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Review Article

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Iron Oxide Biomagnetic Nanoparticles (IO-BMNPs); Synthesis, Characterization and Biomedical Application – A Review

Nochehdehi AR[1]*, Thomas S[2], Sadri M[3], Afghahi SSS[4] and Mehdi Hadavi SM[5]

[1]Biomaterials Research Group, Biomedical Engineering Department, Materials and Biomaterials Research Center (MBMRC), Tehran, Iran
[2]Polymer Science & Engineering, School of Chemical Sciences and Hon. Director of International and Inter UniversityCentre for Nanoscience and Nanotechnology (IIUCNN), Mahatma Gandhi University (MGU), Kottayam, Kerala, India
[3]Department of Biochemistry and Biophysics, Education and Research Center of Science and Biotechnology, Malek Ashtar University of Technology, Tehran, Iran
[4]Materials Science and Engineering, Imam Hossein University, Department of Engineering, Babaei Highway, P.O. Box: 15816-18711, Tehran, Iran
[5]Materials and Biomaterials Research Center (MBMRC) and Iran National Institute of Materials and Energy (MERC), Tehran, Iran

Abstract

Nanotechnology is a multidisciplinary branch of science which encompasses numerous diverse fields of science and technology, ranging from biomedical, pharmaceutical, agricultural, environmental, advanced materials, chemical science, physics, electronics, information technology, and so on. Physical and Chemical properties as a major advantages of Nanoparticles can be used in various applications from Industries to medicine. Besides, Magnetic nanoparticles for medical applications have been developed by many researchers. In recent decades, it has received attention by virtue of their potential for applications in different fields. Due to several advantages and widespread applications of magnetic Nanoparticles in biotechnology, medical, material science, engineering, and environmental areas, much attention has been paid to the synthesis of different kinds of Biomagnetic nanoparticles (BMNPs). Core-shell nanoparticles include of coated various materials like: biopolymers (Chitosan, PAA) and bioceramics (Hydroxyapatite) as a shell on top of them and different hard and soft materials like metal oxide (Iron oxide and Cob alt composite) as a core. Improved properties of core-shell nanoparticles like less cytotoxicity, increase biocompatibility, decrease in an interactions with biomolecules, increase physicochemical stability and sort of that, can be due to their use in biological applications. After reviewing several research and review articles and synthesis procedure of Iron based Bio-magnetic Nanoparticles (BMNPs), we should emphasize that, It can be used in different applications like magnetic resonance imaging (MRI), drug delivery systems (DDS), immunoassay, also specially in diagnosis and treatment of cancer via hyperthermia (heat therapy) method.

Keywords: Nanotechnology; Nanoscience

Introduction

Nanomedicine

Nanoscience researches has been developing and growing in the various fields, recently. Indeed, a whole new field of "Nanomedicine" is emerging. Increasing application of Nanostructure materials in medicine will bring remarkable advances in Diagnostics, prevention and treatment of prevalent diseases. The reason for using this approaches in Nanomedicine are evaluation of the pato-physiological basis of disease, perceived diagnostic opportunities and effective performance of therapies in contrast, preventive measures. Perspectives of nanotechnology and nanostructured materials in medical applications include Analytical Tools (AT), Nano Imaging (NI), Nanomaterial and Nanodevices (NM/ND), Modern Clinical Therapeutics (MCT) and Drug Delivery Systems (DDS), Regulatory and Toxicological Issues (RTI) [1,2]. Development of multifunctional nanostructured materials, various engineered nanosized systems for targeted drug delivery has already been considered as one of the priorities in the medical specialy clinical fields. Design of multifunctional applications, ability and allowing of nanostructured materials in drug targeting for crossing the biological obstacles are the important issues to use of nanotechnology in medicine which should be considered. Specifically, One of the essential needs for expanding the applications of nano-structured materials in medicine is clinical study about relation between specific properties in nano scale and toxicological implications of nanomedicines should lead to the formation of an interdisciplinary branch of science, technology, engineering and medical science [3], to remove the barriers as well as increasing relations between academia, industry and regulatory agencies for solving problems associated with delayed diagnosis and treatment in medicine [4].

Magnetic property

Medical advances of nanoscience and nanotechnology is depend on accurate knowledge of magnetic properties of nanoscale materials. Investigation indicates that the magnetic properties in nano scale fundamentally different form their bulk ones. So, nanosized Bio-magnetic nanoparticles (ranges from 1 to 100 nm) have attracted core focus of researchers in the biotechnological fields to their importance. Therefore, these materials based on the interaction with the external magnetic field are divided into 3 categories like: diamagnetism, paramagnetism, ferro and antiferromagnetism [5-9]. Diamagnetism refers to a material that exhibits a negative magnetism. Even though the substance is composed of atoms that have no net magnetic moment (paired electrons), it reacts in a particular way to an applied field. Wilhelm Weber and Paul Lange in theorized that an applied field acts on a single electron orbit to reduce the effective current of the orbit, in turn producing a magnetic moment that opposes an applied field [6,9].

