Recent Bio-medical applications of iron oxide magnetic nanoparticles

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Abstract

In recent times, pronounced consideration has been dedicated to the amalgamation of several magnetic nanoparticles because of their widespread smart and encouraging biological solicitations. The magnetic IONPs, magnetite (Fe_3O_4), and maghemite (γ-Fe_2O_3) have shown some remarkable applications in nanomedicines, diagnosis tools, and pharmaceuticals. Iron oxide magnetic nanoparticles (IOMNPs) have been explored for an extensive collection of biomedical and healthcare solicitations built on their surface properties, biocompatibility, and exceptionally, great magnetic susceptibility. In this logic, the magnetic properties of IOMNPs permit their usage in numerous biomedical applications, such as targeted drug delivery, hyperthermia, magnetic tissue engineering, MRI contrast agents, in vitro magnetic bio-separation, bio-analysis, magnetic transducers, and theranostic platforms. The functionalized hybrid IOMNPs have also been utilized against fungal infections and numerous pathogenic strains of microorganisms. Iron oxides play a significant role in the field of bio-catalysis, nanotechnology, and bio-medicines; therefore they are the main focus of this review. Keeping in mind the state-of-the-art, this review is intended to report the latest information about IOMNPs from methods of synthesis to modern bio-medical applications. Moreover, in-vivo and in-vitro uses of IOMNPs have conversed in detail. The challenges and restrictions in the biological usage of IOMNPs are also highlighted. This review based on IOMNPs will deliver a convincing vision for the investigators in nano-biotechnology and pharmacy.

Keywords: *Magnetic, Bio-medical, Iron oxide, Hyperthermia, Drug delivery*

1. Introduction

Nanomaterials are at the forefront of speedy progress in nanotechnology. They have fascinated extensive devotion as these nanomaterials display rare possessions when related to bulk substance[1-3]. The physicochemical properties of nanomaterials are much reliant on their dimensions, shape, structure, morphology, and crystallinity. Metallic nanoparticles possess unusual thermal, chemical, optical, and physical properties[4-8]. Iron oxide magnetic nanoparticles (IOMNPs) like magnetite and maghematite have been extensively studied for their commercial applications in nano bio-medicines and diagnosis. Ferro-fluid usages in blended magnetic nano-biosensors and as intermediaries of heat in hyperthermia have been testified. Developments in the construction of magnetic nanoparticles have managed their innovative usages in cell tracking, cell separation, bio sensors, enzyme immobilization, hyperthermia treatment, immunology, drug delivery vehicles (Ferrofluids), diagnosis, etc. For these applications, the perfect IOMNPs should display a trivial size (<100 nm), splendid magnetism with negligible polydispersity, safe, biodegradable eco-friendly surface crust, and extraordinary magnetization properties[9-13]. IOMNPs are most popular in biomedical applications due to their low cost, less toxicity, and their unique magnetic properties. Magnetite and maghematite usually show super magnetic properties when possessing a size of less than 20 nm and are utilized for various biomedical applications. Mandarano et.al.[14] reported applications of SPIONPs as contrast agents in MRI and their potential applications to a range of pathologies and processes involving MRI. Kayal et.al.[15] reported applications of versatile IONPs for drug release and drug delivery. Chen et.al.[16] reported that functional magnetite-TiO_2 core-shell NPs act as killing mediators for pathogenic bacteria in presence of light. Zhang et.al.[17] reported applications of modified magnetic NPs for MRI of surgically induced endometriosis models in rats. Lee et.al.[18] summarized the recent advances in the design and fabrications of core shells and hetero-structured SPIONPs and progress in their applications for diagnosis and biophotonics. Nithya and coworkers[19] explained the in-vitro biological activity of iron oxide nanocomposites. Rani et.al.[20] reported Fe_3O_4/RGO for the extremely sensitive and selective sensing of dopamine. Gamarra et.al.[21] reported applications of hyperthermia induced by SPIONPs in glioma treatments. Wang et.al.[22] studied magnetic SiO_2 NPs for magnetically attributed suicide gene remedy of carcinoma of liver cells. Mahmoudi and coworkers[23] have reviewed the applications of super magnetic iron oxide nanoparticles in chemotherapy. Biocompatible SPIONPs with proper surface coating and in conjugation with proteins have fascinated abundant devotion for drug delivery uses. Kievit et.al.[24] reported the applications of surface -modified SPIONPs for targeted cancer chemotherapy. Ciobanu et.al.[25] has reported biomedical applications of IONPs@dextron thin films obtained by the maple technique created by the co-precipitation technique. Dhanish et.al.[26] justified applications of magnetite nanoparticles for targeted drug delivery. IOMNPs play a noteworthy part in the arena of pharmacy and bio-medicines; therefore they are the main focus of this review. Keeping in mind the state-of-the-art, this review is proposed to report the latest facts about IOMNPs. Moreover, in-vivo and in-vitro uses of IOMNPs have been communicated in detail. The challenges and restrictions in the biological usage of IOMNPs are also highlighted. This review based on IOMNPs will deliver a convincing vision for the investigators in nano-biotechnology and pharmacy.

