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"STUDIES ON NANOPARTICLE BASED MAGNETITE (FE_3O_4) NANOPARTICLES & IT'S APPLICATIONS IN BIOMEDICAL SCIENCES"

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Abstract :

The main attentions of this paper are focused on magnetic features and applications of nanoparticles which are less considered. In previous years, many review articles have been presented and published about applications of magnetic nanoparticles by some researchers with different expertise faculty such as chemistry, biology, medicine, pharmacology, and materials science and engineering, the majority of these reviews are insufficiently comprehensive in all related topics like magnetic aspects of process Accordingly, the review article contains essential magnetic properties and their synthesis techniques, surface modification processes, and applications of magnetic nanoparticles. In this review, it is attempted to carry out the inclusive surveys on importance of magnetic nanoparticles and especially magnetite ones and their required conditions for appropriate performance in bioapplications.

INTRODUCTION

A nanoparticle or ultrafine particle is usually defined as a particle of matter that is between1 and 100 nanometres (nm) in diameter. The term is sometimes used for larger particles, up to 500 nm, or fibers and tubes that are less than 100 nm in only two directions. At the lowest range, metal particles smaller than 1 nm are usually called atom clusters instead.

Definition

ISO

According to the International Standards Organization (ISO) technical specification 80004, a nanoparticle is an object with all three external dimensions in the nanoscale, whose longest and shortest axes do not differ significantly, with a significant difference typically being a factor of at least 3.

IUPAC

In its 2012 proposed terminology for biologically related polymers, the IUPAC defined a nanoparticle as "a particle of any shape with dimensions in the 1×10^{-9} and 1×10^{-7} m range". This definition evolved from one given by IUPAC in 19

Common usage :

"Nanoscale" is usually understood to be the range from 1 to 100 nm because the novel properties that differentiate particles from the bulk material typically develop at that range of sizes. For some properties, like transparency or turbidity, ultrafiltration, stable dispersion, etc., substantial changes characteristic of nanoparticles are observed for particles as large as 500 nm. Therefore, the term is sometimes extended to that size range. The terms colloid and nanoparticle are not interchangeable. A colloid is a mixture which has particles of one phase dispersed or suspended within an other phase. The term applies only if the particles are larger than atomic dimensions but small enough to exhibit Brownian motion, with the critical size range (or particle diameter) typically ranging from nanometers (10^{-9} m) to micrometers (10^{-6} m). Colloids can contain particles too large to be nanoparticles, and nanoparticles can exist in non-colloidal form, for examples as a powder or in a solid matrix.

Nanoclusters are agglomerates of nanoparticles with at least one dimension between 1 and 10 nanometers and a narrow size distribution. Nanopowders are agglomerates of ultrafine particles, nanoparticles, or nanoclusters. Nanometer-sized single crystals, or single-domain ultrafine particles, are often referred to as nanocrystals.

History

Natural occurrence

Nanoparticles are naturally produced by many cosmological, geological, meteorological, and biological processes. A significant fraction (by number, if not by mass) of interplanetary dust, that is still falling on the Earth at the rate of thousands of tons per year, is in the nanoparticle range; and the same is true of atmospheric dust particles. Many viruses have diameters in the nanoparticle range.

Pre-industrial technology

Nanoparticles were used by artisans since prehistory, albeit without knowledge of their nature. They were used by glassmakers and potters in Classical Antiquity, as exemplified by the Roman Lycurgus cup of dichroic glass (4th century CE) and the lusterware pottery of Mesopotamia (9th century CE).The latter is characterized by silver and copper nanoparticles dispersed in the glassy glaze.

19th century

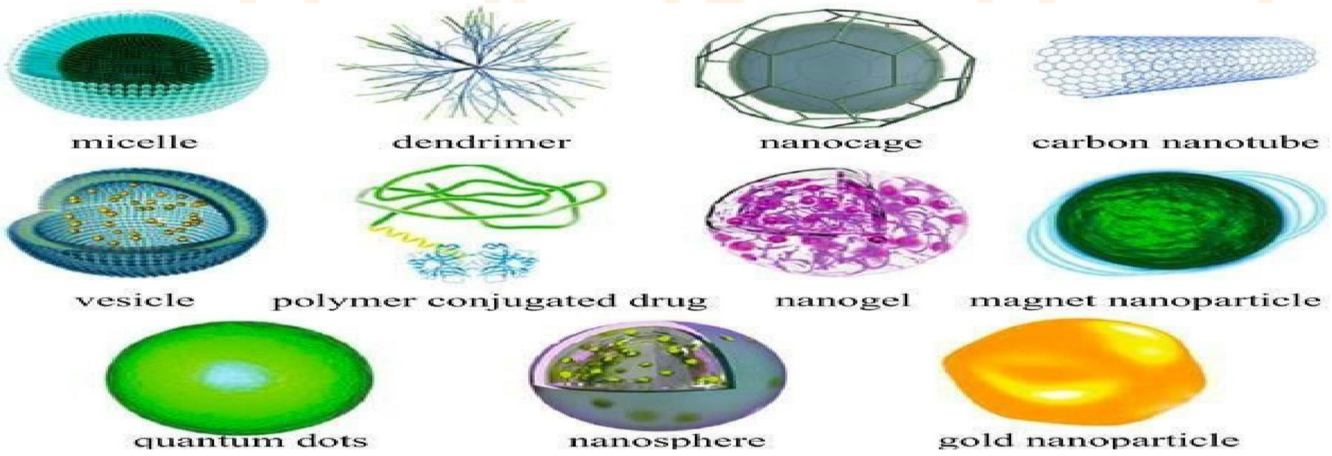
Michael Faraday provided the first description, in scientific terms, of the optical properties of nanometer-scale metals in his classic 1857 paper. In a subsequent paper, the author (Turner) points out that: "It is well known that when thin leaves of gold or silver are mounted upon glass and heated to a temperature that is well below a red heat (~500 °C), a remarkable change of properties takes place, whereby the continuity of the metallic film is destroyed. The result is that white light is now freely transmitted, reflection is correspondingly diminished, while the electrical resistivity is enormously increased.