***Corresponding author:** Amirsadegh Rezazadeh Nochehdehi, Fellow Researcher, Biomaterials Research Group, Biomedical Engineering Department, Materials and Biomaterials Research Center (MBMRC), Tehran, Iran, Tel: 98-9128406846; E-mail: amir.rezazadeh20@yahoo.com

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The common diamagnetic materials are water, wood and most organic compounds [5-10]. Electrons are arranged in energy states of successive order, and for each energy state there can only be two electrons of opposite spins as established by Paul's principle. The electron has a spin that is equivalent to the strength of the magnetic moment which can generate magnetic moments through orbital moving of an unpaired electron around the nucleus and the electron's spin around its own axis. Since the magnetic moment of electron pairs are not in an energy level, there is no net magnetic moment whenever an energy level is an entirely full by the reasons why, per atoms should have a pure net magnetic from unpaired electron. Decreasing the pure magnetic moment in nanoscience originates from interaction between unpaired electron is in the valence band to other ones. Nevertheless, special elements like Cobalt (Co) and Nickel (Ni) Contain internal energy which has not been completely filled. For example, there is permanent magnetic moment in per metallic atoms which is equal strength of unpaired electrons [5]. In the other cases, atoms whose shells contain electrons with spins that are not compensated by another electron of an opposing spin will have a resultant magnetic moment; this is due to the unpaired electrons. These moments tend to align (positively) with the applied field; however, they kept from total alignment by thermal energy. This scenario is referred to as Paramagnetism [5,10]. Lastly, if the atoms are in close enough contact with each other so that the electrons can be exchanged between neighboring atoms, a cooperative magnetization may occur which spontaneously aligns all atoms in a lattice and creates a synergistic and strong magnetic moment. When the spins between neighboring atoms are aligned parallel, the material is said to be ferromagnetic. In some cases, the spins between neighboring atoms are anti-parallel and are referred to as antiferromagnetic [11]. In antiferromagnetic minerals like Goethite, Lepidocrocite and Oxides like Hematite (Fe_2O_3) and Fe_2TiO_2, the resultant magnetization is small because the opposite spins cancel each other out. Lastly, if two atoms have anti-parallel magnetization of unequal magnitude a resultant magnetization remains in the direction of the stronger magnetic moment and applied field. This is referred to as ferrimagnetism.

Magnetic nanoparticles

In recent years, cancer is one of the most common and severe disorders due to the complexities of diagnosis and treatment of cancer, physicians have faced numerous obstacles. In order to overcome the existing shortcomings in the process of diagnosing and treating cancer, the most common cause of morbidity and mortality; Use of multidisciplinary knowledge in nanotechnology, chemistry, materials and molecular biology can be useful to creating of multifunctional nanoparticles in biomedicine applications for solving these barriers. The particular physical properties of Biomagnetic nanoparticles (BMNPs), special chemical procedure along with their completely biocompatibility into the human bodies, enables them to specific applications consisting of imaging probes for locating and diagnosing cancerous lesions through targeting drug as a therapeutic agents at the same times. The recent attempts of researchers around the world are developing and optimizing the properties of Biomagnetic nanoparticles (BMNPs) along with integration of an expected various applications as BMNPs-based nano-theranostics which have diagnostic and therapeutic multifunctionalities with consider the real-time biological responses to the treatment. So, it always felt this requirement that should be gathering the knowledge of science and engineering of synthesis and application of different BMNPs from diagnostics to treatment in medical field [12].