2. Synthesis Methods and Surface Modifications

2.1 Synthesis methods of IOMNPs

In the preceding decade, improved surveys with several types of iron oxides have been carried out in the arena of IOMNPs which typically comprises the magnetite (Fe_3O4), hematite (α-Fe_2O_3), maghemite (γ-Fe_2O_3), wϋstite (FeO), ε-Fe_2O_3, β-Fe_2O_3. Consequently, iron oxide is found in numerous forms (Fig.1.) which might be magnetic or non-magnetic in nature[27-30].

For the production and surface management of IO nanoparticles primarily two methodologies viz., a top-down and bottom-up approach is expansively studied (Fig.2.). The bulk ingredients are sliced down by physical or chemical methods in top-down tactic till they attain desired size. The top-down approach results defects in surface structure, damages in the crystal structure as well stresses because of the harsh and severe reaction conditions used during synthesis of nano materials. It leads into the alterations in the morphological and surface properties of nanomaterials. The bottom up method is largely applied for the synthesis of materials having nanometer/micrometer size the fabrication as well as method. Further this method has wide applications and significance in the synthesis of nanomaterials as it possesses a homogeneous chemical composition[31-40]. A number of methods have been implemented for the synthesis of IOMNPs, namely, microemulsion, electro-chemical, hydrothermal/solvo-thermal, sol-gel, ultrasonic, and co-precipitation, etc. Among these, co-precipitation is the utmost general and exploited process (Fig.3.) for the synthesis of magnetic iron oxide nanoparticles[41-45]. These approaches have the capacity to make IOMNPs by adjusting reaction settings. Magnetite (Fe_3O_4) and maghematite (γ-Fe_2O_3) are magnetic iron oxides which are found to have extraordinary bio medical applications. Magnetite has positively charged Fe ions occupying tetrahedral and octahedral situates of a cubic inverse spinel assembly. Maghematite has an inverse spinel structure like Fe_3O_4 however has an imperfect lattice structure. Pure magnetite is typically black while maghemite is brown in colour[46]. Several man-made green paths have been established in order to attain suitable control of size, polydispersity, shape, morphology and the magnetic nature of IOMNPs. A number of synthesis methods to attain nature, type, shape, size, dispersity, crystallinity and magnetic performance of IOMNPs have been established. Each synthetic approach has its own benefits and difficulties. Even though physical dry approaches are stress-free, monitoring the nano size is a challenging task. Although in a wet approach, nano size can be fairly organized by altering the synthetic conditions. The chemical synthesis approaches include electrochemical, hydrothermal, chemical coprecipitation, sol-gel, sonochemical decomposition, supercritical fluid method, flow injection, and nonreactors. The chemical approaches are typically accepted also due to small fabrication cost and greater yields[27]. A common reaction sequence which occurs during IOMNP synthesis is as follows,

$$Fe^{3+} + 3OH^- \longrightarrow Fe(OH)_3\,(s) \quad \text{(1)}$$
$$Fe(OH)_3\,(s) \longrightarrow FeOOH\,(s) + H_2O \quad \text{(2)}$$
$$Fe^{2+} + 2OH^- \longrightarrow Fe(OH)_2\,(s) \quad \text{(3)}$$
$$2FeOOH\,(s) + Fe(OH)_2\,(s) \longrightarrow Fe_3O_4\,(s) + 2H_2O \quad \text{(4)}$$
$$2FeOOH \longrightarrow \text{alpha } Fe_2O_3 + H_2O \quad \text{(5)}$$

In general, magnetite (Fe_3O_4) nanoparticles are prepared by addition of an alkali to a mixture of Fe^{2+} and Fe^{3+} salts at 1:2 molar ratios, ensuing in a black nanomaterial. The general reaction may be written as follows:

$$Fe^{2+} + 2Fe^{3+} + 8\,OH^- \longrightarrow Fe_3O_4 + 4H_2O \quad \text{(6)}$$

Magnetite, is a mixture of Fe_2O_3 and FeO, is unstable and can easily suffer from oxidation i.e. conversion of Fe^{2+} into Fe^{3+} to form maghemite in the presence of air, moisture and light[12-13].

$$\underset{\text{Magnetite}}{Fe_3O_4 + 2H^+} \xrightarrow{(O_2)} \underset{\text{Maghematite}}{\text{Gamma } Fe_2O_3} + Fe^{2+} + H_2O \quad \text{(7)}$$

The phase changeover of γ-Fe_2O_3 into α-Fe_2O_3 occurs during calcination at about 400-500°C. Manipulation of synthesis factors is essential to achieve controlled nanoparticles with respect to particle size, shape, morphology, purity, agglomeration and crystallinity.

