structure of ferrite, M (II) is located at tetrahedral sites while Fe(III) lies at octahedral sites. In an inverse spinel structure of ferrite, Fe (III) is equally distributed at both sites while M (II) occupies only the octahedral sites. In a mixed spinel structure of ferrite, both ions randomly occupy the tetrahedral and octahedral sites. $ZnFe_2O_4$ is an example of normal spinel ferrite. Also, Fe_3O_4 and $NiFe_2O_4$ are common examples for inverse spinel ferrite while $MnFe_2O_4$ is a good example for mixed spinel ferrite such as $Mn_{0.8}Fe_{0.2}(Mn_{0.2}Fe_{1.8})O_4$. The structure of spinel ferrite is presented in Fig. 1. Nanostructured ferrite exhibits unusual physical and chemical properties, which are significantly different from those of conventional bulk materials, due to its extremely small grain size or large specific surface area [11]. Fig. 2 demonstrates some advantages of spinel ferrites and Fig. 3 exhibits the SF MNPs applications. According to them, it is clear that a great variety is possible in the chemical composition of spinel ferrites, as found by the thousands of papers published during the last fifty years dealing with these materials. The diversity in composition also results in a wide range of physical properties allowing for tuning the properties for specific applications, making spinel ferrites of particular interest.

2.1. $CoFe_2O_4$ NPs (CFO NPs)

The preparation and characterization of the nanocrystalline ferrite powder have gained a great deal of attention recently. Inverse spinel

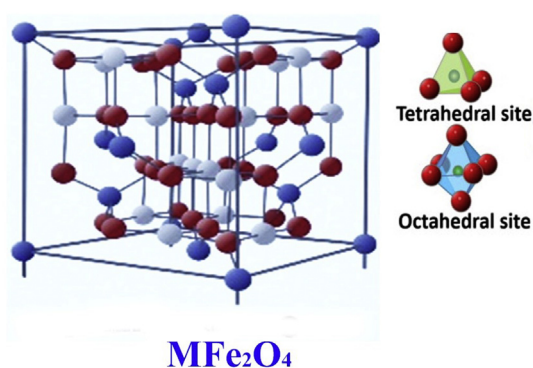


Fig. 1. The octahedral and tetrahedral spinel ferrite structure.

ferrite, CoFe_2O_4 , is well known as a hard magnetic material with high cubic magnetocrystalline anisotropy, high coercivity as well as moderate saturation magnetization. These characteristics make it a suitable material for magnetic storage. Spinel ferrites are an important class of composite metal oxides. Among them, cobalt ferrite (CoFe_2O_4) magnetic material has been extensively studied because of its potential application [12]. Fig. 4 displays the application of magnetic $\text{CoFe}_2\text{O}_4/\text{SiO}_2$ nanocomposite fabricated by the sol-gel method for electrocatalytic oxidation and determination of L-cysteine (our previous work). Among the various mixed ferrite materials, cobalt ferrite is of particular interest due to its remarkable physical properties such as high coercivity, high magnetocrystalline anisotropy constant, moderate saturation magnetization, along with good mechanical hardness and chemical stability [13]. Fig. 5A indicates the magnetic CFO in the absence and presence of magnetic fields and Fig. 5B depicts the magnetic property of alginate beads prepared by CFO MNPs. In another work, we have synthesized cobalt ferrite silica magnetic nanocomposite via green sol-gel autocombustion synthesis and investigated their ability for removal of malachite green (a toxic dye) from water [14]. Cobalt ferrite nanoparticles dispersed in silica matrix synthesized by sol-gel autocombustion method indicated a novel anticorrosive application [15]. CFO NPs possess an inverse spinel structure with Co^{2+} ions in the octahedral site and Fe^{3+} ions equally distributed among tetrahedral and octahedral sites. The magnetic properties of these ferrites are mainly due to a predominant superexchange interaction between cations in the A-site and B-site via oxygen ions. Variations in magnetic properties of CFO NPs can arise when there is a replacement of magnetic ions by non-magnetic ions. Many studies suggest that the properties of CFO NPs are heavily affected by the synthesis method. Recently, a strategy has been developed and used to obtain nano/micro-materials with different morphologies. For example, Meng et al. [16] synthesized CoFe_2O_4 hollow spheres under hydrothermal conditions with glucose as a template. For the biomedical applications of CFO NPs, in most cases, the nanoparticles must

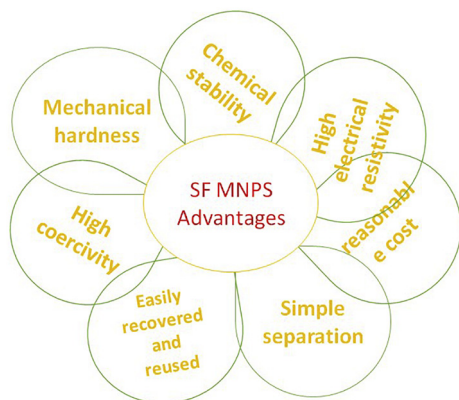


Fig. 2. Some advantages of spinel ferrites magnetic nanostructures.

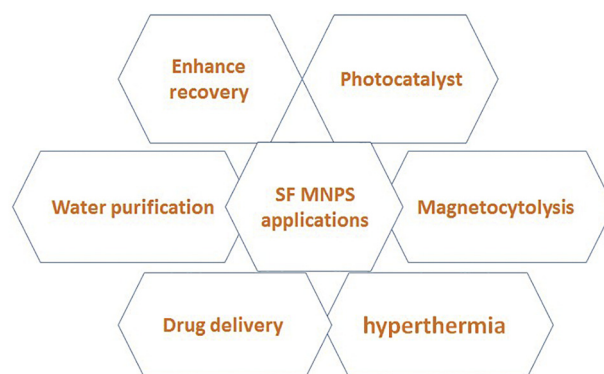


Fig. 3. Some applications of the SF MNPs.

be released into the bloodstream. Therefore, the biosafety of the nanoparticles is an important issue in medical applications. Surface passivation of magnetic nanoparticles is used to enhance the biocompatibility of magnetic nanoparticles. Hydroxyapatite (HAP , $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) has been used for decades as a biomaterial in orthopedic, drug delivery, and dental applications thanks to its biocompatibility and similarity of the inorganic components of bone [17]. Foroughi et al. [18] reported synthesis of hydroxyapatite-encapsulated CFO nanoparticles via one-step reverse microemulsion method. Wu et al. [19] reported solvothermal synthesis of cobalt ferrite nanoparticles loaded on multiwalled carbon nanotubes for magnetic resonance imaging and drug delivery. Bin Cai et al. [20] indicated bio-inspired formation of 3D hierarchical CoFe_2O_4 porous microspheres for magnetic controlled drug release. In addition, CFO NPs have also been used in other bioapplications [21]. Oh et al. [22] recently prepared magnetic CoFe_2O_4 nanoparticles functionalized by DMSA ligand groups for magnetic hyperthermia applications and pH-sensitive drug delivery.

2.2. NiFe_2O_4 NPs (NFO NPs)

Among spinel ferrites, nickel ferrite is of great interest (NiFe_2O_4) because of its extensive and varied applications. NFO NPs are commonly used in a number of electronic devices because of their high permeability at high frequency, remarkable high electrical resistivity, mechanical hardness, chemical stability, and reasonable cost [23]. It is a well-known inverse spinel with Ni^{2+} ions on B (octahedral) sites and Fe^{3+} ions distributed equally among A (tetrahedral) and B sites. Their properties are size- and shape-dependent and known to be sensitive to the processing techniques [24]. Various methods have been developed to synthesize nanocrystalline NFO, including a sonochemical process [25]. However, there are only a few reports on the morphology-controlled synthesis of nickel ferrite nanomaterial. Chu et al. [26] prepared NFO nanocubes and nanorods by a hydrothermal method. Zhang et al. [27] synthesized NFO nanorods via a polyethylene glycol-assisted route.

2.3. ZnFe_2O_4 NPs (ZFO NPs)

Zinc ferrite (ZnFe_2O_4) is of particular interest among ferrite spinels because of its application in magnetic materials [28]. Thus, it requires an acceptable control over the size, crystallinity, stoichiometry, and phase purity of the nanopowders. There have been various reports demonstrating the feasibility of wet chemical preparation of the ZnFe_2O_4 nanoparticles via different approaches and a variety of morphologies [29] fabricated by various researchers.