20th century

In the 1970s and 80s, when the first thorough fundamental studies with nanoparticles were underway in the United States (by Granqvist and Buhrman) and Japan (within an ERATO Project), researchers used the term ultrafine particles. However, during the 1990s, before the National Nanotechnology Initiative was launched in the United States, the term nanoparticle had become more common.

Morphology and structure

The shapes of nanoparticles may be determined by the intrinsic crystal habit of the material, or by the influence of the environment around their creation, such as the inhibition of crystal growth on certain faces by coating additives, the shape of emulsion droplets and micelles in the precursor preparation, or the shape of pores in a Nanoparticles occur in a great variety of shapes of nanocage, nanotubes, nanospheres, magnet nanoparticle. which have been given many informal names such as nanospheres, nanorods, nanochains, nanostars, nanoflowers, nanoreefs, nanowhiskers, nanofibers, and nanoboxes surrounding solid matrix. Some applications of nanoparticles may require specific shapes, as well as specific sizes or size ranges.



Variations :

Semi-solid and soft nanoparticles have been produced. A prototype nanoparticle of semi- solid nature is the liposome. Various types of liposome nanoparticles are currently used clinically as delivery systems for anticancer drugs and vaccines.

The breakdown of biopolymers into their nanoscale building blocks is considered a potential route to produce nanoparticles with enhanced biocompatibility and biodegradability. The most common example is the production of nanocellulose from wood pulp. Other examples are nanolignin, nanchitin, or nanostarches.

Nanoparticles with one half hydrophilic and the other half hydrophobic are termed Janus particles and are particularly effective for stabilizing emulsions. They can self-assemble at water/oil interfaces and act as Pickering stabilizers.

Hydrogel nanoparticles made of N-isopropylacrylamide hydrogel core shell can be dyed with affinity baits, internally. These affinity baits allow the nanoparticles to isolate and remove undesirable proteins while enhancing the target analytes.

Properties of Nanoparticle

Large area/volume ratio

A bulk material should have constant physical properties (such as thermal and electrical conductivity, stiffness, density, and viscosity) regardless of its size. However, in a nanoparticle, the volume of the surface layer (the material that is within a few atomic diameters of the surface) becomes a significant fraction of the particle's volume; whereas that fraction is insignificant for particles with diameter of one micrometer or more.
1 kg of particles of 1 mm3 has the same surface area as 1 mg of particles of 1 nm3
The properties of a material in nanoparticle form are usually very different from those of the bulk material even when divided into micrometer-size particles. A number of causes contribute to that effect.

Mechanical Properties

The reduced vacancy concentration in nanocrystals can negatively affect the motion of dislocations, since dislocation climb requires vacancy migration. In addition, there exists a very high internal pressure due to the surface stress present in small nanoparticles with high radii of curvature. This causes a lattice strain that is inversely proportional to the size of the particle, also well known to impede dislocation motion, in the same way as it does in the work hardening of materials. For example, gold nanoparticles are significantly harder than the bulk material. Furthermore, the high surface-to-volume ratio in nanoparticles makes dislocations more likely to interact with the particle surface. In particular, this affects the nature of the dislocation source and allows the dislocations to escape the particle before they can multiply, reducing the dislocation density and thus the extent of plastic deformation.

Interfacial layer

For nanoparticles dispersed in a medium of different composition, the interfacial layer — formed by ions and molecules from the medium that are within a few atomic diameters of the surface of each particle — can mask or change its chemical and physical properties.Indeed, that layer can be considered an integral part of each nanoparticle.

Solvent affinity :

Suspensions of nanoparticles are possible since the interaction of the particle surface with the solvent is strong enough to overcome density differences, which otherwise usually result in a material either sinking or floating in a liquid.

Melting point depression :

A material may have lower melting point in nanoparticle form than in the bulk form. For example, 2.5 nm gold nanoparticles melt at about 300 °C, whereas bulk gold melts at 1064°C.

Quantum mechanics effects

Quantum mechanics effects become noticeable for nanoscale objects.They include quantum confinement in semiconductor particles, localized surface plasmons in some metal particles, and superparamagnetism in magnetic materials. Quantum dotsarenanoparticles of semiconducting material that are small enough (typically sub 10 nm or less) to have quantized electronic energy levels.

Quantum effects are responsible for the deep-red to black color of gold or silicon nanopowders and nanoparticle suspensions. Absorption of solar radiation is much higher in materials composed of nanoparticles than in thin films of continuous sheets of material. In both solar PV and solar thermal applications, by controlling the size, shape, and material of the particles, it is possible to control solar absorption.

Core-shell nanoparticles can support simultaneously both electric and magnetic resonances, demonstrating entirely new properties when compared with bare metallic nanoparticles if the resonances are properly engineered. The formation of the core-shell structure from two different metals enables an energy exchange between the core and the shell, typically found in up converting nanoparticles and down converting nanoparticles, and causes a shift in the emission wavelength spectrum.

Diffusion across the surface

The high surface area of a material in nanoparticle form allows heat, molecules, and ions to diffuse into or out of the particles at very large rates. The small particle diameter, on the other hand, allows the whole material to reach homogeneous equilibrium with respect to diffusion in a very short time. Thus many processes that depend on diffusion, such as sintering can take place at lower temperatures and over shorter time scales.

Ferromagnetic and ferroelectric effects:

The small size of nanoparticles affects their magnetic and electric properties. For example, while particles of ferromagnetic materials in the micrometer range are widely used in magnetic recording media, for the stability of their magnetization state, those smaller than 10 nm can change their state as the result of thermal energy at ordinary temperatures, thus making them unsuitable for that application.

Coatings :

Semiconductor nanoparticle (quantum dot) of lead sulfide with complete passivation by oleic acid, oleyl amine and hydroxyl ligands (size ~5nm)

Nanoparticles often develop or receive coatings of other substances, distinct from both the particle's material and of the surrounding medium. Even when only a single molecule thick, these coatings can radically change the particles' properties, such as and chemical reactivity, catalytic activity, and stability in suspension.

