



OVERVIEW ON IRON OXIDE MAGNETIC NANOPARTICLES AND POLYOL METHOD OF SYNTHESIS

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Article Received on 15/11/2021

Article Revised on 05/12/2021

Article Accepted on 26/12/2021

ABSTRACT

In recent times, the arena of nanoparticles and their wide range of applications have amassed interest in the domain of diagnostics and medical therapeutics. The following review entails their diverse array of chemical and electromagnetic properties, along with their correlation concerning particle size.^[1] Furthermore, superparamagnetic behaviour is of sheer eminence in medical research, cell isolation devices, enzyme immobilization, controlled release systems, and the separation of biological materials.^{[1][8]} In contrast with other magnetic nanoparticles, magnetite and maghemite displayed higher biocompatibility and lower toxicity during in-vitro/in-vivo studies.^{[2][10][11][12][13]} This review also summarises a brief on the pre-existing methods of preparation, properties, and applications of nanoparticles.^[1] In addition, the polyol method of synthesis has also been emphasized.

KEYWORDS: Nanoparticles, iron oxide nanoparticles, superparamagnetism.

INTRODUCTION

Nanoparticles (NPs) are a diversified facet that has gained intense attention in terms of therapies and diagnosis, due to their distinctive physicochemical properties that transform medical treatments and imaging with a more effective, less noxious, and wiser outcome. Previously, they were primarily used to curate building materials, pigments, and stained glass before their identity and qualities were revealed and thoroughly understood.^[1]

Due to their sub-micron dimensions, they have a significant surface area per unit volume, a high proportion of surface atoms and near-surface layers, and the ability to demonstrate quantum phenomena that cannot be predicted from bulk material properties. They are a broad class of materials that include particulate compounds with at least one dimension smaller than 100 nm. Depending on the overall shape, these materials can be 0D, 1D, 2D, or 3D. The International Organisation for Standardisation (ISO) differentiates nano-objects based on their external dimensions in nano-scales as 1D (nanotubes, or nano-fibres), 2D (nanoplates, or nano-discs), and 3D (nanoparticles).

NPs are not simple molecules themselves, and therefore composed of three layers, i.e., (a) The surface layer, which may be functionalized with a variety of small molecules, metal ions, surfactants and polymers, (b) The

shell layer, which is a chemically different material from the core in all aspects, and (c) The core, which is essentially the central portion of the NP and usually refers the NP itself. Depending on their chemical and electromagnetic characteristics, nanoparticles can exist as suspensions, colloids, or dispersed aerosols.^{[4][32]} Because of their extraordinary properties, these materials have piqued the curiosity of researchers in a variety of disciplines over time.

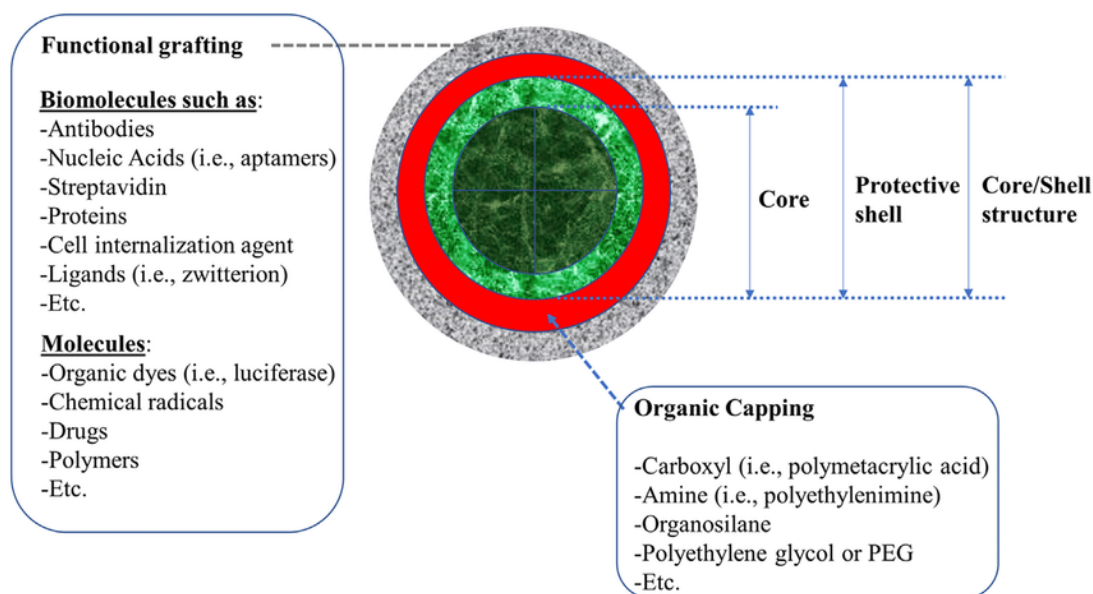


Fig. 1: Layers of a nanoparticle.