The nanorods exhibited good photocatalytic decomposition activity for methylene blue (MB). Nanoparticles of ZnFe_2O_4 and $\text{ZnO}/\text{ZnFe}_2\text{O}_4$ composites exhibiting bifunctional properties have received remarkable attention for MRI and catalytic applications [30]. There are also sparse reports on the synthesis of ZnFe_2O_4 nanoparticles exhibiting

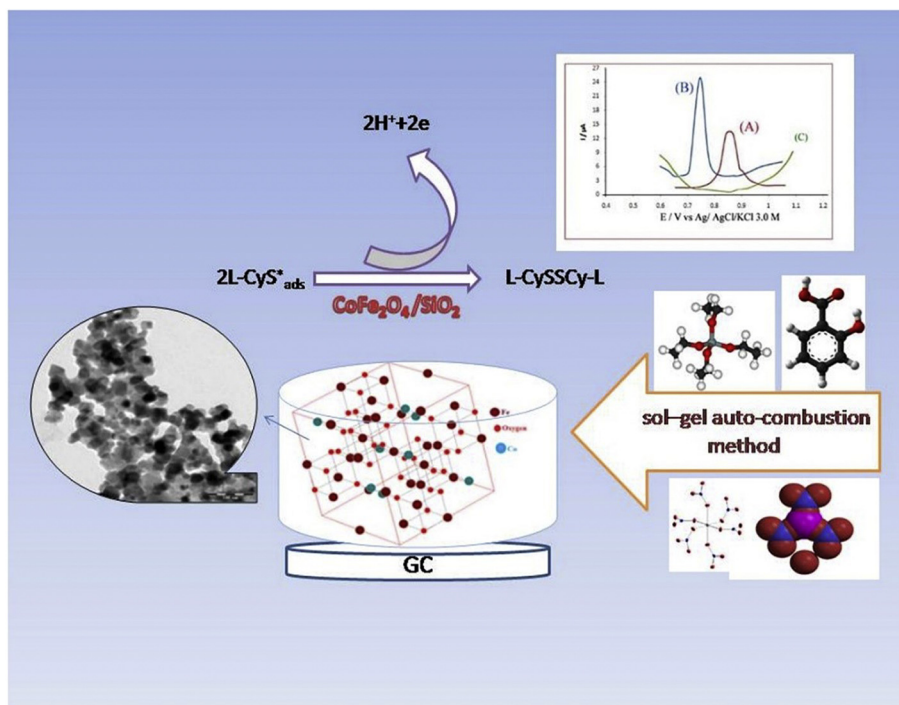


Fig. 4. The application of magnetic $\text{CoFe}_2\text{O}_4/\text{SiO}_2$ nanocomposite fabricated by the sol-gel method for electrocatalytic oxidation and determination of L-cysteine [12].

ferromagnetism or photoluminescence [31]. Zhang et al. reported microstructure, mechanical, and corrosion properties and biocompatibility of Mg–Zn–Mn alloys for biomedical application [32]. Dandan et al. [33]

investigated the synthesis and application of ZnFe_2O_4 hollow microsphere core/mesoporous silica shell composite particles in drug release. Ansari et al. [34] reported that MgZnCu ferrite nanocarrier is expected to be a promising drug releasing agent and could be used in biomedical applications. Maiti et al. [35] reported a novel approach to synthesize multifunctional ZnFe_2O_4 nanoparticles with excellent photoluminescence and ferromagnetism properties as hydrophobic and hydrophilic anticancer drug molecules loading. In a recent work, YooCheon et al. [36] grafted geldanamycin, a heat shock protein (HSP) inhibitor, to $\text{Zn}_{0.4}\text{Fe}_{2.6}\text{O}_4$ zinc ferrite MNPs (15 nm) modified with amine groups using a thermo-labile diazo linker. The authors found an impressively high magneto-thermal control of geldanamycin release.

2.4. Magnetic properties of SF MNPs

The unusual structural and magnetic properties of the magnetic nanoparticles have improved interest in these materials owing to wide applications such as high-density magnetic recording media, magnetic resonance imaging (MRI), hyperthermia, and magnetically guided drug delivery [37]. In our previous work, caffeine was used as a novel green precursor for synthesis of magnetic CoFe_2O_4 nanoparticles. Finally, we synthesized pH-sensitive magnetic alginate beads for drug delivery [38]. Fig. 6 reveals the schema of bioapplication of CFO MNPs. When the particle size of the magnetic materials shrinks to nanosized ranges, new uncommon properties such as superparamagnetism, spin-glass-like behavior, and spin canting effect emerge, depending on elevation of surface-to-volume ratio. Meanwhile, through synthesis of nanoparticles, aggregation frequently occurs, which largely limits their potential applications. Encapsulating magnetic nanoparticles in nonmagnetic material is an important approach in order to promote their usage in many applications [39]. A single nanoparticle has several thousands of crystal units within the formula. Each crystal has a single magnetic domain with a magnetic dipole greater than the net dipole of all unpaired electrons of atoms of the crystal. Thermal motion is sufficient to freely rotate the domain resulting in zero net magnetic dipole. When a magnetic field is applied to nanoparticles, all the domains are aligned in the direction of the external magnetic field, creating a large magnetic momentum.

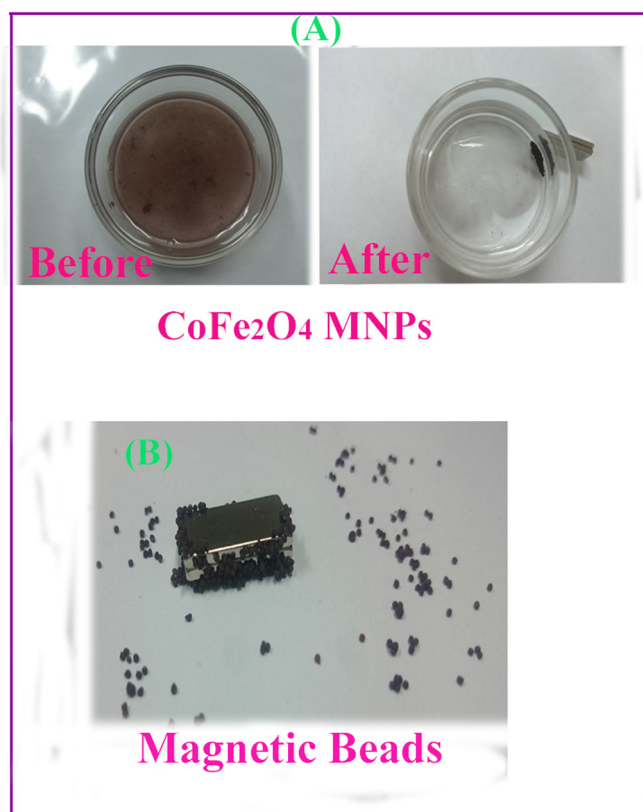


Fig. 5. (A) Magnetic separation of CoFe_2O_4 particles from aqueous solutions, (B) The magnetic property of alginate beads prepared by CFO MNPs.

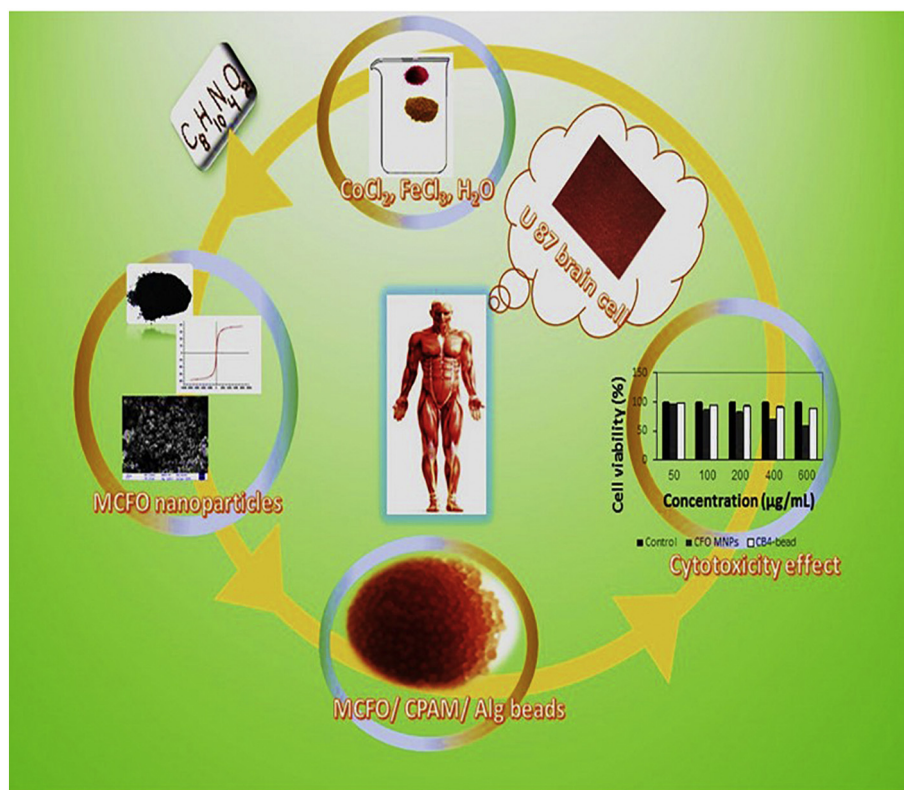


Fig. 6. The schematic of bioapplication of CFO MNPs [38].