Applications of Nanoparticles in biology and medicine:

Cancer therapy

Photodynamic cancer therapy is based on the destruction of the cancer cells by laser generated atomic oxygen, which is cytotoxic. A greater quantity of a special dye that is used to generate the atomic oxygen is taken in by the cancer cells when compared with a healthy tissue. Hence, only the cancer cells are destroyed then exposed to a laser radiation.

Unfortunately, the remaining dye molecules migrate to the skin and the eyes and make the patient very sensitive to the daylight exposure. This effect can last for up to six weeks.

To avoid this side effect, the hydrophobic version of the dye molecule was enclosed inside a porous nanoparticle . The dye stayed trapped inside the Ormosil nanoparticle and did not spread to the other parts of the body. At the same time, its oxygen generating ability has not been affected and the pore size of about 1 nm freely allowed for the oxygen to diffuse out.

Multicolour optical coding for biological assays :

The ever increasing research in proteomics and genomic generates escalating number of sequence data and requires development of high throughput screening technologies.

Realistically, various array technologies that are currently used in parallel analysis are likely to reach saturation when a number of array elements exceed several millions. A

three-dimensional approach, based on optical "bar coding" of polymer particles in solution, is limited only by the number of unique tags one can reliably produce and detect.

Single quantum dots of compound semiconductors were successfully used as a replacement of organic dyes in various bio-tagging applications . This idea has been taken one step further by combining differently sized and hence having different fluorescent colours quantum dots, and combining them in polymeric microbeads . A precise control of quantum dot ratios has been achieved. The selection of nanoparticles used in those experiments had 6 different colours as well as 10 intensities. It is enough to encode over 1 million combinations. The uniformity and reproducibility of beads was high letting for the bead identification accuracies of 99.99%.

Manipulation of cells and biomolecules

Most of the magnetic particles studied so far are spherical, which somewhat limits the possibilities to make these nanoparticles multifunctional. Alternative cylindrically shaped nanoparticles can be created by employing metal electrodeposition into nanoporous alumina template . Depending on the properties of the template, nanocylinder radius can be selected in the range of 5 to 500 nm while their length can be as big as 60 µm. By sequentially depositing various thicknesses of different metals, the structure and the magnetic properties of individual cylinders can be tuned widely.

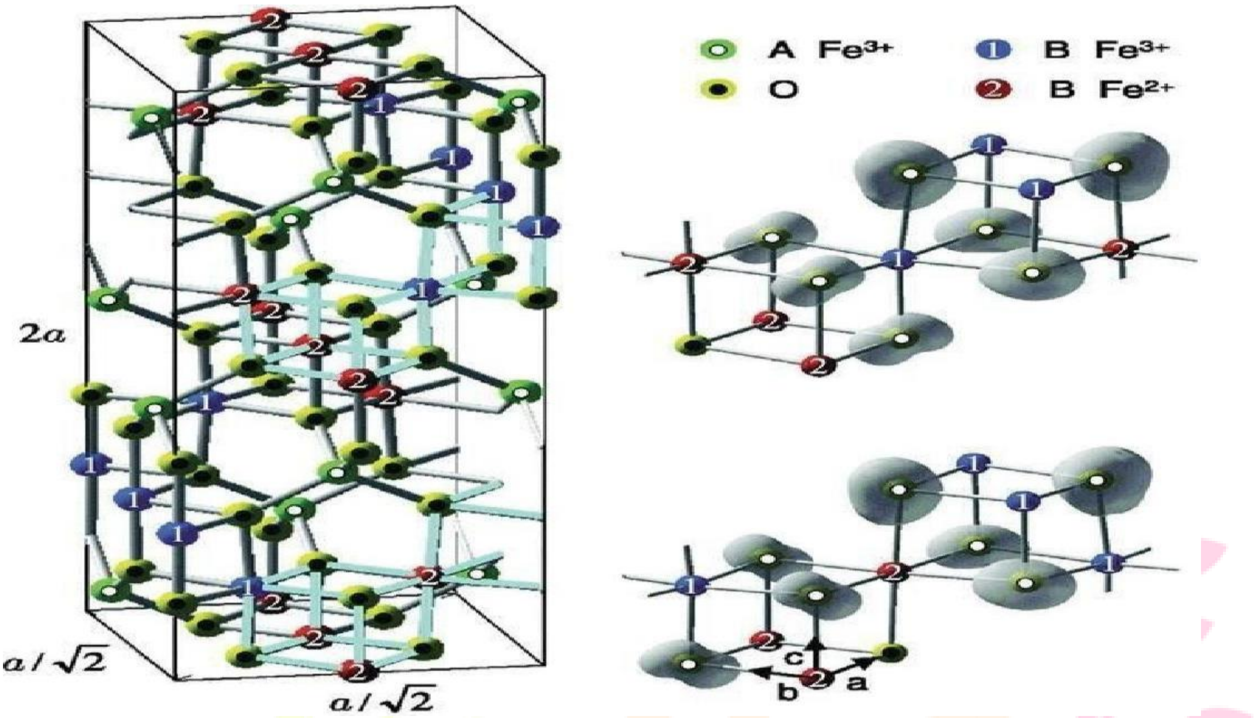
As surface chemistry for functionalisation of metal surfaces is well developed, different ligands can be selectively attached to different segments. For example, porphyrins with thiol or carboxyl linkers were simultaneously attached to the gold or nickel segments respectively. Thus, it is possible to produce magnetic nanowires with spatially segregated fluorescent parts. In addition, because of the large aspect ratios, the residual magnetisation of these nanowires can be high. Hence, weaker magnetic field can be used to drive them. It has been shown that a self- assembly of magnetic nanowires in suspension can be controlled by weak external magnetic fields. This would potentially allow controlling cell assembly in different shapes and forms. Moreover, an external magnetic field can be combined with a lithographicallydefined magnetic pattern ("magnetic trapping").