The characteristics of nanoparticles vary with their size. In many circumstances, the form of a nanoparticle has a direct influence on its physical properties, such as the frequency of electronic oscillation/surface plasmon resonance in gold and silver nanoparticles or the polarisation of luminescence in semiconductor nanorods. Magnetic nanoparticles' physical and chemical characteristics are heavily influenced by their form, crystalline structure, size, and chemical composition. Magnetic nanoparticles have precise magnetic properties, such as low Curie temperature, high magnetic susceptibility, and super para-magnetism, i.e., the flipping of magnetisation in a random direction under temperature ascendancy; for example, copper nanoparticles smaller than 50 nm are super hard materials and do not exhibit the malleability or ductility of bulk copper. Numerous different changes that are influenced by nanoparticle size include superparamagnetism in magnetic materials, quantum confinement (or a change in electronic and magnetic properties) exacerbated by quantum mechanical effects in semiconductor materials (Q-particles), and surface plasmon resonance in certain metal particles. According to investigations, the absorption of solar radiation in photovoltaic cells is larger in nanoparticles than in thin films of continuous sheets of bulk material. This is due to the fact that nanoparticles are smaller and may absorb more solar light.

Nanoparticles displayed an escalated level of diffusion at upraised temperatures, attributing to their high surface area to volume ratio. In comparison to bigger particles, this property of nanoparticles permits sintering to occur at lower temperatures. While the diffusion feature of nanoparticles may not influence the product's density, it might induce agglomeration.

The importance of these materials was known when researchers found that particle size can influence the

physiochemical attributes of a substance, for instance, their optical properties. A 20-nm gold (Au), platinum (Pt), silver (Ag), and palladium (Pd) NPs have characteristic wine red colour, yellowish grey, black and dark black colours, respectively.

Types of Nanoparticles

Magnetic nanoparticles enclosed with eccentric characteristics have the potential to be used as catalytic scaffolds in organic transformations. Importantly, numerous attempts have been made to regulate the magnetic and surface characteristics of magnetic materials by modifying reaction parameters such as temperature, duration, and reactant concentration. Magnetic nanoparticles can be divided into four categories:

- Metals (Fe, Co, Ni)
- Metal oxides (FeO , Fe_2O_3 , Fe_3O_4)
- Alloys (FePt, FePd)
- Ferrites (CoFe_2O_4 , CuFe_2O_4)

The likelihood of toxicity and oxidation of iron and its oxides is lower than cobalt nanoparticles, Fe-Co alloys, and ferrites.^[1] The iron nanoparticles' tendency to oxidize also limits their biomedical application. To tackle this, it is recommended that a polymer covering, such as biopolymer nano skin, be used, which prevents the undesirable process of oxidation or contact with external fluids without impairing the magnetic interaction of iron nanoparticles. Superparamagnetic iron oxide nanoparticles (SPIONs), such as maghemite ($\gamma\text{-Fe}_2\text{O}_3$) or magnetite (Fe_3O_4), are the primarily used magnetic nanoparticles for biomedical purposes, owing to their inexpensiveness, simple preparation perspective, low toxicity, super para-magnetism, and biocompatibility.

Magnetic nanoparticles (MNPs) based on metals such as iron, cobalt, and nickel, as well as metal oxides/mixed-

metal oxides, have contributed in the meticulous development of contemporary technology. They are now employed in a variety of sectors, including bioimaging and sensing; on a lesser scale, they are used as catalysts and in medicine. They feature magnetic elements such as iron, chromium, gadolinium, cobalt, manganese, and nickel, as well as their chemical compounds such as oxides, ferrites, and alloys, and may be guided using magnetic field.

Super para-magnetism is a form of magnetism that manifests itself in small ferrimagnetic and ferromagnetic particles. If such particles are small enough (150 nm or less, the exact size depends on the chemical composition of the particle), they become single-domain, i.e., the unwavering orientation of isolated spins over entire particle volume and generation of sustained magnetized state.^{[16][17][18]} Attributing to thermal fluctuation, the magnetic moment of such particles can arbitrarily flip direction, culminating superparamagnetic particles with zero average magnetization. However, when an external magnetic field is applied, such particles display paramagnetic behaviour (i.e., particles generate an induced magnetic field due to a weak attraction to the externally applied field) even at temperatures below the Curie or Néel points.^[19] The magnetic susceptibility of such superparamagnetic systems substantially transcends as that of paramagnetic ones.