A nanomaterial synthesis path must assist control over various reaction constraints such as temperature, concentration, pH, speed of stirring, particle size distribution, shape control, configuration and composition, which comprises crystallinity, purity, quick assay and various other modifications[28].

The biological application of IOMNPs is regarded by the practice of coating particle surface with diverse coating materials. IOMNPs can be encapsulated with various biomaterials like nucleotides, proteins, antibodies, drugs, surfactants etc. for their biological applications.[29-32]

2.2 Surface modification of IOMNPs

Recently, widespread research has been committed to the capping and functionalization of IOMNPs. The exterior alterations are found to be crucial features for improved control of particle morphology and shape, as well as to yield mono-dispersed IOMNPs, having a straight impact on their various properties and solicitations. The biocompatibility and toxicity of IOMNPs are the most vital measures to be considered for their biomedical applications. The IOMNPs must have extraordinary magnetization as their movement in the blood can be controlled with an exterior magnetic field till it is halted near the directed tissue[33-36]. The IOMNPs with an extensive biodegradability blood retention period and stumpy toxicity have arisen as the basic criteria aimed at in-vivo and in-vitro biomedical applications. Selected biological applications necessitate superficial capping, particularly core-shell type IOMNPs. There are four important reasons for the surface modification of IOMNPs; they are as follows:

for improving the dispersion of NPs, to enhance the surface activity, in order to boost the physicochemical and mechanical properties, and to increase the biocompatibility.

3. Biomedical solicitations of IOMNPs

3.1 In-vivo biomedical solicitations

3.1.1 Targeted Drug Delivery

Thermotherapy/Hyperthermia is the most encouraging biological solicitation of IOMNPs in sarcoma chemotherapy. Targeted drug delivery states the magnetically aided delivery at the location of concern. In this technique, magnetic nanoparticles are persuaded into the body by injection. Then, IOMNPs are exposed to an outer magnetic meadow produced by induction coils to create heat in the body. The induction coils produce distress on IOMNPs and the resulting electromagnetic energy is carried to the neighboring cells in the form of heat, which raise the temperature of cancer cells by about $2 - 3°C$. In order to improve or increase the heating efficiency of IOMNPs, they may be directly injected to targeted tumor cells. Typically, it is expected that the surface belongings of IOMNPs are most significant than the core properties, owing to the straight association of surface materials with the biotic surroundings. Henceforth, it’s crucial to maintain the IOMNPs surface coating with biocompatible constituents. Functionalized IOMNPs as an exporter can deliver a varied array of drugs to most of the body parts. In a drug hauler scheme, the dimensions, surface assets, and firmness are the vital topographies. Not only cancer diagnosis, but diverse types of IOMNPs have been established for new biomedical applications, such as the revealing of brain swelling or the premature identification of thrombosis etc. Furthermore, targeted drug delivery of drugs to the brain has massive prospective for the treatment of quite a few neural ailments like Alzheimer's syndrome and brain cancers[37-40.]

3.1.2 Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging is an influential nonionizing method that delivers body structural pictures with great perseverance and without depth restraint in the entity. IOMNPs have been established as a clever alternative to conservative contrast agents (CAs) for MRI. Within body cells finding or labeling by MRI can offer the scrutiny of biotic practices and display cell remedy directly, which is an additional prevalent solicitation of IOMNPs in MRI. Magnetic Particle Imaging is a comparatively fresh tracker imaging technique that hires IOMNPs and received substantial awareness from medical investigators. MRI is one of the leading in-vivo imaging modalities, besides Positron Emission Tomography (PET), Computed Tomography (CT), and ultrasound imaging. In order to perform as a contrast agent, IOMNP must be covered with polar coating agents. These coatings must be hydrophilic, comprising small polar groups, polymer, protein, etc. to disperse in an aqueous solution. Moreover, the simplicity of surface functionalization with diverse kinds of ligands unlocks the prospect of bringing out MRI. Multicomponent iron oxide nanoparticles offer novel prospects for MRI diagnosis, as well as combined therapies[41-44.]