Iron and iron oxide nanoparticles

Iron Oxide (IO) is a ferromagnetic material with high magnetic moment density (about 220 emu/g) and is magnetically soft. Iron Oxide Nanoparticles (ION) in the size range under 20 nm are super paramagnetic nanstructured materials. Processes leading to synthesis and characterization of Fe and Co nanoparticles have been well documented [13]. Nevertheless, the preparation of nanoparticles consisting of pure iron is a complicated task, because they often contain oxides, carbides and other impurities. A sample containing pure iron as nanoparticles (10.5 nm) can be obtained by evaporation of the metal in an Argon atmosphere followed by deposition on a substrate [14]. When evaporation took place in a helium atmosphere, the particle size varied in the range of 10-20 nm [15]. Relatively, small (100-500 atoms) Fe nanoparticles are formed in the gas phase on vaporization of pure iron by laser [16]. The common chemical methods used for the preparations include thermal decomposition of $FeCO_5$ (the particles so prepared are extremely reactive), reductive decomposition of some Iron (II) salts, or reduction of Iron (III) acetyl acetone; there is a chemical reduction with TOPO capping [17]. Sonochemical synthesis of functionalized amorphous iron have been already developed by several scientists around the world. The method of reducing metal salts by NaBH has been widely used to synthesize iron-containing nanoparticles in organic solvents [18]. Normally, reductive synthesis of Fe nanoparticles in an aqueous solution with $NaBH_4$ yields a mixture including FeB [19,20]. In order to use in biological systems like magnetic resonance imaging (MRI) as contrast agent, biomaterials seperation and Immunoassay require to Well-dispersed colloidal iron. Nevertheless, the stability of iron dispersed in aqueous solution is still considered one of the serious obstacles in the processing of nanoparticles. The phase composition of the obtained nanoparticles was not always determined reliable. The range of specific methods was proposed to prepare nanoparticles of the defined phase composition. Thus, the α-Fe nanoparticles with a body-centered cubic (BCC) lattice and an average size of ~10 nm were prepared by grinding a high-purity (99.999%) Fe powder for 32 h [15,21,22]. Iron oxide magnetic nanoparticles have several extensive applications from industry to medicine like Multi-functional nanostructured coatings (MFNC), water purification catalysts (WPC), edible pigments (EP), gas sensors (GS), optical and electromagnetic devices (OED), magnetic resounancs imagining, seperation, diagnostics and treatments carriers (DTC) [23]. Generaly, physical and chemical properties of Iron Oxide magnetic nanoparticles (IO-MNPs) will change with particle size and degree of hydration which is classified through the size of Super Paramagnetic Irox Oxide Nanoparticles (SPIONs) with large hydrodynamic diameters (greater than 30 nm), Ultra-Small of SPION with small hydrodynamic diameters (less than 30 nm). It means that, increasing the relaxation of pathological tissues and also reducing the vulnerability of healthy tissue along with high saturation magnetization and lowest toxicity shows the highest biocompatibility of SPIONs with human bodies regard to use them in medical applications. Shape and size of UPION depend on synthesis procedure of nanoparticles which ultimately effects the bio-distribution contrast of these particles in medical imaging applications.

Synthesis and characterization of bio-magnetic nanoparticles (BMNPs)

Iron oxide (Fe_3O_4) nanoparticles (ION): Iron Oxide Bio-Magnetic Nanoparticles (IO-BMNPs) as a multifunctional nanostructured materials have an exclusive physical, chemical and biological properties along with several application from different industries to medical fields. Use laboratory equipments and different novel procedure for preparing Fe_3O_4 nanoparticles and coating biocompatible materials on it, has been describing in numerous articles. In this research [24] $FeCl_3$ (0.5 mol/L) and $FeSO_4$ (0.5 mol/L) solutions provided individually and transferred into a three-neck round bottom flask equipped with a mechanical stirrer (magnetic stirrer). Immediately after adding the iron salt solutions, 5 mL $NH_3.H_2O$ (50%, v/v aqueous) was quickly syringed into the flask with stirring. After appearing a black gelatinous, drop of $NH_3.H_2O$ was added into the mixture steadily until PH value's solution reached to 9.0. In order to complete the reaction, the solution was remained in the same state for 30 minutes. Then, the black solution aged at 70°C for 30 min. These Fe_3O_4 nanoparticles were coated through using sodium oleate solution at 80°C for 1h. Eventually, coated Fe_3O_4 nanoparticles (participates) filtered and gathered by external magnetic field, washed with ethanol and deionized water 3 times, thus dried under controlled conditions.

In other way, $FeCl_3.6H_2O$ and $FeSO_4.7H_2O$ were dissolved in deionized water according to a molar ratio of 3:2, and put into a flask. NaOH was slowly dropped into the solution with stirring. When the PH reached 6.5, a black gelatinoids appeared. NaOH was added into the mixture steadily until PH value's solution increased to 13.0. The mixture was stirred with high magnetic intensity for 30 min, thus was aged for 30 min at 80°C and cooled till room temperature. The nanoparticles were filtered and gathered by external magnetic field, washed with ethanol and distilled water 3 times until the PH decreased to 7.0. finally, these Fe_3O_4 nanoparticles were coated by different biocompatible materials. Magnetic Fe_3O_4 Nanoparticles less than 10 nm demonstrated super paramagnetism. Since the magnetization dope vectors of Biomagnetic Nanoparticles (BMNPs) is under the impression of an external magnetic field; when applied magnetics field was absence, BMNP's magnetization dope vectors will be less than normal values. Finally, it couldn't exhibit any overall magnetism. The Fe_3O_4 nanoparticles synthesized by co-precipitation method using $NH_3.H_2O_4$ as catalyst have had higher than saturation magnetization those prepared using NaOH. Shape optimized of Fe_3O_4 nanoparticles may be improved saturation magnetization of those particles. However, the Fe_3O_4 nanoparticles prepared by co-precipitation using NaOH cannot be coated successfully. Recent researches show that diameter of Fe_3O_4 biomagnetic nanoparticles prepared by co-precipitation using $NH_3.H_2O$ in alcohol was the smallest size, meanwhile its agglomeration was intense. Co-precipitation using NaOH can be easily carried out, requires the least time, and has the highest yield. Co-precipitation using $NH_3.H_2O$ in water needs the longest time. Co-precipitation using $NH_3.H_2O$ in alcohol calls for precise control of PH, consumes large quantity of alcohol and has the least yield [25].