Protein detection

Gold nanoparticles are widely used in immunohistochemistry to identify protein-protein interaction. However, the multiple simultaneous detection capabilities of this technique are fairly limited. Surface-enhanced Raman scattering spectroscopy is a well-established technique for detection and identification of single dye molecules. By combining both methods in a single nanoparticle probe one can drastically improve the multiplexing capabilities of protein probes.Proteins are the important part of the cell's, machinery and structure, and understanding their functionalities is extremely important for further progress in human being. The group of Prof. Mirkin has designed a sophisticated multifunctional probe that is built around a 13 nm gold nanoparticle. The nanoparticles are coated with hydrophilic oligonucleotides containing a Raman dye at one end and terminally capped with a small molecule recognition element (e.g. biotin). Moreover, this molecule is catalytically active and will be coated with silver in the solution of Ag(I) and hydroquinone. After the probe is attached to a small molecule or an antigen it is designed to detect, the substrate is exposed to silver and hydroquinone solution. A silver-plating is happening close to the Raman dye, which allows for dye signature detection with a standard Raman microscope. Apart from being able to recognise small molecules this probe can be modified to contain antibodies on the surface to recognise proteins. When tested in the protein array format against both small molecules and proteins, the probe has shown no cross-reactivity.

Commercial exploration

Most of the pharmaceutical companies are developing pharmaceutical applications, mainly for drug delivery. Several companies exploit quantum size effects in semiconductor nanocrystals for tagging biomolecules, or use bio-conjugated gold nanoparticles for labelling various cellular parts. A number of companies are applying nano-ceramic materials to tissue engineering and orthopaedics. Some of the companies that are involved in the development and commercialisation of nanomaterials in biological and medical applications are listed below. The majority of the companies are small recent spinouts of various research institutions. Although not exhausting, this is a representative selection reflecting current industrial trends.



Content :

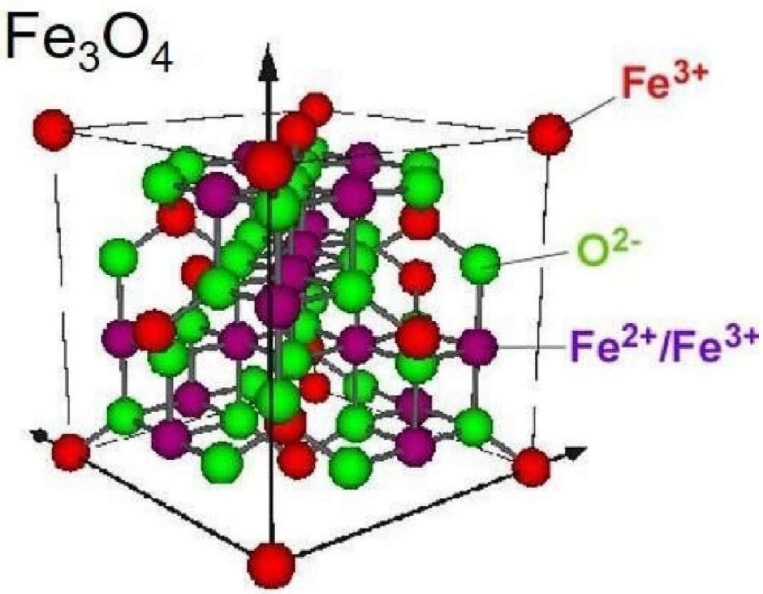
Fe_3O_4 structure

Crystal Structure

For the primary time, the magnetite crystal structure had been studied in 1915 as one of the first mineral structures evaluated through X-ray diffraction method by Bragg and Nishikawa. In 1979, Hill et al. found that the magnetite structure is a reverse spinel ($MgAl_2O_4$) . The unit cell of magnetite is face centered cubic and contains 32 close packed oxygen ions, crystallized in 8 formula units per unit cell of space group with structural parameter equal to 0.839 nm . Simultaneously, the spinelstructureof magnetite includes both Fe II and Fe (III) ions that are located at two sublattice sites with tetrahedral and octahedral coordination according to special order . The Fe (III) ions completely occupy the eight tetrahedral sites and are randomly distributed in octahedral sites with Fe (II) ions . In fact, the tetrahedral sites only contain Fe ions while the octahedral sites apply both of Fe (III) and Fe (II) ions . Although in normal magnetite structure with stiochiometric formula of , the ratio of is equal to 0.5 sometimes the Fe (II) ions can be completely/partially substituted with other divalent metal ions by change of the unit cell length parameter , which caused formation of metal ferrites . In the magnetite unit cell, the atomic position parameters of Fe(I), Fe(II) (16d), and O (32e) atoms are “8a, 0.1250, 0.1250, 0.1250,” “16d, 0.5000, 0.5000, 0.5000,” and “32e, 0.2549,0.2549, 0.2549,” respectively . The polyhedral and ball models of magnetite crystal structure are shown in Figure

Magnetite Nanoparticles

Magnetite is the one of iron oxides known as an oldest magnetic material and also called black iron oxide, magnetic iron ore, and loadstone . Magnetite mineral crystallized with Fe3O4 chemical formula in spinel structures can exhibit strongest magnetism among other phases of iron oxides. Typically, the natural magnetite with density of 5.2 g/cm3 can be found as fine grains in sedimentary rocks with hardness of 5.5 to 6.5 in Mohs scale.



The polyhedral and ball models of magnetite crystal structure.

Since the magnetic spins of octahedral and tetrahedral sites are opposite in direction and create two sublattice sites, thus, based on these two sublattice directions, the magnetite structure is ferrimagnetic . Various exchange interactions can occur between iron ions in both intra- and intertetrahedral and octahedral sites due to presence of these different crystal sites . In addition, in the magnetite structure, the Fe-O bonds length can be calculated based on the fractional atomic position of oxygen atoms ((O)) and lattice parameter, according to valence sum rules . Hence, these bonds lengths in tetrahedral and octahedral sites are equal to and , respectively, while for Fe_3O_4.