3.1.3 Antimicrobial and Fungicidal Activity

Ferro-fluids are the emulsions or sols of IOMNPs in aqueous or non-aqueous solutions that display robust magnetic characteristics. Moreover, ferro-fluids have demonstrated as active agents against microbial and fungal infections. They are active against Staphylococcus species, E. coli, Xanthomonas, and Proteus vulgaris. Magnetite/silver nanocomposite ferro-fluids coated with oleic acid have too displayed antibacterial bustle against Bacillus subtilis, Staphylococcus aureus, and pathogenic C. albicans. Moreover, ferro-fluids have been operative in diminishing the advancement of fibroid-associated soreness. IOMNPs are believed to constrain the development of microorganisms by generating oxidative stress and responsive oxygen species that restrict the production of amino acids, triglyceride peroxidation, and DNA duplication. It also alters the corpuscle plasma membrane penetrability and creates irreversible destruction[45-50].

3.2 Ex-vivo biomedical solicitations

The surface modified IOMNPs have tremendous demand for developing novel investigative products. Some of the innovative in vitro applications are discussed below,

3.2.1 Theranostic systems

The term “theranostic” means a substance that syndicates the methods of remedy and diagnostic imaging. Magnetite IONPs are possibly the most exploited forum for theranostic schemes. The foremost advantages of biocompatible stabilized IOMNPs are, extraordinary drug stuffing as per their physico-chemical characteristics, capacity of magnetic control through mutual stimuli-sensitive and careful generates, adaptive pharmacokinetics, bio distribution, with boosted half-life, and opportunity to custom the particles for regulating targeted drug deliveries and the various therapeutic responses.

3.2.2 Enzyme Immobilization

In bio-catalytic methods, the parting of immobilized enzymes from the reaction muddle is biggest challenge that must overcome. In order to solve this challenge, linking bio-molecules with IOMNPs offers a simplistic split-up of the bio-catalyst with the help of an exterior applied magnetic field. Recently, IOMNPs have attracted an excessive courtesy as hopeful support transporters in enzymes arrest due to the enormous outer surface domain. The presence of polar hydrophilic groups on the surface permits their stress-free capping and powerful binding of the enzyme. For enzymatic cripple, IOMNPs are frequently altered with polymeric materials like peptides, chitosan, PAA, polyethylene imine and poly-dopamine owing their remarkable bio-degradability and bio-compatibility characteristics[30-43.]

3.2.3 Bio-separation

Bio-separation is another vital type of ex-vivo applications of IOMNPs which involves separation of antibodies, tissue, DNA, RNA, enzymes, genetic material and, micro-organisms, etc. For getting enhanced separation, the surface-altered IOMNPs with suitable materials are generally cast-off. To host various functional assemblies (e.g., −COOH, $-NH_2$, −OH and −SH) over the surface a number of ligands, polymeric materials and surfactants are used through careful surface assimilations. Furthermore, the greater aspect ratios, adsorption characteristics, chemical arrangements, stumpy toxicity, surface structures, stability, magnetic properties, size and its dissemination are extremely vital in the IOMNPs established magnetic bio-separation[35-45.]

3.2.4 Bio-sensors

Bio-sensing is a current manifesto for the identifying microorganisms, bio-molecules, tissues, genetic materials, etc. with focused thoughtfulness for early detecting premature ailments. Bio-sensors are diagnostic strategies exploited in the medical field. Their chief purpose is altering bio-chemical response into electrical signals. Furthermore, IOMNPs functionalized with appropriate capping agents are advantageous for detecting targeted bio-molecular connections[35-44.]

3.2.5 Rapid detection of bacteria

Lateral flow immunoassay (LFA) bands, demonstrate the combination of the benefits of nanomaterials and chromatographic separation and have turned out to be a quick, economical, and accessible point-of-care testing tool (POCT) for numerous bio-analysis uses. In recent times, certain new signal labels, with quantum dots, magnetic nanoparticles (MNPs), and surface-enhanced Raman scattering nano-tags, were used in LFA bands as an alternative to the usually used colloidal gold to create a stronger and legible signal for the assessable recognition of targets. C. Wang et. al. [45a] reported the application of magnetic quantum dots PEI-mediated electrostatic adsorption technique for the selective and rapid detection of bacteria.