Iron oxide core/shell nanoparticles (IOCSN)

Fe_3O_4@ag core/shell nanoparticles: In view of an extraordinary properties of Iron Oxide Biomagnetic Nanoparticles (IO-BMNPs) with smallest size, surface modified (biocompatible coatings), chemical, biological and significant magnetic properties can expect to have multifunctional applications in biomedicine like Drug Delivery (Targeting) systems (DDS/DTS), Magnetic Hyperthermia Treatment (MHT) [26], Magnetic Optical Devices (MOD) [27], Magnetic Resonance Imaging (MRI) [28], immunoassay and sort of that. In order to synthesis coated Iron Oxide magnetic nanoparticles (Fe_3O_4@Ag) through Polyol method, 1.35 g iron (III) chloride hexahydrate ($FeCl_3.6H_2O$) was dissolved in 40 mL polyethylene glycol using an ultrasonic bath to reached acidic PH. After added 3.7 g sodium acetate and 1.0 g polyethylene glycol using magnetic stirrer around 30 min. To achieve a red solution it remained at the same state at 190°C for 16 h. in the next round, the solution cooled down to room temperature, separated with magnet and washed several times with ethanol and distill water. Finally, the black magnetic nanoparticles appeared when it dried at 80°C for 8 h. these IO-MNPs was spherical shaped. Figure 1a, shown silver (Ag) coating procedure of Iron Oxide (Fe_3O_4) magnetic nanoparticles. Use this technique (polyol procedure) due to its saturation magnetization as high as bulk's values and also low coercivity caused by using polyethylene glycol as a seperator and also minimum agglomerated particles that is finally increased magnetic stability. It has had strong enough of magnetization which could be intended to use these nanoparticles in biomedical application mentioned above like magnetic seperators, Hyperthermia treatment by further researches [29].

Fe_3O_4@chitosan core/shell nanoparticles

There are various ways to prepare Fe_3O_4 nanoparticles, which have been reported earlier, such as arc discharge [30], mechanical grinding

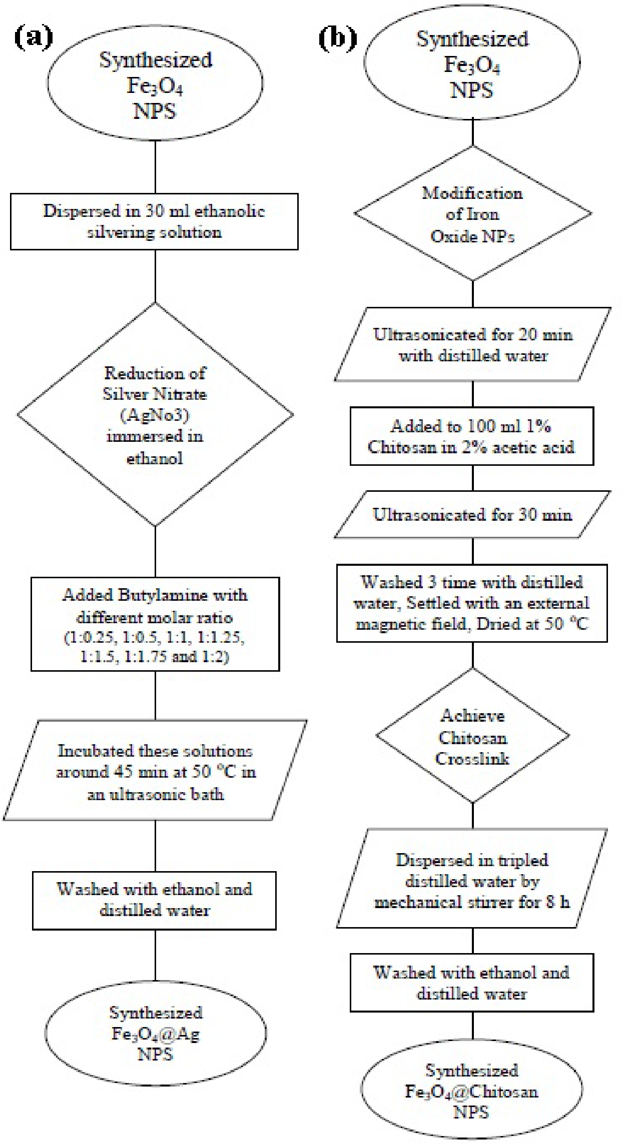

Figure 1: a) Silver and b) Chitosan coatings procedure of Iron Oxide (Fe_3O_4) magnetic nanoparticles.