Nevertheless, this magnetic momentum is completely lost when the external magnetic field removed. Therefore, superparamagnetic nanoparticles do not have magnetic dipoles and will not aggregate on their own or in an induced magnetic field. In this model, it is assumed that the magnetic interaction between the tetrahedral and octahedral metal ions (AB interaction) is strongly negative and the interactions between the ions of the same sublattice (AA and BB interactions) are weak. These interactions favor an antiparallel arrangement of the A- and B-lattice, the so-called collinear N6el configuration. Consequently, the resultant magnetization is the difference between the A- and B-lattice magnetizations. Most of the technically applied spinel ferrites are based on a limited number of chemical systems. Depending on the specific properties desired, like high permeability, high induction, temperature and time stability, low losses and operating frequency, a choice has to be made for a certain composition. Nevertheless, the final physical properties of ferrite material determined are by these parameters: (1) basic composition; (2) the presence of small concentrations of impurities; and (3) the characteristics of the microstructure, i.e., grain size, porosity, grain boundaries, and crystallographic texture. It is obvious that before developing a synthesis technology of a specific ferrite material, an appropriate choice of the composition has to be made based on the intrinsic magnetic properties: saturation magnetic moment, magnetic anisotropy, and magnetostriction. From the high saturation magnetization at room temperature, it is evident that ferrites based on Co, Li, Mg, Mn, and Ni ferrite indicated the most applications. The saturation magnetization can be enhanced by reducing the A-site moment through substitution with non magnetic Zn-ions. Nevertheless, cobalt ferrite has the disadvantage of high magnetic anisotropy, making ferrites with a high co-concentration not suitable for high permeability applications. Most technical ferrites can be found in Mn—Zn, NiZn, Mg—Mn, and Li—Zn—Ti ferrite systems [40].

3. Magnetic metal oxide nanoparticles

Mixed and metallic oxide nanoparticles indicate unique properties such as great magnetic properties, high surface area, high adsorption

capacity, and high chemical stability, thereby attracting great attention in various fields. Among these nanostructures, some of them such as spinel ferrites, Fe_3O_4 , TiO_2 , Al_2O_3 , ZrO_2 , MnO , and CeO_2 , both in bare form or modified with different functional coatings, are of particular interest [41]. Hedayatnasab et al. [42] investigated magnetic nanoparticles extensively and magnetic metal oxide nanoparticles (MMONPs) in particular. These are oxides that consist of two different structural oxidation states: (1) mixed-valence cationic states and (2) anionic deficiencies (vacancies) [43]. These MMONPs belong to a wide family of smart and functional materials possessing semi-conductivity, superconductivity, and magnetism [44]. MMONPs are organized in different metal groups with dissimilar structures and properties. These NPs contain metal oxides (e.g., iron oxides, nickel oxide, and even lanthanum strontium manganite) and ferrites. Among oxides, iron oxides have been recognized as a prominent candidate for hyperthermia therapy thanks to possessing varied features such as localized elimination of cancerous cells via magnetically induced heating [45]. They are a combination of Fe and oxygen, generally comprising 16 pure phases, including oxides (Fe_3O_4 , $\gamma\text{-Fe}_2\text{O}_3$, hematite, and iron oxide beta phase), oxyhydroxides (feroxyhyte, akaganeite, goethite and lepidocrocite), and hydroxides (iron (II) hydroxide and iron (III) hydroxide) [46]. Ferrites are covering iron oxides and at least one metal in their chemical mixture has valuable magnetic and dielectric properties. Ferrites are expressed by $\text{M}(\text{Fe}_x\text{O}_y)$, where M represents any metal cation such as (manganese, magnesium, copper, aluminum, barium, Ni and Co, or even Fe itself), and x and y values are variables [47]. Given the diversity of ferrites, they are extensively employed in various applications such as sensors, MRI, biomedical imaging, catalysts, as well as electromagnetic and optical devices [48]. The realization of these purposes depends on the monodispersity of NPs as the majority of MMONPs' applications require that the size and shape of NPs be uniformly oriented. As such, several methods have been applied to synthesize MMONPs; these methods include co-precipitation, hydrothermal, sol-gel, microemulsion, and mechanical ball milling processes [49]. However, the synthesized MMONPs have proved to be partly unsuitable and suffered some

difficulties such as aggregation, hydrolysis, condensation, and non-uniformity in shape and size for the above-mentioned applications [50].

4. Magnetic nanoparticles

Magnetic nanoparticles (MNPs) are popular nanostructures in targeted drug delivery and targeted therapy. The popularity of MNPs is mainly based on their smart structure which can be controlled not only magnetically but also by temperature [51]. Magnetic nanoparticles (MNPs) are inorganic and zero-dimensional materials with a metal-based configuration. These NPs have found increasing importance as they can be easily manipulated using an alternating magnetic field (AMF) and, subsequently, be employed in several applications. Nanometer-sized MNPs have revealed intrinsic and unique properties such as high saturation magnetization (M_s), less toxicity and biocompatibility. Accordingly, MNPs have been applied in various fields such as industrial, environmental, analytical, and biomedical applications. In particular, MNPs have gained attention for biomedical applications because of their easy controllability, biological compatibility, physico-chemical properties, and superior magnetic properties. Biomedical applications depend on the MNPs properties which can be affected by synthesis methods, particle size distribution, interaction between particles, as well as particle size and shape of NPs. Therefore, size and shape represent the key features governing the physical stability of magnetic nanoparticles (MNPs). As demonstrated in various papers, size can strongly influence the magnetic property and subsequent response to magnetic fields. For example, when the size shrinks, the saturation magnetization of iron oxide particles declines, while the particles can exhibit supermagnetism, which confers greater capabilities of magnetization compared to the abilities of paramagnetic materials. Therefore, a suitable synthesis method should be selected to attain a specific performance (based on certain biomedical applications). MNPs' biomedical applications are generally classified into in-vitro (outside the body) and in-vivo (inside the body). In-vitro applications are mainly used in diagnostic processes such as separation/selection, magnetic relaxometry, and magnetic resonance imaging (MRI). On the other hand, in-vivo applications include diagnostic processes such as nuclear magnetic resonance imaging as well as therapeutic applications (e.g., drug delivery and magnetic hyperthermia) [52]. MNPs allow magnetic targeting and hyperthermia applications thanks to their ability to generate heat under a magnetic field. MNPs are utilized in treating hypothermia, killing cancerous cells of the bones by heating the infected parts through applying alternating magnetic field [53]. Detection of metastatic infestation in lymph nodes was investigated using MNPs as a magnetic resonance imaging contrast agent, offering information about tumor angiogenesis, identifying dangerous atherosclerosis plaques, following the course of stem cell therapy, and other biomedical research. For instance, Fig. 7 indicates an effective strategy for magnetic stem cell delivery for spinal cord injury therapy [54]. Consequently, MNPs provide therapeutic heating.

Another benefit of use of MNPs is destabilization of weak interactions between the drug and polymer matrix in order to trigger drug release. Generally, materials present a multidomain phase that is transformed into a single-domain phase once they reach the nanometer scale. When the magnetostatic energy reaches and equalizes the threshold energy of the domain wall of nanomaterials, the single-domain phase can monopolize under certain dimensions, bringing unique properties to the nanomaterial. At this single-domain monopolized domain, MNPs possess a huge magnetic property and exhibit their supermagnetic characteristics at temperatures above the blocking temperature, while the thermal energy exceeds the anisotropy of magnetic materials [55].

Superparamagnetic (SPM) properties of MNPs have attracted a great deal of attention in recent years. Magnetic nanoparticles are a group of engineered particles (typically smaller than 150 nm) which can be controlled under the influence of an external magnetic field [56]. The factors that influence the magnetic properties of nanoparticles include

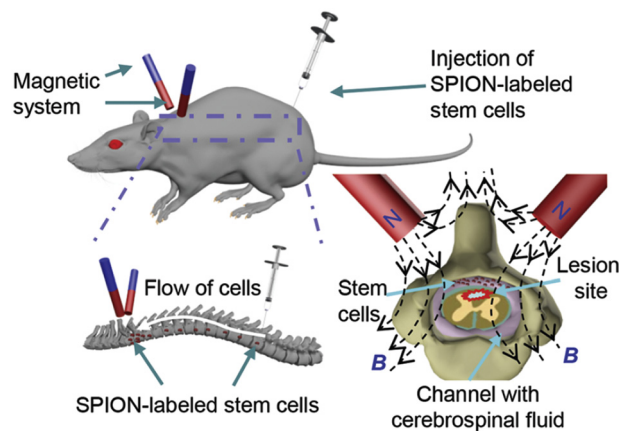


Fig. 7. An effective strategy of magnetic stem cell delivery [54].

their chemical composition, crystal lattice, particle shape and size, morphology, and finally the manner in which the magnetic nanoparticles interact with adjacent particles or with the surrounding matrix [57]. When the size of the nanoparticles shrinks, the surface-to-volume ratio grows. Exploring the properties of the large surface-to-volume ratio of nanoparticles is of critical importance which has led to novel physical, chemical, and mechanical property discoveries compared to those of the corresponding bulk material [58]. Consequently, the attraction of MNP is that it usually does not reach deeper tissues, making this alternative available only to treat tumors that are relatively superficial [59].

4.1. Synthesis methods of MNPs

Nanofabrication involves methods of building engineered nanostructures which in most cases have minimum dimensions and a size of smaller than 100 nm. This technology emphasizes the use of nanomaterials for complex multifunctional devices including medicine and human health care. In this regard, the last ten years have witnessed the development of a wide diversity of nanofabrication techniques fulfilling high expectations surrounding nanotechnology and nanofabrication. Numerous methods have been used for the synthesis of magnetic nanoparticles.