3.2.6 Biodegradable Micro-robots for drug delivery

Molecularly targeted treatment has been projected to elucidate the struggle of lack of specificity in existing chemotherapy treatments. Micro-robots have been newly anticipated and aggressively investigated as a means to overawe the restrictions of the drug treatments. Mostly, micro-robots comprise an anti-cancer medicine and IO magnetic nanoparticles for their electromagnetic actuation. The newly projected micro-robots contain a gelatin-based hydrogel, IOMNPs, and modified poly lactic-co-glycolic acid (PLGA) particles. The biodegradable hydrogel micro-robot reaches a pre-determined target abrasion and thereafter, the gelatin hydrogel micro-robot is decomposed. The IOMNPs and PLGA drug particles are left in the target area and then lastly, the anti-cancer medication can be released to generate a therapeutic effect in the target lesion[45b].

Following are few recent ex-vivo and in-vivo bio-medical solicitations of IOMNPs,

3.3 Challenges in Bio-medical applications of IOMNPs

IOMNPs are extensively cast-off biocompatible nanomaterials to improve plentiful biomedical solicitations. Nevertheless, undecorated IOMNPs have revealed inadequate claims due to columbic forces that upturn the accumulation, causing in increased size. Consequently, altering the surface charge and design of IOMNPs are of considerable concern when thinking about their claims in remarkably established biomedical technologies[52-56]. Another limitation of IOMNPs is their aqua-phobic non-polar surface which makes them suitable only to be solvable only in non-polar solvents, like n-hexane, toluene, etc. The exterior surface of IOMNPs needs to be transformed into a polar, hydrophilic surface to overawe this limitation. Surface functionalization also consequences a bio-compatible surface for bio-conjugation functions, but also delivers added physical properties like improved amplitude. Another important limitation of IOMNPS is their toxicity and bio-compatibility. The ex-vivo and in-vivo toxicity of IOMNPs may disclose critical evidence regarding the danger of these nanoparticles. Nevertheless, the toxicity of IOMNPs may hinge on several elements such as, physico-chemical properties like composition, particle size, solvability, and surface chemistry, biotic accomplishments like bio-degradability, pharmaco-kinetics, and circulation in the body, drug delivery etiquette with reference to the dosage and its path.

Furthermore, when IOMNPs are employed as nano-transporters, the toxicity of the drug may be altered as a concern of an adjustment of its bio dispersal. For these motives, an in-depth assessment of the cell toxicity is hence required for each case about the planned solicitation[57-62].

4. Future Scope of IOMNPs in Biomedicines and pharmaceuticals

At present, IOMNPs have been productively applied in bio-medicines and diagnostics as a probe for revealing diseases or illnesses, drug deliveries, etc. Furthermore, with progressions, nowadays IOMNPs are set in combinations to attain multiple utilities in a solitary stage like MRI, and PET/CT imaging, etc. Recently IOMNPs based nano-hybrids were altered for hyperthermia and PTT, where even small concentrations are capable to boost the heat generation at the tumor spot and can be competently cast-off for cellular remedies. Recent advances in nano-hybrid IOMNPs synthesis paved the path to introduce enzyme mimetic, oxidase, and catalase activities. In addition, the conjugated IOMNPs made it easy finding of biomolecules in a solo step and put down the foundation to generate novel nano-sensors and nano-devices. Moreover, to overcome the obstacles in diseases like cancer and multi-drug resistant diseases, multifunctional IONPs were being designed for diagnosis, targeting, nano-carrier, chemo/ phototherapy agents. In conclusion, more progression in the novel synthesis of nanocomposites with multifunctional modalities can find better ways to use IONPs as nano-theranostic entities in biomedicine. The future of IONPs in biomedical applications holds great promise, especially in the area of disease diagnosis, early detection, cellular and deep tissue imaging, drug/gene delivery as well as multifunctional therapeutics. Custom-made medicine is also gaining courtesy and it is anticipated that the amalgamation of nanotechnology could result in predominant outcomes. In coming years, multifunctional IOMNPs would be smart materials for pharmaceutical requests and may change the typical commercial model of pharmaceutical industries[62-63]. IOMNPs physicochemical properties have to be custom-made in order to boost anti-tumor properties at a lesser magnetic field, growing the acceptability of the treatment and improving effectiveness for deep-rooted tumor growths. Desperate and productive exploration is necessary to plan and formulate IOMNPs for assorted solicitations in varied arenas in mandate to overcome challenges[64-66].

5. Conclusions

Original methods of production and solicitations of IOMNPs have been of concern in the field of nano-technology. Diverse synthetic methods have been improved, but the main challenge in the synthesis meadow that remains is the care of size and phase controlled synthesis with reproducibility. Reusability and robustness are tough to accomplish in the prevailing synthesis approaches. The undesired reactions disturb the desired properties of the IOMNPs.