Superparamagnetic Properties

In 1930, Frenkel and Dorfman offered a theory about the change of magnetic structures during the decrease of particle size. They believed the ferromagnetic materials can transfer from multidomains to single-domain state byparticle resizing to nanoscales. In the subsequent researches, this idea gradually developed and finally in the 1960s, the superparamagnetism theory was suggested. Therefore, two phenomena occur in ferromagnetic nanoparticles; the first one is the creation of single-domain structure and the other one is the development of superparamagnetic behavior.

Magnetic Properties

The various materials can show the wide range of magnetic behaviors such as paramagnetic, ferromagnetic, ferrimagnetic, antiferromagnetic, and super paramagnetic properties. Generally, in paramagnetic materials, the magnetic moments are randomly aligned while the external magnetic field is absent; thereby the overall net magnetization is zero. On the other hand, under the magnetic field, these moments are partially or even completely oriented to the field direction and indicated the sensitive net magnetization. In the ferromagnetic crystals, all of the magnetic moments are coupled to each other, are aligned to the applied external field, and maintained this parallel order even after elimination of field.

The magnetic materials with the similar antiparallel moments that show no net magnetization are called antiferromagnetic. Moreover, in the ferrimagnetic materials, although the alignments of moments are antiparallel, the net magnetization is not equal to zero because the vectors lengths of these moments are different.

The statement of moment orientation in different magnetic structures such as paramagnetic, ferromagnetic, ferrimagnetic, and antiferromagnetic structures. As we know, based on the electronic configuration of iron atoms, there are four unpaired electrons in their “3d” orbitals. Accordingly, the magnetic behaviors of iron compounds are caused by activity of these itinerant electrons as exchange (between magnetic atoms like Fe-Fe), double exchange (between atoms of same element with different valences like Fe2+-Fe3+), and super exchange (between magnetic and nonmagnetic atoms like Fe-O) processes in the atomic energy bands range. The broadening of these ranges depends on the interatomic separation between the atoms, so that the width of bands is strongly reduced by increasing interatomic separation values.

Synthesis Methods :

Historically, for the first time in the 1960s, the ferrofluid systems had been provided based on use of Fe3O4 particles by NASA researchers. According to literature, magnetite nanoparticles can be synthesized by different physical andchemicalmethods suchascoprecipitation, microemulsion, sol gel, thermal decomposition, hydrothermal and sonochemical methods , and mechanical alloying technique . Commonly, the chemical techniques have more advantages than physical ones, such as the possibility of synthesizing new materials with suitable properties, and more chemical homogeneity owning to combination of precursors in the molecular scales; thus the nanosize materials are directly produced. In the following, the widespread synthesis methods of magnetite nanoparticles are studied.

Coprecipitation

Due to simplicity and mass production ability in industrial scale, co-precipitation is the most common method for synthesis of magnetite nanoparticles. In this technique, the initial solution including $Fe^{2+}$and Fe^{3+} salts is reduced with alkaline solution like NaOH and $NH_3 \cdot H_2O$. Usually, the reaction is designed with Fe^{2+}/Fe^{3+} ratio equal to 1/2 that is sometimes partially varied in order to compensate for oxidation probability . In general, coprecipitation method is applied in two parts such as precipitation of iron hydroxides and formation of iron ferrite.

According to literature, although the synthesized particles by co-precipitation have higher crystallinity degree than other methods, the size of these particles is relatively larger with wide size distribution which is not appropriate to use in many bioapplications. In order to improve these conditions, employment of experiment design methods and some theoretical models like Avrami model can be useful to control kinetic parameters such as temperature, pH, mixing rate, and integration rate of initial materials. For example, the increasing of mixing rate can lead to faster nucleation and thereby formation of smaller particles.

Microemulsion

Microemulsion is the novel method to synthesize different kinds of nanoparticles such as organic, metallic, and nonorganic nonmetallic materials that has attracted much interest in recent years. Microemulsions, especially the reverse micelle methods (water in oil), are the appropriate techniques of magnetic nanoparticles formation due to large interfacial area, low interfacial tension, thermodynamic stability of immiscible solutions, and unique properties. In these systems, owing to microemulsion dynamic and Brownian motion of micelles, they can collide with each other and lead to intermicellar exchange that is the main mechanism of the syntheses reactions. Moreover, considering that the reactions are carried out in the nanoreactores called micelle, the size distribution of particles can be controlled in suitable narrow range. According to literature, in order to synthesize magnetite nanoparticles by microemulsion, some parameters are impressive such as type of precursors, reaction temperature and time, and especially amounts ratio of water/oil/surfactant phases. In fact, the relationships between these amounts have been represented as the ternary phase diagrams that can be very useful to control the final properties like size, distribution, morphology, crystallinity, and magnetic properties of particles when coupled with temperature effect.