[31], laser ablation [32], micro emulsions [33], and high temperature decomposition of organic precursors [34]. These methods can be used to prepare magnetite with controllable particle diameters. Since the Chemical Co-precipitations method which is very simple procedure, so cheap, increasing the supply and demand for preparing of well dispersed Fe_3O_4 biomagnetic nanoparticles. So, it's possible to control of IO-MNPs size by various surfactants in this procedure. In these research Articles [34-37], Magnetite nanocrystals were prepared using $FeCl_2.4H_2O$.

In brief, 2 g $FeCl_2.4H_2O$ was dissolved in 30 mL HCl 1 M. To this, 30 mL NaOH 3M was added drop wise with continuous stirring till black precipitate was formed. The precipitate was then washed 2 several times with distilled water till neutral PH was obtained. The precipitate was then separated out using external magnetic field and dried at 100°C. The prepared nanoparticles were further used for the coating procedure. Figure 1b, shown chitosan coating procedure of Iron Oxide (Fe_3O_4) magnetic nanoparticles. The purpose of this work is develope a simple and cheap technique to prepare of Biocompatible Fe_3O_4 magnetic nanoparticles and specify their exact applications in the medical field. In this study, could determined that achieve the stable Fe_3O_4 biomagnetic nanoparticles can use only Iron (II) Cloride ($FeCl_2$) without any other oxidants which are nature polycrystalline. Hence the conventional method is more simplified and made cost-effective in the present work. TEM images showed that the particles are round-shaped having a size 20.573.8 nm and 22.273.4 nm in cases of bare and coated particles respectively. The resulting Fe_3O_4 nanoparticles were super paramagnetic at room temperature with a high saturation magnetization value. CH can be efficiently coated on the surface of Fe_3O_4 nanoparticles using a simple technique of ultrasonication. Cross-linking of amino groups in CH using GLD increases the stability of coating. Potential and DLS measurements of both the particles prove to have higher colloidal stability for the coated nanoparticles which is important in order to use them for in vivo applications. The obtained results from properties study of coated Iron Oxide Biomagnetic Nanoparticles (IO-BMNPs) like particles size and shape, values of saturation magnetization, SAR values, toxicity, cytotoxicity, etc. shown that they can use in magnetic hyperthermia treatment (specially in diagnostic and treatment of cancer).

Biomedical applications of Fe_3O_4 magnetic nanoparticles

Over the past two decades, researchers have been working on synthesis procedure, characterizations and specially multifunctional properties and applications of biomagnetic nanoparticles (BMNPs) in medicine like diagnostics and treatment of various diseases [38-41]. Since the particle size of BMNPs depend on physical and chemical properties it's important to control synthesis procedures. One of the requirements for tissue engineering is design and synthesis of nanostructured scaffold for physically targeting treatment as a local therapeutics like skin, lung, eye and sort of that [2]. Because diameter of cells usually ranges from 2 micron to 10 micron. So, the nano-sized magnetic particles has caused the copacetic applications in medicine [42]. However, biomagnetic nanoparticles (BMNPs) can be use in several *in-vitro* and *in-vivo* application. Till now, have already determined diagnostics and therapeutics practical approaches like magnetic hyperthermia in medicine field. In addition, many biomedical applications include magnetically diagnostics like resonance imaging, targeted delivery and therapies like clinical hyperthermia, magnetically separations like immunomagnetic of cells, have been identified. It is notable that, an extensive researches on different biomagnetic nanostructured materials have been already developed by several scientists around the world. Magnetic nanoparticles use in cancer imaging as a diagnostic devices and therapeutic instrument as targeting drugs entrapped biomaterials to the area of interest. In this case, Identification of the target point will be done by magnetic force along with surface which is bounded with different antibodies as a carrier [43]. The important and significant medical and biological applications of biomagnetic nanoparticles like fluorescent [44] and magnetic imaging as a contrast agents, immunogenes and DNA and gene therapy, pathogenes, phagokinetic and proteins detectors, magnetic fluid hyperthermia, separators and purifications, have already noted in numerous articles [45-60]. In addition, if the biomagnetic nanomaterials (BMNM) to be as the same size of the proteins, can use as a bio susceptibility tagging usefully regard to interact with a biological targets. In this case, they should have biological coatings like amino acids, chitosan, collagen [19], PAA, sugar, Hydroxy apatite and sort of that which can be include antibodies. these nanoparticles are so biocompatible for using in medical applications mentioned above [15-22]. Besides, it's important to use them as magnetic and optical detection techniques which can show fluorescence characteristics. On the other hand, has been develope multifunctional biomagnetic nanoparticles for molecular and cellular imaging as speciall application in the targeted imaging. These magnetic nanoparticles has been composed the nano bio-materials as a core which can assembly or coating by biocompatible materials or nano-layers as a shell which it can modify and surround surfaces of MNPs by nanostructured membrane. Normally, the shape of those particles can be spherical, plate and cylindrical like.