To overawe the current disputes faced with IOMNPs the subsequent particulars ought to be achieved such as , straight active and comprehensive mixing of chemical constituents, robotics and automation of processes, acceptable reaction constraints organized specifically, accurate characterization tools to categorize and approve the oxide phase of iron, knowing the perfect reaction mechanism is furthermore significant as it enables thorough consideration of the reaction so as to achieve good control over the synthesis parameters and hence control of the nanoparticle size, morphology, shape, magnetic properties, etc. Several functionalized and hybrid IOMNPs can offer wonderful opportunities in detection tools like hyperthermia, MRI, photo-thermal therapies, etc. In addition to the above state-of-the-art different arenas such as bio-medicine tools, nano-medicines, bio-catalysis, and innovative diagnostic tools etc.

Figures:

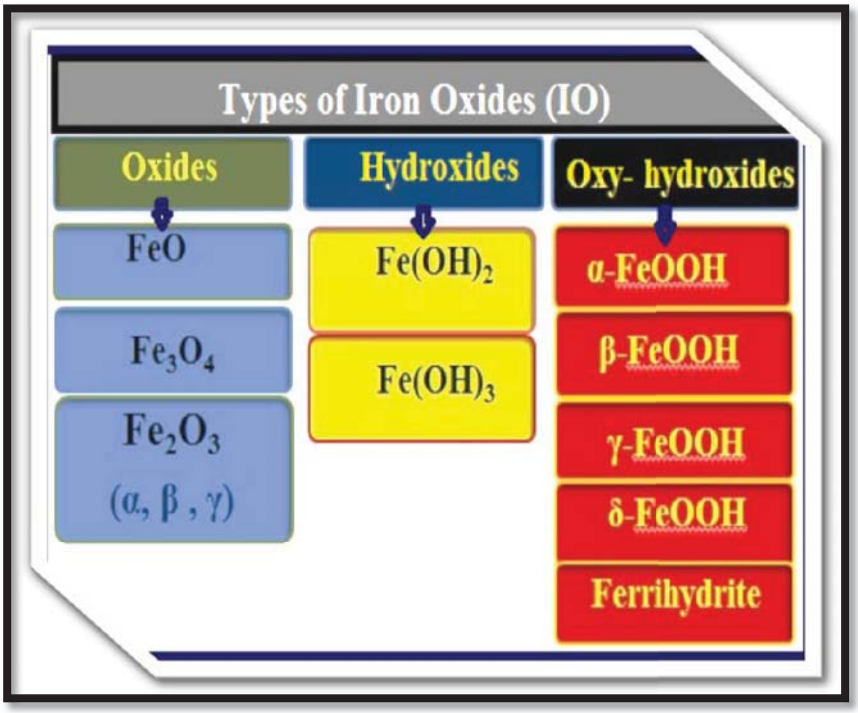

Fig.1. Types of Iron Oxides

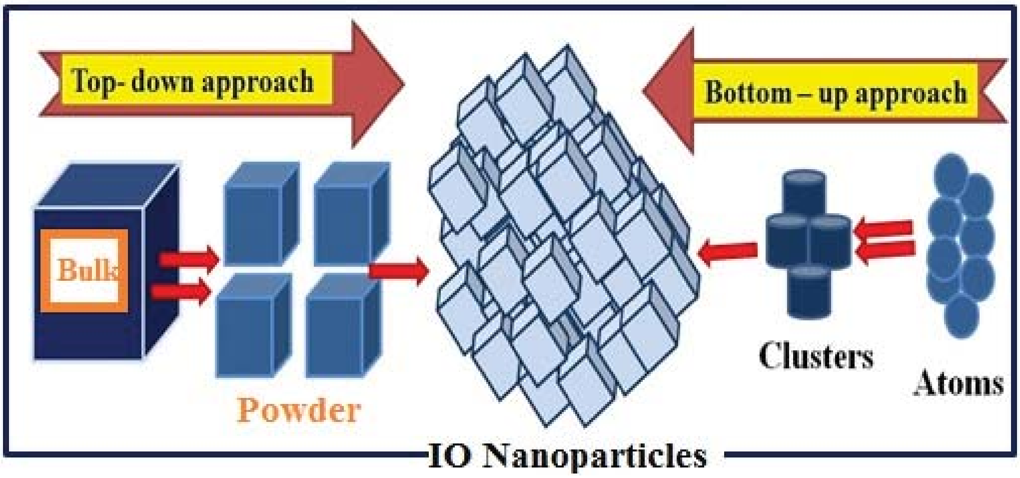

Fig.2. Top-down and bottom-up approach

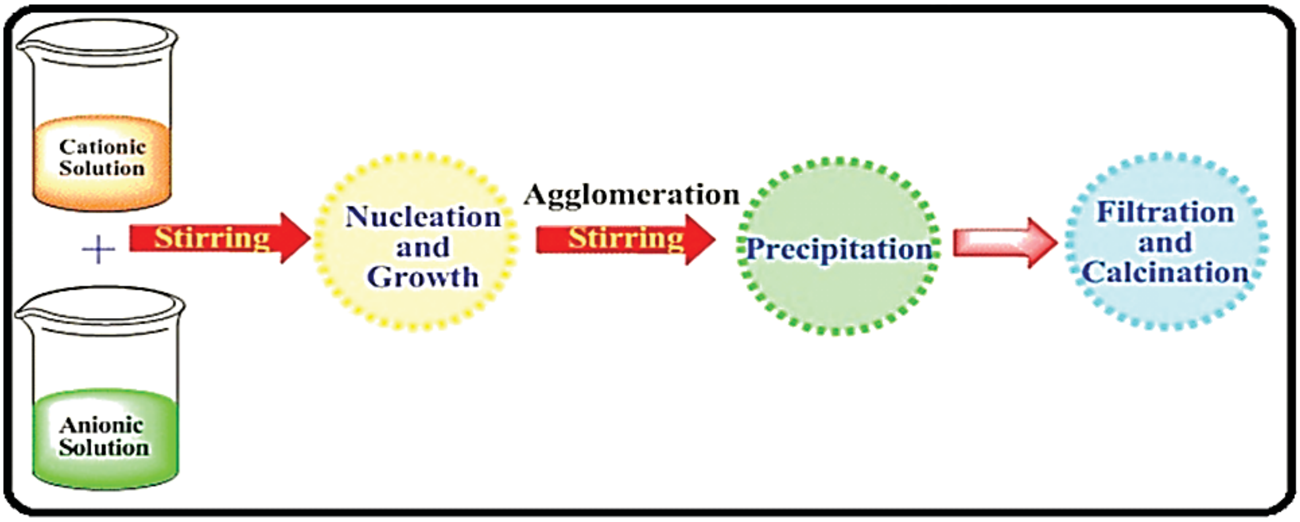

Fig.3. Co-precipitation method of synthesis

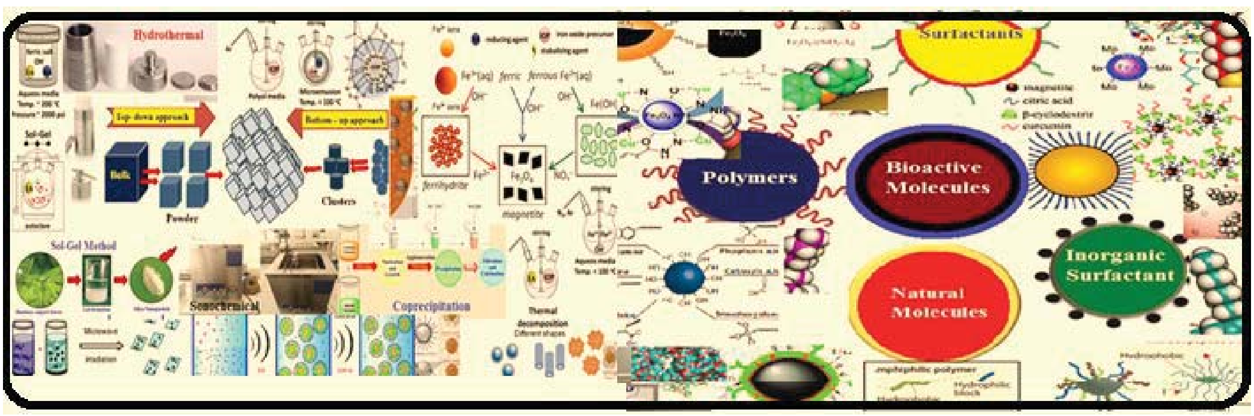

Fig.4. Common methods of synthesis and stabilization of IONPs

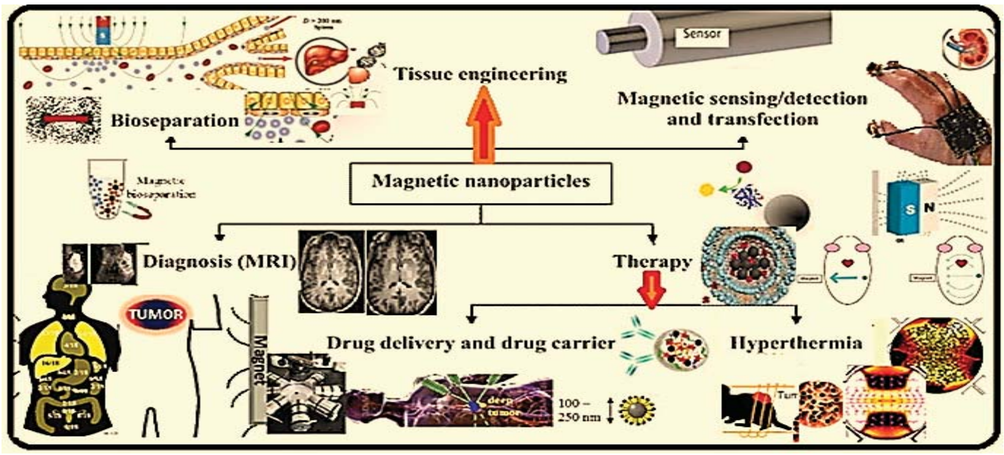

Fig.5. In-vivo and ex-vivo applications of IOMNPs