These include:

- ✓ Mechanical milling
- ✓ Co-precipitation
- ✓ Nanoreactors/microemulsion techniques
- ✓ Sonochemical processing
- ✓ Sol-gel methods
- ✓ Flow injection
- ✓ Electrochemical production
- ✓ Supercritical fluid techniques
- ✓ Thermal decomposition
- ✓ Hydrothermal routes
- ✓ Microwave techniques
- ✓ Spray pyrolysis
- ✓ Laser pyrolysis
- ✓ Flame spray pyrolysis
- ✓ Gas phase synthesis
- ✓ Arc discharge
- ✓ Oxidation
- ✓ Microbial methods

It is well known that the magnetic properties of ferrite nanoparticles strongly depend on the particle size, chemical composition, shape of the nanoparticles, interactions between nanoparticles, and preparation

method in particular. Ferrites have been synthesized using various methods such as solid-state reaction, co-precipitation, microemulsion, solvothermal, mechanosynthesis hydrothermal, sol-gel, and combustion techniques. Co-precipitation method is a simple route to prepare fine, nano-crystallized, high-purity, and homogeneous powders of single or multicomponent oxides [60]. Fig. 8 presents the different methods used to prepare ferrites with a spinel structure, all of which use Fe(III) and M(II) salts as precursors. In each of these methods, an iron salt, usually $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ or $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, or salt of the metal commonly $\text{M}(\text{NO}_3)_2$, M-SO_4 , or M-Cl_2 are used. Salts are dissolved in water or another solvent under stirring with the pH being adjusted to between 7 and 12, depending on the metal salt that is used. The mixture is placed into an autoclave and heated for 12–24 h, followed by natural cooling to room temperature. The solid is collected by filtration or centrifugation and washed, followed by drying at approximately 85 °C overnight. Sol-gel and citrate methods involve addition of the metal and iron precursors, along with citric acid, to form a gel. After dissolving the precursors in water or ethanol and vigorously stirring at pH ~9, a gel-like material is made. Citric acid assists in the homogeneous distribution of metal ions into the solution. The gel is dried and then sintered at temperatures ranging 450–800 °C at various periods of time. The sintering time is normally varied and tested to determine the effects on the photocatalytic activity [61]. Co-precipitation methods to prepare ferrites are similar to thermal methods. Fe (III) and metal salts are dissolved in water along with a surfactant, oleic acid, under stirring and gentle heating. The reaction mixture pH is elevated to 7–10 in order for precipitation of the ferrite particles. The solid nanoparticles are then filtered and washed with deionized (DI) water and/or ethanol followed by drying at 80–100 °C. Once dried, the nanoparticles can then be calcined at various temperatures to determine the effects of the high temperature on the activity of the nanoparticles [62].

4.2. Bioapplication of MNPs

In the pharmaceutical field, nanotechnology has revolutionized the traditional drug-design concept and the art of drug delivery. The idea of a highly specific nanoscale drug for the targeted therapy of diseases is now considered a feasible treatment for serious health conditions. Scientists have manifested an impressive interest in the field of pharmaceutical nanotechnology research in recent years. The five most important properties of MNPs for successful utilization not only for hyperthermia but also for other bio-applications are the following: prevention of aggregation, water compatibilization, magnetic controllability, protection and surface-stability, and biocompatibility. Prevention of aggregation and improvement of colloidal stability is an important

property required to obtain stable MNPs in both biological media and a magnetic field. Our group designed a novel magnetic drug delivery system in which a proecological method was applied for preparing CoFe_2O_4 nanostructures [63]. Fig. 9 demonstrates the ability of MNPs for targeted drug delivery. The colloidal stability can be improved by controlling the agglomeration of MNPs, which can be achieved by controlling the strength of repulsive forces. There are a couple of ways to achieving steric stabilization which will help improve colloidal stability. Steric stabilization can be improved by coating MNPs with a ligand shell or with an inorganic or polymeric matrix. Electrostatic stability also depends on the ionic strength and pH of the solution, which can be improved by studying the balance between the number of collisions between particles and the number of collisions resulting in aggregation [64]. Compatibility of MNPs with water is another property which has to be taken into consideration when synthesizing MNPs for bio-applications, as most biological reactions occur in an aqueous environment. That is why surface functionalization should help overcome this problem. Another important property is magnetic controllability. The magnetic property is significant not only since it allows MNPs to be magnetically separated, but also because it allows for easier transportation of MNPs toward specific locations. Also, the protection and stability of the surface of MNPs are essential factors in preventing side reactions with other biological components. Finally, the biocompatibility of MNPs should be non-toxic for biological applications. Biocompatibility can be achieved using various coatings. Negatively-charged coatings exhibit good biocompatibility, while positively-charged coatings show enhanced interaction with numerous biosystems. All the mentioned properties can be achieved by surface functionalization of MNPs, an important step to create useful MNPs not only for hyperthermia but also for any intended biological application. There are multiple ways in which magnetic nanoparticles can be classified based on their properties. In this chapter, we will concentrate on biological applications. Initially, magnetic nanoparticles must be biocompatible and non-toxic. Further, the size-related properties are important to yield reasonable colloidal and chemical stability. Choosing a versatile magnetic nanoparticle can be very helpful in the cases where the nanoparticle suspension is delivered intravenously, as aggregation (e.g., in blood vessels) must be avoided. For these reasons, in recent years, magnetic nanoparticles have been researched extensively. One solution to this problem has been developed by modifying their surface chemistry [65]. Recently, Li et al. reported a new synthesis of sodium-citrate-modified iron oxide nanoparticles where the 3 T3 cell line maintained cell viability higher than 70% at medically relevant concentrations [66]. Regarding diamagnetic shell-enhanced magnetic properties, Ye et al. have shown that mesoporous silica coated superparamagnetic iron oxide nanoparticles

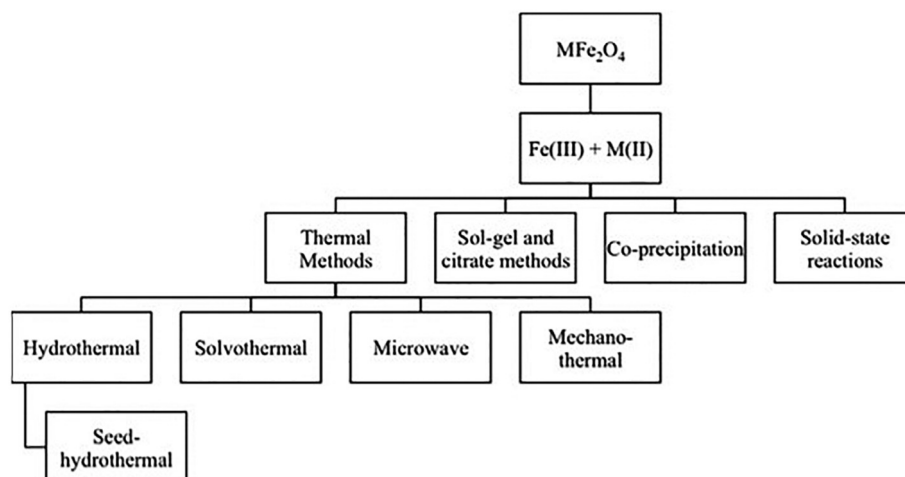


Fig. 8. The different methods used to prepare ferrites with a spinel structure.

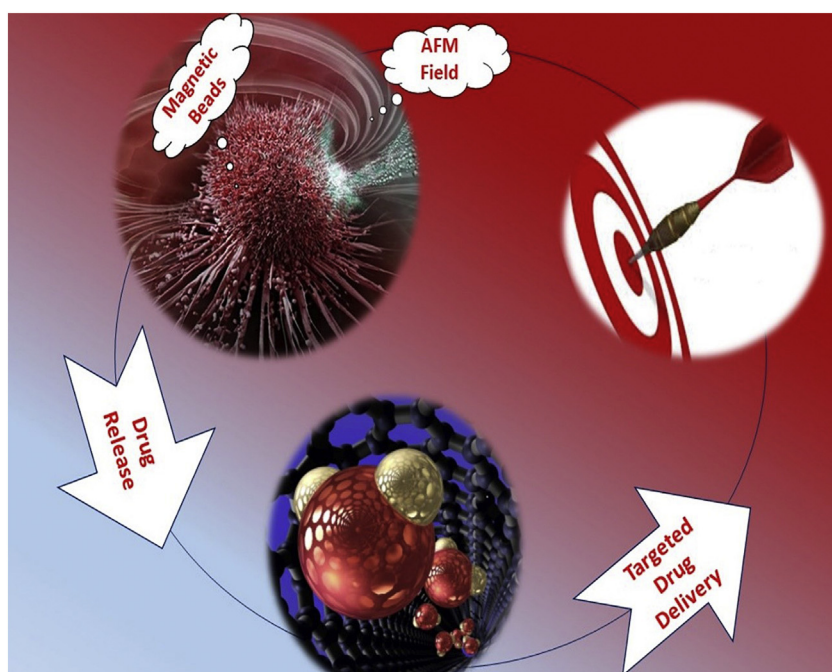


Fig. 9. The ability of MNPs for targeted drug delivery [63].

exhibited a 21-fold enhanced MRI efficiency when compared to a commercial T2 contrast agent [67]. A high magnetization value is critical for magnetic nanoparticles, as it will permit control over the movement of particles in blood or lymphatic fluid. Magnetic nanoparticles can be moved closer to a targeted pathological tissue through strong magnetic fields. Practically, the desired high magnetization can be obtained by synthesizing nanoparticles that belong to the group of transition metals and their oxides.