3] *Hydrothermal*

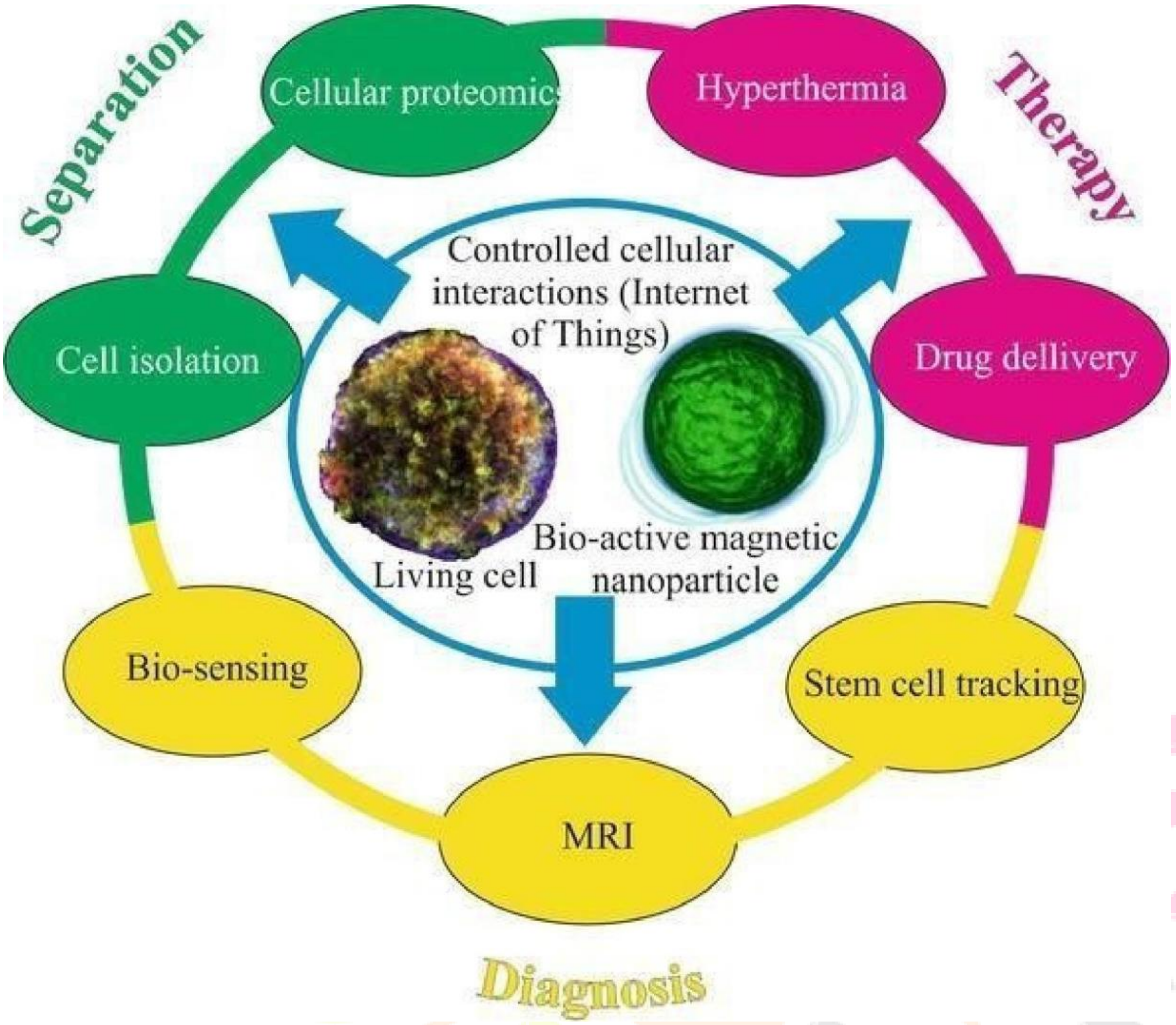
Among various processes to synthesize magnetite nanoparticles, the hydrothermal technique has significant ability of particles fabrication with very narrow size distribution. The main reason of these properties is raised from use of high temperature in hydrothermal reaction that can affect nucleation kinetics. Furthermore, for Fe_3O_4 synthesis by this method, sulfates and chlorides are used as cations source and water or ethanol is usually used as solution medium; thus, hydrothermal method is known as an environment friendly process. Due to employment of high temperature and particularly pressure in hydrothermal method, the relatively complex equipment like autoclave is required. Accordingly, some researchers have attempted to modify process, recently. For instance, Ahmadi et al. revealed modified systems to magnetite nanoparticles synthesis at low temperatures (140°C) without having to autoclave and have studied kinetics of reaction, although their magnetic properties are comparatively inadequate in short reaction time (below 2 h). In addition, the major drawback of hydrothermal technique is the long time consuming reaction at any given temperatures and thus the amounts of fabricated yields are low. In order to overcome this problem, one of the best approaches is the microwave assistant hydrothermal method that can improve the kinetics of reaction up to two orders of amount by localized heating of solution. Komarneni et al. have synthesized the magnetite nanoparticles with suitable magnetic properties by this process. More details about method have been found in Sreeja and Joy researches.

Thermal Decomposition

Thermal decomposition is one of the most effective synthesis methods of magnetite particles. The main advantages of this method include excellent particle size controllability with narrow size distribution and high crystallinity of productions. Accordingly, the particles synthesized by thermal decomposition are very appropriate candidates for bioapplications like targeted drug delivery, magnetic hyperthermia, and MRI contrast agents.

The base of thermal decomposition method is funded on the nucleation and growth steps of magnetite particles from initial materials in the high temperature processes. The precursors of this process are categorized into two classes, for example, the organometallic components nitrosophenylhydroxylamine of iron (such as $Fe(acetylacetonate)_3$, $Fe(N\text{-})_3$,or/and $Fe(CO)_5$) and the organic surfactant and solvents (such as fatty acid, steric acid, oleic acid, and hexadecylamine).

Thermal decomposition process includes two steps: the first one is the nucleation of initial seeds by reaction of precursors and the next level is the propagation of nucleated seeds under reflux reaction at different temperatures and times. Typically, the thermal decomposition method occurs from two approaches including the addition of hot solvents to reaction medium that can lead to fast nucleation process and the heating up of the reaction mixture up to decomposition temperatures. In the last approach, due to the relatively slow nucleation, the homogeneity of particles size and morphology is less than the first one. The main disadvantages of this method include high required temperature (up to 300°C) for reflux process, complexity of long time consuming reaction, and depending on nonpolar organic solvents. In recent years, many efforts have been focused on the modification of this process to achieve higher stability and magnetic properties of synthesized particles.