In addition; one of the most important case on synthesize procedure, characterization and applications can be the particle size and their distribution. When control material's properties affected on quantum sized, considering particles size and distribution it's extremly important. It is notable that, in order to develop the fluorescent probes along with the wide range of wavelengths, must be controlled the average of particles size and distribution in the synthesis procedure. Since the core have several multifunctional layers, can use as a biomarker whit combined magnetic and luminescent layers. There are some special kind of nanostructured materials like bio-magnetic nanoparticles which is important to consider the physico-chemical and electro-magnetic properties of nanostructured materials specially MNPs which will be composed at least magnetic element. So, these materials has attracted much interest which has been caused to extend wide range of applications like ferro fluid solutions, magnetic storage devices, bio-sensing application, magnetic power generations and conversion, magnetic controlled drug delivery, magnetic resonance imagining as a contrast agents [61-74]. For biomedical applications, magnetic nanoparticles must (1) have a good thermal stability; (2) larger magnetic moment; (3) be biocompatible; (4) be able to form stable dispersion so the particles could be transported in living system; and (5) well response to AC magnetic fields. The active molecular layer as a bio-inorganic coupler for interacting with biological target tissues should be use in the coating of magnetic nanoparticles include of bio-ceramic like hydroxyapatite or bio-polymers like chitosan [75], antibodies, mono or poly layers of molecules as bio-compatible coatings [76]. Magnetic particles as carriers for therapeutic agents have been used in experimental animals and clinical applications in humans. However, these magnetic nanoparticles have used in multifunctional application (With the compilation of multiple applications at the same-class) like concomitant use of diagnostic imaging with oncological therapeutic. The purpose of most current researches are the feasibility study of synthesise the various kind of biomagnetic nanoparticles (BMNPs) with considering their clinical application specially in musculoskeletal abnormalities like joint capsules, bone, ligaments or removing the existing challenges in the diagnosis and treatment of cancer and sort of that. Biocompatible magnetic nanoparticles in vitro experiments insignificantly influence the cell's survival. Biocompatibility usually caused by chemical surface modifying through applying biological materials or bio-molecules coatings like phospholipids, chitosan and polyvinyl alcohol or also in iron oxide magnetic nanoparticles (IO-MNPs) [77]. One of the widest areas of application is in the non-invasive diagnosis imaging according to tranquility of proton in tissues, which is known as Magnetic Resonance Imaging (MRI) [78]. Upon accumulation in tissues, SIONPs enhance proton relaxation of specific tissues compared with that in surrounding tissues, serving as an MR contrast agent [79]. For in vivo MR imaging applications, SIONPs should have long half-life time in blood circulation for the improved efficiency of detection, diagnosis, and therapeutic management of solid tumors. Because opsonin plasma proteins are capable of interacting with plasma cell receptors on monocytes and macrophages, opsonin absorbed SIONPs will be quickly cleaned by circulating monocytes or fixed macrophages through phagocytosis, leading to elimination of SIONPs from blood circulation. The POEMA-PMAA coated on SIONPs can be used in these particular cases. The smaller the particle and the more neutral and hydrophilic its surface, the longer its plasma half-life [80]. Therefore, the surface of SIONPs has been modified with hydrophilic polymers to prevent absorption of the circulating plasma proteins. The use of contrast agents and tracers in medical imaging has a long history [81-83]. One of the most important challenges about cancer treatment is sustained drug release which has already remained this issue in the world. So, the researchers has been focusing on targeted cancer treatment. Recent reseaches caused to acheive newest method for supporting the conventional cancer treatment like chemotherapy and radiotherapy regard to preventing the resistance of all drugs along with reducing damage to normal tissues in the available therapeutic procedures. In order to make Innovative treatment of cancer should be considered overall concepts and mechanism of molecular biology of cancer. These cases include stem cell, immunoassay and genetic therapy, bacterial antiangiogenic agents, tyrosine kinase