Because of the widespread applications of magnetic nanoparticles [MNPs] in biotechnology, biomedical, material science, engineering, and environmental areas, much attention has been brought on to the synthesis of various types of MNPs.

Industrial applications of magnetic nanoparticles entail a comprehensive range of magnetic recording media and biomedical applications, for instance, magnetic resonance contrast media and therapeutic agents in cancer therapeutics and medicaments.^[2]

The utilisation of particles that exhibit superparamagnetic behaviour at room temperature is favoured for biological applications. To avert variations in the original structure, the formation of large aggregates, and biodegradation upon exposure to the biological system, the magnetic nanoparticles must be encapsulated with a biocompatible polymer or nanocomposite material during or after the procedure for in vivo applications. Magnetic nanoparticles must be formed of a non-toxic and non-immunogenic substance, with particle sizes small enough to persist in systemic circulation after injection and transit through the capillary network of tissues and organs, avoiding vascular embolism.^[13] They must also have a high magnetization, so that their movement in the blood can be overseen with a magnetic field for their immobilization close to the targeted pathologic tissue.

Iron Oxide Magnetic Nano-Particles

Iron oxide (IO) nanoparticles are composed of maghemite ($\gamma\text{-Fe}_2\text{O}_3$) and/or magnetite (Fe_3O_4) particles, with diameters ranging between 1-100 nanometers. Although Co and Ni are immensely magnetic, they undergo oxidization rapidly and are toxic in nature.^[11] They have numerous applications, including magnetic data storage, biosensing, and drug delivery. In the case of nanoparticles, the surface area to volume ratio increases considerably. This allows for a significant binding capacity and extraordinary dispersibility of NPs in solutions. Magnetic NPs of sizes ranging from 2 to 20 nm display super para-magnetism, which means that their magnetization is zero in the absence of an external magnetic field but can be magnetizable in the presence of one. This characteristic provides additional stability for magnetic nanoparticles in solutions.

These nanoparticles have garnered considerable interest, owing to their superparamagnetic proficiency, along with their potential biomedical applications arising from their biocompatibility and non-toxicity.^{[2][10][11][12]} The current advancement in the amalgamation of iron-oxide nanoparticles by thermal breakdown of iron carboxylate salts has substantially improved the nature of typical IO nanoparticles in terms of size tunability, monodispersity, and crystalline structure. Hydrophobic and organic ligand-coated IO nanoparticles were effectively transformed into water-soluble, bio-accessible IO nanoparticles using an unique monolayer polymer coating approach.

Attributing to the high stability of these water-soluble IO nanoparticles in harsh environmental conditions, like high pH and elevated temperature conditions permits adjunction of these NPs with other biomolecules.

Improvement in the quality of both organic and water-soluble IO nanoparticles unleashes diverse facets for the evolution of IO nanoparticles-based applications^{[4][5][6][7][8]}, for instance:

- As contrast agents for Magnetic Resonance Imaging (MRI) and Magnetic Particle Imaging
- As drug carriers for target-specific drug delivery
- As gene carriers for gene therapy
- As therapeutic agents for hyperthermia-based cancer treatments
- As magnetic sensing probes for in-vitro diagnostics (IVD)
- As Nano-adjuvant for vaccine and antibody production
- Terabit magnetic storage devices, catalysis, sensors, superparamagnetic relaxometry
- Separation of biomolecules, and targeted drug and gene delivery for medical diagnosis and therapeutics.

These applications require coating of the nanoparticles by agents such as long-chain fatty acids, alkyl-

substituted amines, and diols. They have been put into use in formulations for supplementation.

Iron oxide magnetic nanoparticles can be formulated via three generalised methods, namely physical, chemical and biological methods.^{[4][5][6][7][9]}

1) Physical methodologies

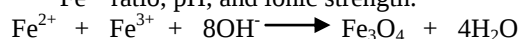
- a) Top-down method: Milling is done in order to reduce the size of macroscopic magnetic materials to magnetic nanoparticles. A major drawback of this method is that it is difficult to regulate the size and shape of particles. Apart from that, the grinding procedure may lead to the formation of crystal lattice defects, which cause deviations in magnetic properties as compared with particles of the same size.
- b) Bottom-up method: Laser evaporation of micron particle-sized metal oxide powders is performed in order to produce iron oxide magnetic nanoparticles. There is a sharp temperature gradient beyond the evaporation zone, thus, very rapid condensation and nucleation from the gas phase occurs, and nanoparticles with sizes from 20 to 50 nm are formed.