Tables:

Table1. Common methods of synthesis of IOMNPs

S. No.	Synthesis method	Temp.(°C)	Solvent	Size distribution	Shape control	Yield
1	Coprecipitation	25-90	Water	Relatively narrow	Not good	High
2	Thermal	100-350	Organic	Very narrow	Very good	High
3	Hydrothermal	200-250	Water/ Organic	Very narrow	Medium	Medium
4	Micro-emulsion	20-50	Organic	Relatively narrow	Good	Low
5	Polyol	253-300	Polyol solvents	Relatively narrow	Good	Low

Table2. Method of synthesis, functionalization and bio-medical applications of IOMNPs

S. No.	Nanoparticles	Surface Modification	Method of synthesis	Ex-vivo/ In-vivo bio-medical application	Reference
1	Fe_3O_4	Chitosan	Co-precipitation	Lipase immobilization	Liu et. al. [27]

2	IOMNPs	17β-estradiol	Molecular imprinting	Selective separation and detection of estrogen	Wang et.al.[28]
3	Magnetite	RGO	Ultrasonic	Biosensor	Lu et. al.[29]
4	Fe_3O_4	Sodium carbonate-oleic acid	Co-precipitation	Cancer therapy	Jadhav et. al.[30]
5	IOMNPs	Sodium citrate	Co-precipitation	CA/MRI of liver fibrosis	Saraswathy et. al.[31]
6	Magnetite	Polymer assembly	Co-precipitation	Dual drug delivery	Pothayee et. al.[32]
7	IOMNPs	Graphene	Co-precipitation	Bio-seperation/ Alzheimer's disease biomarkers	Demeritte et. al.[33]
8	Fe_3O_4	Polymers	Co-precipitation	Targeted drug carriers	Ulbrich et.al.[34]