receptors and sort of that. In addition, regard to special attention to immunotherapy's method of cancer, it's important to consider some parameters like immunogene therapy and monoclonal antibodies and etc. [84]. Use of monoclonal antibodies have been already established the major revolutions in the pharmaceutical industries and medicine as a biological achievements. There are two different kind of monoclonal antibodies for clinical applications. The first one is toxin MABs which can target the fusion protein of respiratory syncytial virus and the second one is an antitoxin MAbs like raxibacumab and obiltoxaximab which can protect antigen of bacillus anthracis and prevent cell entry of the exotoxins edema factors. Both agents can be used in the prophylaxis of inhalation anthrax. The innovative pharmaceutical treatments obviously require novel modern methods of administration. The possibility of using ferro-fluids for drug localization in blood vessels and in hollow organs is a contemporary task for drug development [85]. Pure magnetic particles are not stable in water-based solutions and suspensions; therefore, they cannot be used for medical application without biocompatible coating. The choice of polymers for magnetic nanoparticles coating to prevent them from adhering toxicity occurred to be not an easy one-step task, because these compositions should satisfy both the requirements of biocompatibility and biodegradability. In the recent years, have been conducted several studies on drug delivery systems, particularly hydrogels systems based polyacrylic acid (PAA) has concentrated on backbone which is recognized as an extraordinary properties such as very high ability of absorbance and creating an interconnected polymeric network through the existing hydrogen bonds. So, these materials are considered as an excellent bio-adhesives which can release their encapsulated drugs slowly during the time. The interaction of nanoparticles with human cell has been a topic of profound interest among researchers, as they are thought to hold the key for future developments in the fields of biodiagnostic and therapeutic, among other fields. The range of nanoparticles between 50-200 nm has been deemed most effective for uptake in cells and this has opened new avenues of applications [86]. Gene is essentially the functional component of the DNA and incorporation of a DNA sequence into another both *in-vitro* and *in-vivo* is a common technique of genetic engineering. Gold nanoparticles are most commonly used for the detection of DNA and spectroscopic and electrophoretic technique has been applied to evaluate the interaction of Au with calf thymus DNA [87]. Gold coated magnetic NPs (Co and Fe_3O_4) core/shell nanoparticles and their interaction with thiolated DNA was also studied Reduction of Au salt overpre formed magnetic cores resulted in composite type NPs. Core/shell NPs with Co gave Co–Au alloy type deposition shell; while in Fe_3O_4 core NP has distinct magnetite and gold phases. In general, functionalized magnetic NPs with Au shell facilitates thiol mediated conjugation of DNA on nanoparticle's surface. Mesoporous silica nanoparticle containing Fe_3O_4 inner core and silica shell has been prepared to study the DNA adsorption and desorption process and it has the added advantage of separation by the application of external magnetic field [88]. One of the best application of magnetic mesoporous silica nanoparticle (M-MSN) is the manipulation of adsorption and desorption of DNA which can be use in separate it from solution simply through applying an external magnetic field [89-100]. Furthermore, there are multifunctional applications of biomagnetic nanoparticles which by relying on an extraordinary properties has caused to develop and improve multitasking processes in clinical diagnosis and treatment like MRI quality, drug delivery, malignant cells therapy (magnetic fluid hyperthermia) and sort of that. One of the novelty methods for treating various cancer (malignant cells) is the magnetic fluid hyperthermia which the damaged part of body tissues exposed to high temperature around 42°C without harm to healthy tissues. In this procedure, will be used the external AC magnetic field for local heating which is depend on physiological responses. In addition, one the most important case for controlling some different actions is amount of biomagnetic nanoparticles (BMNPs) which is depend on the large extent on the method of administration. For instance, the direct injection will be passed a significant amount of BMNPs to the tumor situation is a reasonable hypothesis to use 4-10 mg of magnetic nanoparticles in each cm^3 of tumor tissues which appropriate for applying different kind of hyperthermia in human patients [89].