4.3. Classification of MNPs applications

The high surface area-to-volume ratio of magnetic nanoparticles means that they exhibit a variety of properties different from bulk material such as lower melting point, lower sintering temperature, and

different magnetic properties. Magnetic nanoparticles are used for a variety of biomedical applications. Fig. 10 demonstrates the broad application of MNPs in cancer therapy [68]. They can be classified roughly into six areas of use:

- (1) They can be conjugated with antibodies and injected intravenously for diagnostic purposes.
- (2) They can be used as contrast agents in techniques such as magnetic resonance imaging.
- (3) They can be employed to deliver drugs via intravenous or local injection with or without conjugated antibodies which can be released over time or all at once.
- (4) They can be used for magnetic hyperthermia.
- (5) They can be incorporated into silica shells or liposomes to enable in-situ ELISA (enzyme-linked immunosorbent assay) measurements.

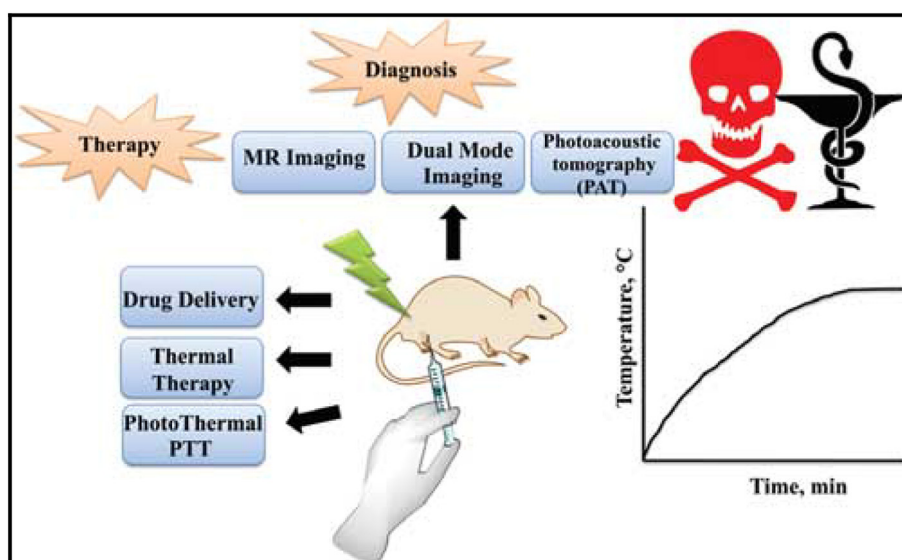


Fig. 10. The broad application of MNPs in cancer therapy [68].

- (6) Antibody-conjugated magnetic nanoparticles can be used to sort ex-vivo rare, magnetically labeled cells from a heterogeneous mixture of cells in blood samples.

In general, all magnetic nanoparticles introduced into the body need to:

- (1) be chemically stable in both aqueous solutions and biological fluids,
- (2) be biocompatible,
- (3) be nontoxic, and
- (4) have a high saturation magnetization.

We describe some MNPs applications here that are more important.

4.3.1. Magnetic hyperthermia

External heating is used to control the temperature such as with a warm water bath radio frequency ablation (RFA), high-intensity focused ultrasound, and magnetic hyperthermia. One of the other characteristics of the tumor environment is a slightly increased temperature compared to normal tissues. This characteristic results from the fact that tumor cells are highly active, constantly dividing and growing. Additionally, the immune response caused by leukocyte infiltration leads to inflammation, contributing to a heightened local temperature. Hyperthermia represents an abnormal increase in the body temperature and can appear in infections in response to the immune system. High temperatures can be used to destroy cancer cells to achieve tumor regression. Cancer cells are sensitive to hyperthermia. Therefore, the apoptosis process will occur at 42–45 °C in comparison to healthy cells. As this heating may produce side effects to the surrounding tissues, magnetic nanoparticles can be used for the magnetic fluid hyperthermia (MFH). Suspension of MNPs is injected at the tumor zone, where these can induce an active or passive accumulation. The active state means using ligands on the nanoparticles' surface that are specific for receptors present on the surface of tumor cells, while the passive refers to the enhanced permeability and retention effect (EPR) of MNPs. MNPs inside the tumor can change electromagnetic energy into heat with the aid of an external magnetic field [69]. Fig. 11 illustrates passive or active

targeting. In this way, nanoparticles will help to generate local temperature without disturbing the cells in surrounding tissues. This type of therapy distinguishes itself from traditional methods by being noninvasive as the small size of the injected particles permits them to pass through biological barriers thereby decreasing the toxicity level [70]. With an external heating source, tumor hyperthermia can be performed by nanocarriers to generate two different effects. For the first, the growth in tumor temperature improves the EPR effect by promoting vascular permeability and better accumulation of nanoparticles in the tumor [71]. The second effect is initiated by heating to a temperature above the lipids gel-to-liquid phase transition temperature (T_g), where the particle lipid membrane or lipid coating is more permeable to water and hydrophilic drugs, promoting drug leakage from the nanoparticles once accumulated in the tumor [72]. For this reason, the most successful current approach using MNP involves experiments using magnetohyperthermia. The use of MNP with an alternate magnetic field raises the temperature in a localized way, without harming the surrounding tissues [73].

4.3.2. Magnetic resonance imaging (MRI)

Concerning magnetic resonance imaging, the MRI signal initiates from changes in the direction of water hydrogen nuclei arrangements in the precession within an applied radiofrequency (RF) signal. After applying RF pulses, the relaxation times T_1 (longitudinal: spin–lattice relaxation) and T_2 (transverse: spin–spin relaxation), through which protons return to the original state, can be useful in producing an MRI image. Both T_1 and T_2 are dependent on the magnetization saturation of NPs and their magnetic interactions with protons from water molecules. The various realignment speeds for tissues and contrast agents are used to shorten the relaxation time parameters of water subsequent with differentiation between tissues [74]. The cobalt nanoparticles present a far higher room temperature M_s (1422 emu cm^{-3}) than the iron oxides (395 emu cm^{-3}), which could lead to a larger effect on proton relaxation. This offers improved MRI contrast and allows for use of smaller magnetic nanoparticles core without compromising sensitivity. However, it is difficult to fabricate water-soluble Co nanoparticles since they are prone to oxidation [75]. Larger magnetic particles allow for greater r_1 relaxivity, as compared to smaller particles. The field strength

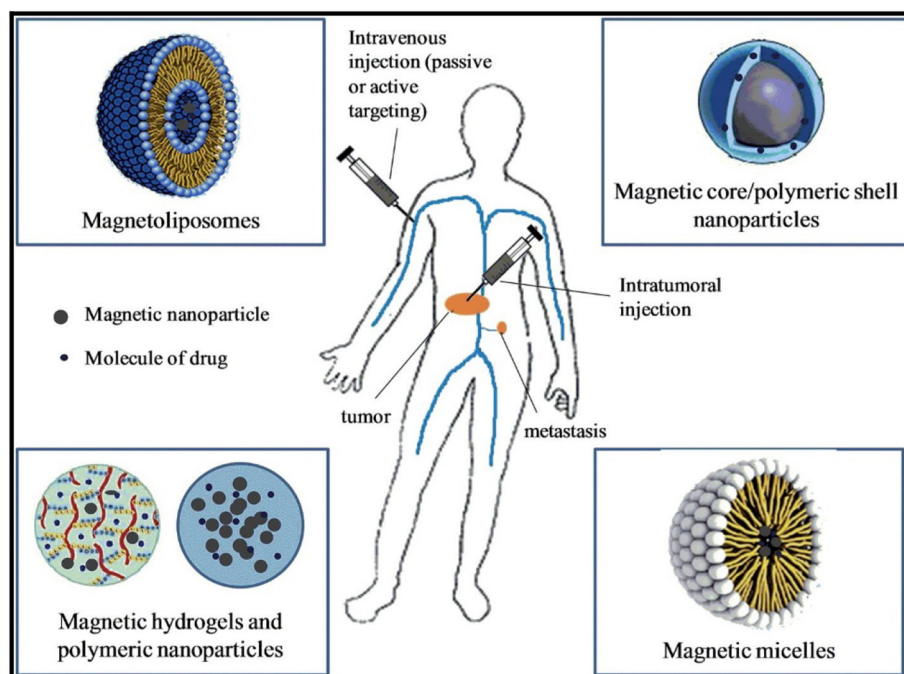


Fig. 11. Passive or active targeting of nanocarriers [69].

and particle size have no significant effect on r_2 relaxivity, while the relatively high value of r_2 makes Co nanoparticles suitable as a negative contrast agent. In addition to Co, other metallic nanoparticles (Fe, Fe–Ni, Fe–Co and Fe–Pt) can be used as MRI contrast agents. For example, the r_2 and r_2^* relaxivity of Fe is significantly larger than that of iron oxide at the same particle size [76]. FePt magnetic nanoparticles are suitable because their r_2/r_1 relaxivity ratio is about 3–14 times larger than that of conventional iron-oxide based contrast agents [77].