Biomedical Applications of Magnetite (Fe_3O_4) Nanoparticles

MNPs have a great potential in the biomedical field (i.e., diagnosis). Given their nano-scaled size, they are very compatible with cells. The biomedical application of MNPs is enforced with strict parameter specifications, including chemical composition; flexibility and hardness; granulometry homogeneous crystal structure; pore volume; adsorption, magnetic, pharmacological, and physical properties; size; solubility; structure and surface area; and uniformity. The parameters determining biocompatibility are the characteristics of magnetically reactive MNPs. A high saturation magnetisation value enables MNPs to mobilise within the blood stream in the presence of an external magnetic field until they reach close enough to the targeted pathologic tissues. The biomedical applications of MNPs can be divided on the basis of their applicability, whether they are inside the body (in vivo) or outside the body (in vitro). In vivo applications can be further classified into diagnostic (MRI) and therapeutic (hyperthermia and TDD) applications. Invitro applications mainly deal with diagnostic separation, magnet or elaxometryand selection

In Vivo Applications

The two main factors that need to be considered in the usage of MNPs in vivo include size and surface modification. MNPs possess huge surface area that can be surface functionalised with a huge quantity of functional groups for crosslinking to tumour-targeting ligands, diagnostic imaging, or therapeutmarily affect their performance in vivo, even in the absence of tumour- targeting surface ligands. A diameter ranging around 10–40 nm is utilised in various applications, such as in cross capillary walls and prolonging blood circulation.

The usage of MNPs in in vivo can be classified into three categories; (i) magnetic vectors that could be driven towards tumour-targeted tissues through a gradient of magnetic field; (ii) magnetic CAs in MRI; and (iii) magnetic hyperthermia, where heat is generated by the application of high- frequency AC magnetic field that causes thermo-ablation of cancer cells. In recent years, due to the advancement of technology in the biomedical field, there are also reports on the combination of in vivo applications simultaneously, like the usage of both TDD and MHT , andalso MHT and MRI. This section discussed recent studies on TDD, MRI, and magnetic hyperthermia, which are the three most common in vivo applications driven by MNPs.

TDD

Traditional TDD, such as intravascular injection and chemotherapy, depends on the systemic blood circulation to distribute anticancer drugs throughout the body, especially tumour tissues. However, only a minuscule amount of dosage reaches these tissues. Moreover, issues on the toxicity of drug attack in healthy tissues are present. Given these drawbacks faced by patients and doctors, TDD has been introduced as a replacement for the traditional chemotherapy treatment. TDD has become one of the most sophisticated technologies in cancer therapy. It focuses the loaded drugs on the cancer site, controls the amount of drug flow towards the tissues of interest and reduces the side effects. The applicationof MNPs in TDD has increased tremendously over the years. MNPs are generally functionalised with biocompatible materials, such as polymers or gold. Functionalisation is carried out to ensure the anticancer drug could either be loaded within the MNPs or conjugated on the surface of MNPs, Once the drug is loaded (drug-loaded MNP), an external magnetic field is utilised to guide the drug-loaded MNP to the desired cancer site. The drug release is influenced by various factors, such as osmolality, enzymatic activity, changes in pH, temperature, electromagnetic trigger, and dual or poly-sensitivity.

MRI

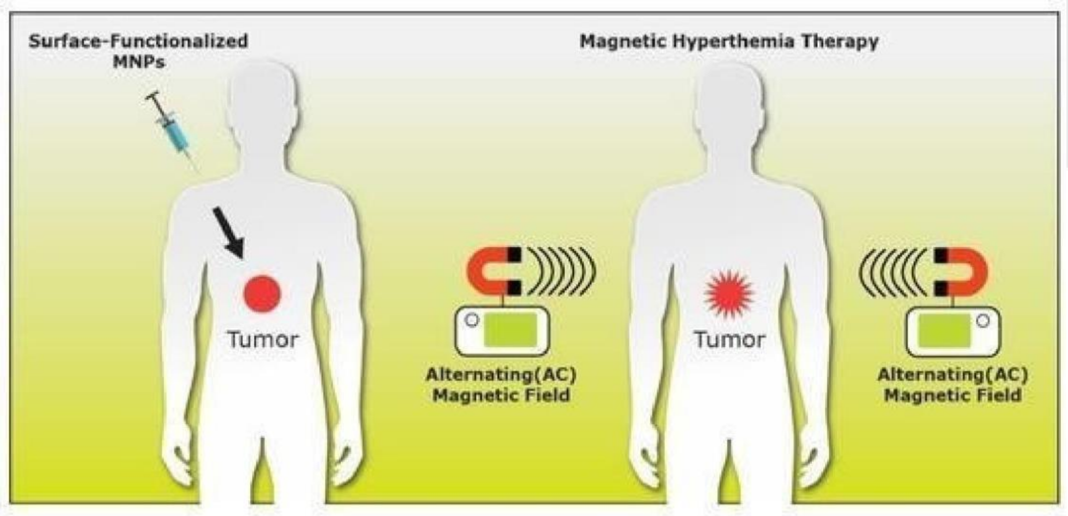
MRI is one of the most well-known biomedical imaging techniques in diagnostic medicine. It is applied primarily to generate high-resolution images of human tissues in 2D and 3D spaces. MRI functions on the principle of nuclear magnetic resonance. However, it requires a CA to increase its sensitivity sharpness for the detection of different kinds of pathological processes. MNPs in the superparamagnetic domain function as a good and reliable CA in in vivo applications due to T1 and T2 relaxation time and a high proton magnetic moment alignment time that results in a much-improved MRI image.Upon exposure to an external magnetic field, MNPs produce gradients with large microscopic area. The microscopic field gradient reduces the relaxation time of nuclear spins (T2*, T1 and T2), thereby resulting in a negative or dark contrast in T2-weighted images. MNPs are less toxic and possesses high colloidal stability in a biological environment. Further enhancement of these properties in MRI application requires these MNPs to be functionalised into CAs.

Specific cell labelling or cell tracking is another niche possessed by MNPs in the field of MRI. In vivo labelling and cell tracking aim to study and observe cell therapeutics and biological processes, respectively. They monitor cell movement and provide molecular information about the viability and functionalityofthe cells. MRI provides resolution as minuscule as the size of the cell when the cells are loaded with highly sufficient amounts of MNPs.