There are different methods for doing hyperthermia. These include: Hyperthermia localized surface, Part of the deep body hyperthermia, Hyperthermia inside the tumor cavity and Whole body hyperthermia. When hyperthermia performed at 45°C to cancers immunotherapy as a simulation of soft and hard response of helathy and damaged tissues. In other case, when hyperthermia performed at 55°C to cancers treating along with kill malignant cells directly [89,90]. With this consideration, one of most effective challenges facing researchers and physicians in that area is localized temperature control in a way that without detrimental effects on healthy tissue leading to the death of cancer cells. So, hyperthermia cancer therapy by using biomagnetic nanoparticles (BMNPs) has already considered as one of the new and promising treatment in this area, recently.

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Core/shell Nanoparticles	Surface Modification	Application
Fe_3O4/SiO_2	Fluorecsein Isothiocyanate dye, Chelated	MRI, Amperometric sensor
Fe_3O_4/PAH/Au		
Fe_3O_4/Chitosan or Oleic Acid	Hemoglobin for H_2O_2 detection/Enqyme, Nucleotides	MRI, Optical Imaging and Drug Delivery
Fe_3O_4/Silica/Au		
Fe_2O_3/PEG or PEI		MRI
Fe_2O_3/2Methacryloyloxyethyl		X-Ray
Fe_2O_3/SiO_2/Au	PEG, Amino Acid, FTIC, Antibody Conjugation	MRI, Bioabeling Optical Imaging, Drug Delivery
$Fe_3O_4/CaCo_3$/PMMA/MnO	PEG, Glucuronic Acid	MRI, Cell Labeling
Fe Oxide or Fe_3O_4/Au	DNA ligase enzyme	Piezometric and Optic sensor
Fe_3O_4 embedded in Poly (D-lactid)/PLA/PVP		MRI, Ultrasound

Table 1: Biomedical Application of different Fe_3O_4 nanoparticles.

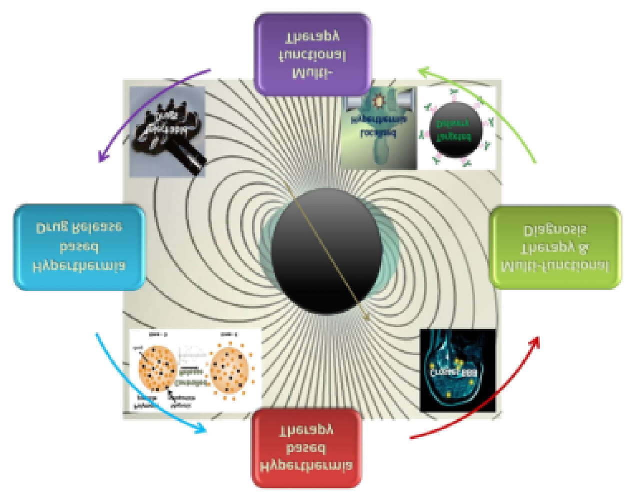

Figure 2: A schematic representation of some of the unique advantages of magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery.

The mechanism of hyperthermia cancer therapy is based on an increasing the localized temperature caused by applying an external magnetic field on Bio-nanoparticles. In this method, In order to achieve biomagnetic nanoparticles to target tissues can use through directly injection. Besides, generating an external magnetic field is possible by applying alternative current (AC) of copper coil which caused to creation heat by various mechanism. In this categories, It should be noted that the overall concept and understanding of biocompatible magnetic materials which used in hyperthermia treatment of cancer has been proven by Gilchrist and et. al. in 1957. Besides, used γ-Fe_2O_3 with under 100 nanometer in particle size through 1.2 MHz magnetic field for applying localized temperature at target tissues. Figure 2 shown a schematic representation of some of the unique advantages of biomagnetic nanomaterials (BMNPs) for magnetic fluid hyperthermia cancer treatment and also targeted drug delivery. Due to develop and improve of synthesis procedure and characterization of nanostructred magnetic particles like control shape and size, biocompatible nano coating, generation safe of an external magnetic field and sort of that [92,93]. First clinical magnetic hyperthermia study reported by Jordan and et. al. in 2007. It showed that aminosilane-coated superparamagnetic iron oxide nanoparticles could be used in brain tumors therapy safely [94-100].

Conclusion

Diagnosis of diseases is very important in health care, which in turn not only enhance the effectiveness of medical treatment but also save human life where early diagnosis is crucial. The application of nanoparticles in the realm of biomedical engineering has ushered in a new era for the development for novel contrast agent and drug delivery vehicle, which has the potential to revolutionize in the area of health care. Biomedical application of Fe_3O_4 magnetic nanoparticles showed in Table 1. The idealistic concept of a single platform for drug delivery to its monitoring of drug-release seems to be feasible in the near future, because of the recent advances in the application of novel nanomaterial in this field. The versatility of nanoparticles has been applied in various studies related to disease diagnostics, early detection studies, and better contrast agents for improved imaging techniques. The development of new drug delivery vehicles has not only reduced the payload of the drugs but has also improved the efficacy of the drug in the system because of improved bio- and cyto-compatibility along with increased circulation time. Thus, the advent of nanoparticles has influenced all the spheres pertaining to medical biotechnology and biomedical engineering, improving and enhancing the already existing techniques along with the experimentation of new and advanced techniques for drug delivery and its monitoring. In this article, two general fields of applications namely diagnosis (analytical-biosensor/nucleotide interactions or visual-bioimaging) and transportation (drug delivery and gene transfection) are discussed. The review clearly shows, except bioimaging, that most other areas of bio-application are concentrated on nanoparticles of noble metals or magnetic materials.

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