4.3.3. Magnetic drug delivery systems

Use of targeting drugs is a particular form of drug delivery where the drug is focused on the action site. This site could be a specific organ structure, a cell, or an intracellular region. Much effort has been made to address the different locations where tumors can occur, and hence, different techniques have been developed. Magnetic implants are utilized to guide various magnetic drug-delivery applications, mostly exploiting blood vessels, but with a few exceptions. One issue is related to intrathecal drug delivery and involves direct drug infusion into the spinal canal. It has become a standard practice for treating many central nervous system diseases and in principal tumors, too, due to the reduced systemic toxicity from the drug bypassing the blood-brain barrier. In order to overcome remaining disadvantages, such as insufficient drug deposition at specific locations, ferric steel implants were placed in the subarachnoid space in an in-vitro human spine model prior to nanoparticle administration into the spine. The results indicated that this approach can enhance the targeting capabilities for intrathecal drug delivery [78]. The overall goal of the targeting strategies should be their translation to clinics. It depends on the feasibility of implementing the synthesis of drug-carrying nanoparticles in a quality controlled environment (GMP manufacturing) and applying a system that can be easily implemented in a clinical environment. Five different approaches of targeting are: (i) chemical, approach-prodrug; (ii) compartment delivery; (iii) natural targeting; (iv) ligand mediated targeting; and (v) physical approach of targeting [79]. The transport of nanocarriers/molecules into the tumor interstitium or tissue through the leaky tumor vasculature via molecular movement within fluids is named passive targeting or passive diffusion [80]. In active targeting, nanocarriers are guided at the tumor sites by tagging targeting ligands against overexpressed receptors on tumor cells or on the tumor vasculature, which are not expressed by normal cells. Nanocarriers are conjugated with targeting ligands/moieties such as folic acid, monoclonal antibodies, integrin, etc., which bind with the receptors/antigens present on the surface of targeted tumor cells [81]. Active-targeting strategies are generating tremendous interest among scientists and researchers as it is capable of eradicating tumor cells. A completely different concept of magnetic drug targeting was performed by Taherkani et al. utilizing directional magnetotaxis, instead of magnetic attraction. Bacteria can act as self-propelling vehicles for reaching hard-to-treat hypoxic regions in solid tumors [82]. As mentioned earlier, the overall goal of the targeting strategies should be their translation to clinics, which depends on the feasibility of implementing both the synthesis of drug-carrying nanoparticles in a quality controlled environment (GMP manufacturing) and the equipment required for applying the system which can be easily performed in a clinical setting. The road to clinical implementation can be difficult and lengthy and many sophisticated approaches, while providing very promising in-vitro and in-vivo results, may fail under these presuppositions. A convincing concept that is close to clinical implementation is Magnetic Drug Targeting based on intra-arterial administration of drug-loaded SPIONs and enrichment by externally applied magnetic fields that are generated by a strong electromagnet. The proof of principle was demonstrated in the worldwide largest study concerning the successful pre-clinical application of SPIONs for cancer treatment [83]. The “switch-on” magnetism of superparamagnetic nanoparticles [84] in magnetic fields and the straightforward functionalization of their surfaces at the molecular level make them good candidates for enhanced drug delivery. According to Elsbahy

and Wooley [85], the barriers that exist with respect to drug delivery by nanoparticle-based drug formulations can be classified into external barriers (skin and mucosa), barriers occurring en-route, and finally, cellular barriers such as limited cellular uptake, endosomal/lysosomal degradation of the nanoformulation, and inefficient transport to cellular targets (e.g., nucleus or mitochondria). Depending on the size and chemical composition of the injected nanoformulations, opsonization is a major en-route barrier to drug delivery. Albumin, immunoglobulins, complement proteins, apolipoprotein, and fibrinogen have been identified as efficient opsonins, which target the nanoparticles and tag them for rapid uptake by phagocytic cells such as blood monocytes/macrophages in lymph nodes, spleen, liver (Kupffer cells), and other tissues. Furthermore, clearance by the reticuloendothelial system (also known as the mononuclear phagocyte system (MPS)) can start severe immunological reactions against nanoformulations in blood, lymphatic fluid, and tissues.

One of the most mutual cancer treatment modalities is chemotherapy. The problem with chemotherapeutic drugs is that they are neither specific nor do they selectively kill cancer cells. They kill both normal and cancerous cells and their severe side effects require doses of drugs that could not be administered to a patient, so the treatment procedures are compromised. Strategies for guided deliveries, which ensure delivery of the maximum amount of drugs to the tumors and reducing their exposure to normal healthy cells, increase the success rate of chemotherapy [86]. A permanent magnet is used to attract magnetic nanoparticles to a well-defined region. Targeting is enhanced by the following mechanisms: (A) the local concentration of the magnetic nanoparticle is enhanced in the region where extravasation occurs due to leaky microvasculature around tumors. (B) Once extravasation has occurred, the presence of a magnetic field keeps the magnetic nanoparticles in the tumor's interstitium. Preventing the escape of the drug against naturally occurring osmotic pressure gradients [87] by means of magnetic attraction is the key to magnetic targeting. (C) Enhanced uptake of nanoparticles by tumor cells from the interstitium occurs due to increased nanoparticle concentration. (D) If the active targeting ligands are present, uptake is further enhanced by tumor cells from the interstitium [88].

5. Further magnetic theranostic agents

Recently, researchers have been focusing on drug delivery systems (DDSs) to be fabricated from intelligent materials, which have environment-sensitive or target agent-specific mechanisms. DDSs can be activated by environmental stimuli such as pH, temperature, ionic strength, electric field, or concentration differences of an analyte. Further, release mechanisms of DDSs can be controlled by swelling degree or degradation of a polymer matrix. The main concept of DDSs is that they should have the ability to release the therapeutic agent at the desired site, with the appropriate dose, and for the required time. DDSs can release therapeutics for prolonged periods and to the targeted locations. The properties of DDSs can be tailored to achieve physicochemical attributes of the drug and intended administration route.

5.1. Magnetoliposomes

Traditional, noninvasive drug delivery routes such as oral or transdermal are limited in their utility. The digestive system's harsh conditions denature or degrade many biochemical formulations. As a result, therapeutics such as insulin (degraded by proteolytic enzymes in the gastrointestinal tract) must be administered using invasive methods which reduce patient compliance and quality of life [89]. The earliest studies of vesicle drug carriers focused on phospholipid-based systems. The inherent biocompatibility of the phospholipids makes these liposomes nontoxic, biologically inert, and biodegradable with (relatively) immunogenic-optimal characteristics for in-vivo applications [90]. Drug delivery systems rest on two actors, the lipid bilayer composition

and the liposome properties. Unilamellar vesicles are coated by a single bilayer and may be small unilamellar vesicles (SUV), as small as 100 nm, or giant unilamellar vesicles (GUVs) as large as 10 μm . The latter is too large for clinical applications, but useful for in-vitro studies [91]. The liposomes contain either natural or synthetic phospholipids. Liposomes can incorporate drugs if they are created in a liquid solution with the soluble drug, using lipophilic drugs, organic solvents, or pH-gradient methods. These structures can reach the zone of interest via extravasation from the blood vessel into the interstitial space; the tissue targeting can be active or passive. Liposomes can be functionalized by adding molecules to their lipid bilayer surface [92].

Furthermore, one of the main issues in drug delivery is prolonging the circulation time, so that carriers can reach their target tissue. Longer circulation times may also reduce the need for frequent administrations. Although composed of biological components, liposomes can trigger phagocytosis and clearance, with typical blood circulation times of hour order [93]. Drug delivery systems based on liposomal nanoparticles are biocompatible because they are comparable with the phospholipidic bilayer of the cell membrane and they do not cause any toxicity. Fig. 12 depicts the ability of magnetic liposomes for targeted cancer therapy. They can integrate hydrophobic and hydrophilic drugs, keeping them away from degradation. Current studies suggest that doxorubicin, curcumin, or resveratrol incorporated in liposome systems inhibit the toxicity of healthy cells even if the drug concentration increases. This method can be used in the treatment of prostate cancer as the liposomal formulations can target prostate tumor cells as they inhibit cell proliferation more than regular drugs do. The issues of liposomes are instability and short half-life; these problems can be solved only by an optimal functionalization. Therefore, developing stable and pH-sensitive liposomes can deliver the drug in acidic conditions [94]. Magnetically doped liposomes have been synthesized through incorporation of magnetic nanoparticles into the bilayer, where release is triggered either as a result of heating or as through field-induced stresses developed under an applied magnetic field [95]. Fig. 13 illustrates the application of magnetoliposomes. Magnetic

liposomes can be prepared by either thin film hydration (TFH) [96] or the reverse-phase evaporation (RE) method [97].