In the study of MRI diagnosis, researchers have utilised several techniques that involved surface modification for MNPs. Smolenskyet al. showed that the integration of a thin organic shell consisting of IONPs and gold chelators significantly increased the magnetic property value of IONPs goldcore–shell. **MHT**

Hyperthermia is one of the most promising biological applications of MNPs in cancer therapy. It is a therapeutic approach whereby heat is induced to kill tumours. MNPs act as thermal seeds. Once MNPs are localised using an external magnetic field, MNPs were heated up under a high frequency alternating magnetic field (AMF) at ~1 MHz due to hysteresis loss. The temperature of the tumour cells is increased to 42–45 °C to annihilate tumour tissues without affecting the healthy ones due to the higher sensitivity to heat of cancer cells than normal cells. When the heating of the cancerous cells and tissues reaches around 42–45 °C, the cancerous cells undergo cell apoptosis (i.e., hyperthermic effect). If the heating of the cancerous tissues reaches >48°C, the tissues undergoes necrosis.

The degree of heat dissipation given out by MNPs for magnetically mediated hyperthermia heavily depends on the anisotropy (magnetocrystalline or shape), magnetic field parameters, saturation magnetisation values and size. The three types of hyperthermia therapy include local, regional, and whole- body hyperthermia. Local hyperthermia therapy focuses on a specific targeted site of the body part, regional hyperthermia therapy is usually targeted on large tissue areas (e.g., limbs and organs), whilst whole-body hyperthermia therapy is generally applied to treat metastatic cancer that has spread throughout the body. Amongst them, local hyperthermia therapy is the most prominently utilised method in modern MHT. Figure shows an illustration of the process of MHT.



InVitro Applications Bioseparation :

Bioseparation is a crucial type of in vitro antibody, cell, DNA, enzyme, gene, bacterial and viral separation, in which MNPs were successfully applied.Compared with the traditional column affinity chromatography, magnetic separation possesses several advantages in terms of efficiency in retrieving or localising with a common magnet and cost. As in other applications, surface- modified MNPs with proper intermediates are normally used for separation enhancement. For surface functionalisation, ligands, polymers and surfactants are used to introduce functional groups (e.g., −COOH, −NH2, −OH and −SH) on the target biomolecules via selective adsorption.

Chang et al. investigated the efficiency of separating bovine serum albumin (BSA) via functionalisation of hydrophobic pockets on the surface of MNP SiO2 at different pH levels and alkyl groups. Theyobserved efficient magnetic separation and achieved strong magnetic separation by controlling the alkyl chain length, pH levels, salt concentration and size of the hydrophobic pocket .

MNPs are mostly preferred due to their superparamagnetic property. Moreover, due to their strong magnetic force, biomolecules could be transported easily towards targeted sites within the human body. Purification and isolation of different biomolecules, such as antibodies, DNAs, proteins, antigens, and nucleic acids could be performed at a highly purified percentage due to the strong magnetic force of MNPs.

Biosensors

In diagnostics, biosensing is an efficient platform for the detection of bacteria, biomolecules, cells, DNA, glucose, and viruses, with high sensitivity for diagnosing early diseases. Biosensors are analytical devices utilised in the biomedical field. Their main function is converting biological, chemical, or biochemical response into electrical signals . In addition, the surface functionalisation of MNPs is advantageous for the detection of molecular interactions; the large surface area of MNPs permits efficient functionalisation for targeted biomolecule interactions. Xia Sun et al. determined carbofuran through composite immunosensors on the basis of Au nanoparticles by developing MNP-functionalised multiwalled CNT-chitosan (MNP-FCNT- chitosan) and BSA composite film. The immunosensors showed excellent stability, sensitivity, and accuracy in detecting carbofuran.

Conclusion:

Nanoparticles are simultaneously surface-modified and guided via an external magnetic field, thus delivering promising tools for several biological applications. MNPs could be modified so they could selectively accumulate at the tumour site and induce ‘targeted’ therapy, which conventional approaches could not do.In Recent progression in nanotechnology has displayed promising development and promptly advanced during the last decade on the basis of their adroitness in new diagnostic and therapeutic concepts in all aspects of nanomedicine. MNPs have multimodal functionality, with applications in therapeutic treatments and

bioimaging diagnostics. In this review article, nanoparticles were widely studied in terms of properties, synthesis methods and surface functionalisation for biomedical application efficiency in vivo and in vitro. For biomedical applications, nanoparticles could be efficiently synthesize through an array of approaches. In the synthesis of biocompatible MNPs, solubility in an aqueous solution should be primarily considered when deciding on the synthesis method to use. Common wet chemical methods, such as co-precipitation and solvothermal methods, fulfil this criteria. Although the co-precipitation method could directly synthesise water- soluble MNPs, poor size control and low crystallisation are the drawbacks. Most researchers prefer the solvothermal method when synthesising MNPs due to its ability to yield MNPs with high magnetic properties; well-controlled shapes and sizes; and high crystalline monodispersity, where tuning synthetic conditions play significant roles. The micro-/nano-emulsion method is used to functionalise MNPs with polymeric species for bioimaging, therapeutic moieties or drug loading.

Surfactants are used to provide excellent control over shape and size of colloidal MNPs to be stabilised and possess superparamagnetism properties for applications in vivo and in vitro.

The main shortcoming of these MNPs is their hydrophobic surface chemistry that enables them to be soluble only in non-polar solvents, such as hexane and toluene. The surface chemistry of MNPs must be converted into hydrophilic to overcome this hindrance, in which organic and inorganic functionalisation were reported in this review. Surface functionalisation not only results in biocompatible surface chemistry for bioconjugation functions, but also provides additional physical properties such as optical resonance.

Previous reports on various biological applications, especially tumour theranostic applications in vivo and in vitro, indicated that enhancing the magnetic properties and SAR values of MNPs improved the theranostic efficacy. However, the usage of MNPs in the early detection of tumours in conjunction with treatment is still in the developing phase.

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