9	IOMNPs	PMAA-graft-PEG copolymer	Co-precipitation	Cis-Platin delivery	Vermesh et. al.[35]
10	IOMNPs	-	Multiple approaches	Antifungal	Nazanin et.al.[36]
11	IOMNPs	Chitosan	Co-precipitation	Cancer therapy	Catalano et. al.[37]
12	Magnetite	Doxorubicin	Co-precipitation	magnetic drug targeting and tumor regression	Nigam et.al.[38]
13	Magnetite	sodium dodecyl sulphate @ oleic acid	Co-precipitation	Nano carriers for drug delivery	Dutta et.al.[39]
14	Magnetite	Fe3O4-MTX@HBc	Co-precipitation	MRI/Photo-thermal therapy	Zhang et. al.[40]
15	Maghematite	-	Sol-gel	MRI contrast enhancement	Marashdeh et.al.[41]
16	Maghematite	-	Hydrothermal	Bio-sensor	Hijiri et.al.[42]
17	IOMNPs	PEG-Arg@IONPs	Co-precipitation	MRI contrast agents	Nosrati et al.[43]
18	Magnetite	Chitosan-ampicillin	Co-precipitation	Antibacterial therapeutics	Allafchian et.al.[44]
19	IOMNPs	-	Co-precipitation	Positive contrast in MRI	Fernández et.al.[45]
20	IONPs	Various capping Agents	Multiple approaches	Cell Labeling	Nene et.al.[46]
21	IOMNPs	-	Extraction Method	Detection of SARS-CoV-2	Zhao et.al.[47]

22	Magnetite	PMAO	Thermal decomposition	Diagnosis	Vuongaf et.al.[48]
23	Magnetite	-	Bacteria mediated	Biomedicine	Rosenfeldt et.al.[49]
24	IOMNPs	Diethyl-amino ethyl-dextran	Co-precipitation	In vitro MRI	Cortés et.al.[50]
25	IOMNPs	-	Bacteria mediated	Antioxidant	Majeed et.al.[51]

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