5.2. Polymer-based theranostic agents

Microspheres are free flowing powders consisting of encapsulated (drugs) spherical particles which can be suspended in the aqueous vehicle and injected by an 18 or 16 number needles. Small enough supra-molecular particles that can circulate through capillaries easily without making embolic occlusion ($<4\ \mu\text{m}$) are magnetic microspheres but are sufficiently susceptible (ferromagnetic) to be captured in micro vessels and dragged into adjacent tissues by magnetic fields of 0.5–0.8 Tesla (T). Methods of preparation of magnetic microspheres include phase separation emulsion polymerization (PSEP) and continuous solvent evaporation (CSE). The extent and rate of drug delivery via magnetic responsive microspheres can be regulated by varying (i) size of microspheres; (ii) drug content; (iii) magnetite content; (iv) hydration state; (v) and drug release characteristics of the carrier. The amount of drugs and magnetite content of microspheres should be delicately balanced in order to design an efficient therapeutic system. Targeting by magnetic microspheres i.e., incorporation of magnetic particles into drug carriers (polymers) and using an externally applied magnetic field, is one way to physically direct these magnetic drug carriers to a desired site [98]. The drug targeting means the delivery of drugs to receptors, an organ, or any other specific part of the body. Various non-magnetic micro carriers (nanoparticles, microspheres, and micro particles, etc.) are successfully utilized for drug targeting, but they reveal poor site specificity, which are rapidly cleared off by reticuloendothelial system (RES) under normal circumstances. Magnetism plays an important role in these cases; magnetic particles composed of magnetite which are well tolerated by the body and magnetic fields are believed to be harmless to biological systems and adaptable to any part of the body [99]. Up to 60% of an injected dose of drugs can be deposited and released in a controlled manner in selected non reticuloendothelial organs. So magnetic micro-carriers were developed to overcome two

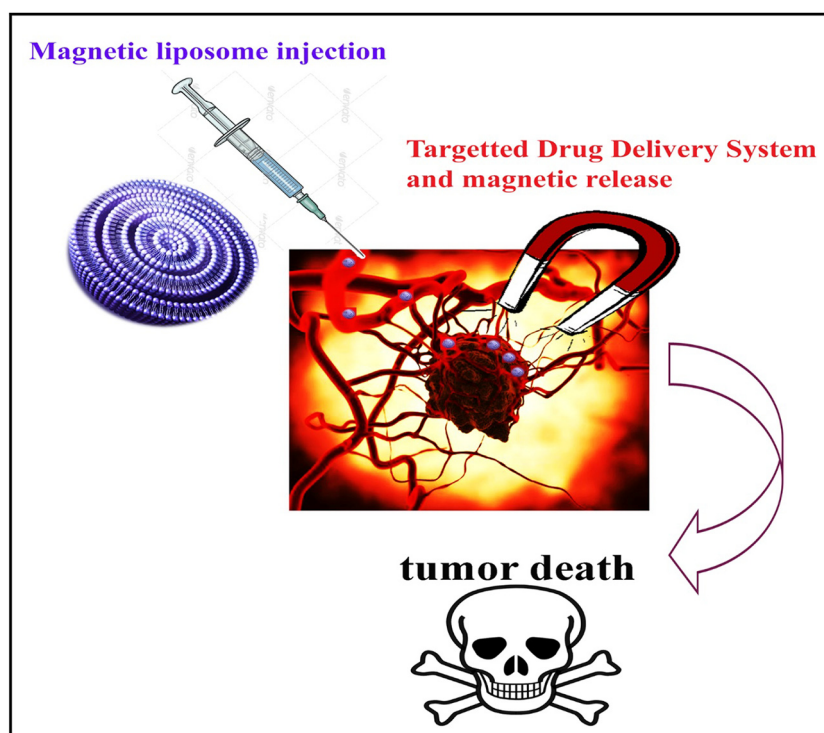


Fig. 12. The ability of magnetic liposomes for targeted cancer therapy.

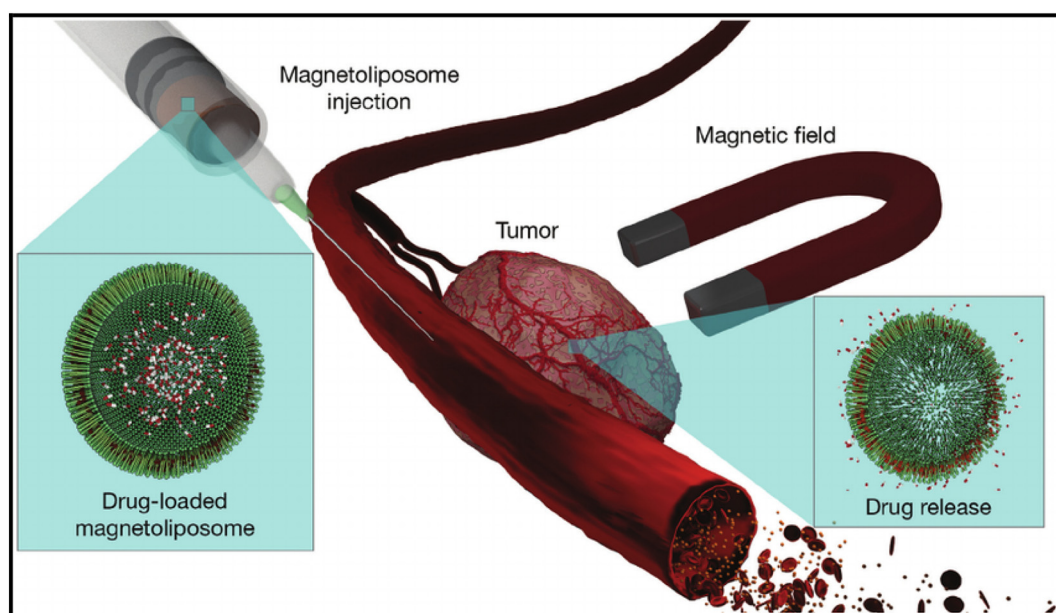


Fig. 13. The application of magnetoliposomes in tumor therapy [95].

major problems encountered in drug targeting called RES clearance and target-site specificity. Magnetism has applications in numerous fields including diagnostics, drug targeting, molecular biology, cell isolation, cell purification, hyperthermia, and radioimmunoassay [100].

6. Impact of static and dynamic magnetic fields on biological systems

The biological effects of magnetic fields can be directly influenced by different parameters. Depending on whether the magnetic intensity changes over time, magnetic fields can be divided into static magnetic field (SMF) or dynamic/time-varying magnetic field, which can be further divided into different categories according to their frequency. When the magnetic field intensity does not change over time, it is called “static magnetic field”. In contrast, if the magnetic field strength changes over time, it is called “dynamic magnetic field” or “time-varying magnetic field”. Pulsed magnetic fields (PMFs) are the most commonly seen dynamic magnetic fields such as the 50 Hz or 60 Hz power frequency alternating current (AC) magnetic fields and radiofrequency magnetic fields. Depending on the magnetic field intensity, there are weak, moderate, strong, (high) and ultra-strong (ultra-high) magnetic fields. Depending on the magnetic field spatial distribution, there are homogeneous or inhomogeneous magnetic fields. Here, we will discuss their differential effects on biological objects. Natural and human-made magnetic fields permeate our environment. The Earth's magnetic fields typically do not exceed 100 mT, and human-made magnetic fields in medical devices or industrial processes such as electrolysis or welding machines, do exceed this level. Magnetic fields will affect both magnetic materials and those that do not show intrinsic magnetism, e.g., water that is a diamagnetic material opposes the magnetic field. The interaction of diamagnetic materials with magnetic fields is typically far less than that of magnetic materials. The magnetic susceptibility of water is small, $-0.9 \times 10^{-8} \text{ m}^3 \text{ kg}^{-1}$, in comparison with the susceptibility of typical ferromagnetic materials ($1000\text{--}10,000 \times 10^{-8} \text{ m}^3 \text{ kg}^{-1}$). An interesting effect of pulsed magnetic fields (7 T, 2 s) on algae-like fungi (*Achlya americana*) and protozoans (*Saprolegnia diclina*) is opening up the pores in the lipid bilayers, which can be performed either reversibly or irreversibly [101]. At the molecular scale, magnetic fields can interact in the presence of unpaired electrons in radicals and transition metal complexes, as well as the charges present at the surfaces of larger molecular structures such as proteins or lipids. It has been shown that the

torque on proteins from magnetic fields or magnetic field gradients can positively influence protein crystallization [102]. Magnetic fields can also facilitate the alignment of lipid bilayers. In biological systems, the presence of static and dynamic magnetic fields can contribute to the changes in the apparent rates of chemical reactions. The impact of typical dynamic and static magnetic fields are minimal on single reactions. However, in biological systems where there is a significant feedback in complex reaction systems, the small impact of magnetic fields can cause considerable effects. For instance, small 50 Hz alternating magnetic fields are capable of influencing the free O_2 radical concentration in rat lymphocytes *in-vitro*. As with temperature and pressure, magnetic field is an important physical parameter which could have a general impact on multiple objects. The effect of magnetic field on an object is mainly dependent on the magnetic susceptibility of the object as well as the magnetic field intensity and gradient. Cells are filled with various cellular contents and biomolecules which could respond to the magnetic field, such as cell membrane, mitochondria, DNA, and some proteins. It is obvious that cells respond very differently to magnetic fields with different types and intensities. For example, a 50-Hz, 1 mT PMF could increase rat pituitary GH3 cell proliferation [103], but a 0.5 T static magnetic field clearly inhibited GH3 cell proliferation [104]. In addition, multiple bodies of evidence revealed that different types of magnetic fields of the same magnetic field intensity could produce totally different effects on the same sample examined. For example, a 0.4 mT 50 Hz and a 2 μT 1.8 GHz PMFs both increased epidermal growth factor receptor (EGFR) phosphorylation, which were reversed by incoherent (noise) magnetic fields of the same intensities [105]. Although the mechanism behind how the incoherent magnetic field reversed the effect of PMF is still unknown, it is clear that the magnetic type can directly affect the field effects. Since PMFs have variable parameters, such as field intensity and frequency, it is relatively difficult to study the biological mechanisms of magnetic effects comprehensively and systematically. For example, it was observed that PMFs with different frequencies can have diverse effects on cell proliferation. In comparison to the time-varying/dynamic magnetic fields, SMFs are more suitable to study the fundamental biological mechanisms because they have less changeable parameters. The most commonly exposed SMFs are the permanent magnets such as the magnets on household refrigerators, toys and accessories, which are usually not very strong (below 1 T). In the meantime, most studies in the literature on the biological and health effects of magnetic fields had been inconclusive or contradictory, largely due to the various parameters

used in individual studies, including the magnet fields themselves, samples examined, as well as the experimental set up. It seems that there is a large gap between atoms/molecular level and cell/tissue/organism level that should be resolved to correctly and scientifically understand the biological effects of magnetic field. Nowadays, experimental and theoretical studies are both at a very preliminary stage. To help us get a more complete understanding of the biological effects of magnetic fields and their underlying mechanisms, more systematic, well controlled studies with fully described experimental details are strongly encouraged. Furthermore, increased collaborations between scientists in physics, biology, and chemists are necessary to make substantial progresses in this emerging field.

7. Toxicity studies

Since the products of nanotechnology industries have gained widespread application, huge potential benefits and massive financial profits are foreseeable. The concept of nanotechnology has long been well established, but only recently toxicity elicitation has started to emerge. Focusing on broad applications of nanomaterials, there is an increasing demand to investigate their toxicity profile. It is imperative to know whether the administration of these nanobiomaterials is safe, or if they impart toxicity to healthy cells and produce long-term health issues. The determination of these attributes for individual materials is easy, and once its properties are established, it becomes easy to determine the different concentration levels under which a material may

be recognized as “safe” or “harmful” [106]. Nevertheless, the potential risks of NMs on human health and the environment must be considered. The relationship between physicochemical characteristics of NMs such as size, shape, and surface chemistry, and their intracellular and in-vivo biodistribution have remained largely unknown. At the nanoscale, NPs may have important, enhanced optical, mechanical, electrical, physical, chemical, and biological properties. This makes knowledge of the nanotoxicology of nanostructured biomaterials imperative. The use of unregulated nanomaterials may lead to undesired effects on the environment and human health as well as on biosystems. These concerns have gained huge attention from investigators throughout the world, who seek to develop a versatile nanomaterial with a balance between its applications and associated toxicities [107]. When NMs enter to the body, their behavior is not predictable from their properties alone. Indeed, evidence suggests that all these characteristics can contribute to the mechanism by which NMs may interfere in or disrupt biological activities [108]. One common fact about all nanostructured biomaterials is that all of them require well-set protocol to be used as biomedical additives. Accordingly, many serious issues like short-term and long-term toxicity, environmental exposure, methods of entry into the human body, amount and dosage, size, and shape must be addressed in an acceptable manner. Once a nanomaterial is categorized as nontoxic, it may be considered safe, but if it is proven to be toxic, then suitable approaches (e.g., functionalization) could be developed to reduce/minimize the toxicity to obtain a reasonable benefit-to-risk ratio. AgNPs represent a suitable choice for cancer applications. The properties that

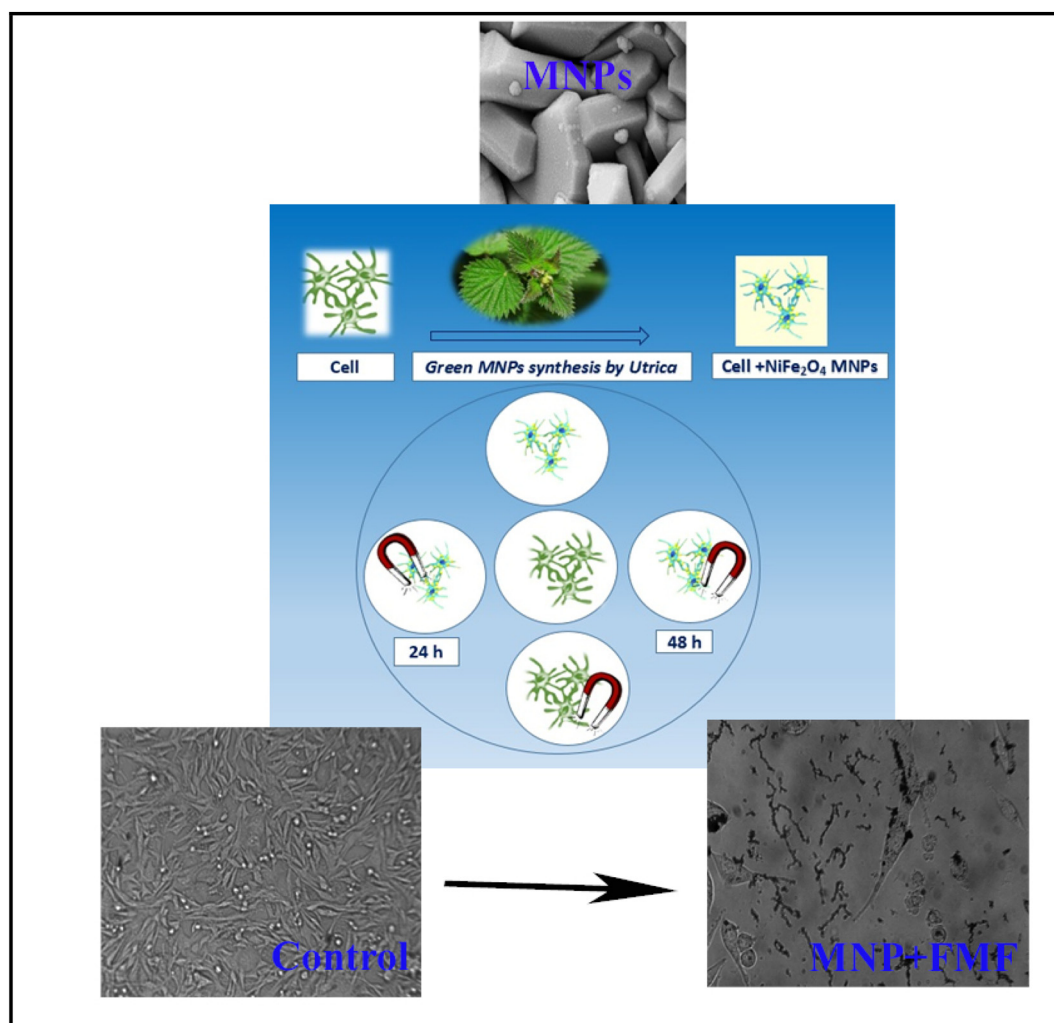


Fig. 14. Schematic of cytotoxic effect of Ni ferrite on neural cells [111].

make them stand out include stability in aqueous solutions, small size, precise distribution, high area negative charge, biocompatibility, and the power to enter cancerous cells and inhibit their viability through induction of apoptosis [109]. Pn-SPION of about 40–50 nm size with a core-shell structure and magnetic core as well as polymeric shell has been prepared. It has proved non-toxic as compared to SPIONs and because of the surface modification, the cellular uptake of Pn-SPION could be enhanced [110]. PVP-coated CoFe_2O_4 were examined nanoparticles using a facile and controllable sonochemical method along with their structure, morphology, magnetization properties and in-vitro cytotoxicity. The in-vitro cytotoxicity experiments exhibited negligible cytotoxicity of PVP-coated CoFe_2O_4 at high sample concentrations after 24 h treatment. The results indicated that the monodisperse PVP-coated CoFe_2O_4 nanoparticles could be a promising candidate for widespread biomedical applications. Amiri et al. [111] observed that the FMF exposure caused an increase in cell death in neural cell types 48 h after treatment with NiFe_2O_4 nanostructures. MNPs indicated dose-dependent cytotoxicity, but the amount of cell death per cell in the absence of MF for SH-SY5Y cells was greater than in U87 cells. On the other hand, cell death induced by FMF exposure was observed specifically in SH-SY5Y cells. Fig. 14 indicates the schema of the cytotoxicity effect of Ni ferrite nanostructures on neural cells.

8. Conclusions

Studying recently published papers on the application of magnetic nanomaterials as drug delivery systems suggested that researchers are interested in the advantages of nanotechnology to improve the efficiency of bioapplication methods. The ideal drug-targeting delivery systems are expected to retain their loaded drugs when they are circulating in the circulating systems. They are desired to release the loaded contents only after they accumulate at the targeted tissues by means of some internal triggers like enzymes and pH, or by external triggers like ultrasound, light, temperature, and magnetic field. In general, compatibility of nanoparticles is achieved by fine-tuning their sizes, shapes, and biophysical properties (especially surface charges and hydrophilicity vs. hydrophobicity). Nanoformulations for targeted drug delivery have several advantages such as lowering dosage, effective pharmaceutical activity, efficient drug accumulation, minimization of side effects, and improved drug stability. Although nanoparticle-based formulations are efficacious in biological systems, their recognition and clearance by the immune system is a major limiting factor competing with the efficacy of drug delivery. Magnetic nanostructures have been investigated for a wide range of biomedical and healthcare applications due to their high biocompatibility, biodegradability, nontoxicity and most importantly, the ease of maneuvering them from a distance using an external magnetic field. These MNPs have been investigated for a variety of biomedical applications including cancer hyperthermia, MDT, magnetofection, and MRI.

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