2) Biological methodologies

Magnetic nanoparticles can also be prepared with the help of certain living organisms by biomineralization. Magneto-tactic bacteria can orient themselves and migrate along the lines of geomagnetic field, due to the constituting intracellular magnetic structures and magnetosomes, which contain nanometer membrane magnetite crystals enclosed within a protein. The accumulation of iron and the deposition of a mineral particles with characteristic size and orientation in the membrane vesicle in certain places in the cell is biologically controlled for the emergence of magnetosomes. By this mineralisation procedure, under anaerobic conditions similar to the living conditions of magneto-tactic bacteria, homogenous particles can be attained, their core diameter being 20-45 nm.

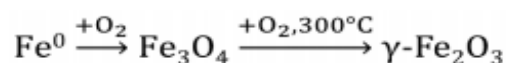
3) Chemical methodologies

- a) SPIONs have been very commonly known to be synthesized by Coprecipitation Technique. This method involves the coprecipitation of Fe^{2+} and Fe^{3+} by addition of a base. The physical properties and the composition of the resultant nanoparticles is governed by the type of salt used, Fe^{2+} and Fe^{3+} ratio, pH, and ionic strength.



This method runs on contriving the nanoparticles by gradual addition of precipitating agent (preferably aqueous solution of ammonia, hydroxide, or sodium carbonate) to the aqueous solutions of ferric and ferrous salts (to be taken in the ratio of 2:1) at room temperature, or by heating. This method produces magnetic nanoparticles that are intermediate in composition

between magnetite and maghemite, because this reaction is associated collaterally with the oxidation of magnetite to maghemite along with atmospheric oxygen. The nanoparticles developed are roundabout 1-40 nm in size.



- b) Oxidation of iron nanoparticles can be employed for the creation of magnetite nanoparticles. Maghemite nanoparticles are acquired by oxidation of iron and magnetite nanoparticles with atmospheric oxygen at 300°C . It is suggested that this particular method must not be carried forth at high temperatures, as it might cause not only sintering of nanoparticles to submicron size, but also result in the transition of a thermodynamically unstable polymorphic modification of iron (III) oxide-maghemite ($\gamma\text{-Fe}_2\text{O}_3$) to hematite ($\alpha\text{-Fe}_2\text{O}_3$) effectively between the temperature range from 300 to 500°C .
- c) One among the most efficient methods of producing maghemite particles with a narrow size distribution is thermal decomposition. This method is a compilation of 2 methods:
 - i) Heating up, which involves the continuous heating of a solution which is composed of a solvent, surfactants, and the precursor compounds to a predefined temperature at which the nanoparticles begin to grow and form clusters.
 - ii) Hot injection induces rapid and congruent nucleation by incorporating reagents into a hot solution of a surfactant and is characterised by a controlled growth phase.

The most commonly used precursor compounds are: iron (III) acetylacetonate ($\text{Fe}(\text{acac})_3$) and iron (II, III) stearate ($\text{Fe}(\text{St})_2$, $\text{Fe}(\text{St})_3$), iron (III) oleate ($\text{Fe}(\text{Ol})_3$) fatty acids are used as surfactants.

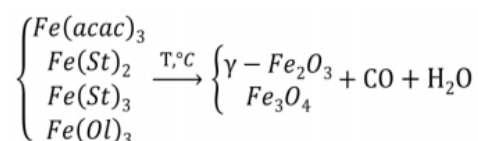


Fig. 2: Reaction resulting in the fromation of nanoparticles via given precursors.

The nanoparticles prepared are 4-30 nm on average in size with a narrow size distribution.

- d) Hydrothermal or Solvothermal methods: At an upraised temperature and pressure, enormous amounts of inorganic substances become highly soluble in water. This dissolved material can subsequently be crystallised and abstracted from the liquid phase. Rapid nucleation is accredited to high temperatures and can also be influenced by addition of precipitants.
- e) Polyol method^{[9][21][22]}: Polyol solvents, like polyethylene glycol, have certain intriguing traits

which are a function of their dielectric constant. Also due to the same property, they can effectively dissolve inorganic compounds. Polyols have relatively high boiling points, thereby, offering a wide operating temperature range, that is 25 °C to the boiling point for the preparation of inorganic compounds. These act as reducing agents as well as stabilisers in turn for aiding controlled particle growth and prevent inter particulate aggregation. Polyols can also be synthesized using precursor salts, namely iron chloride tetrahydrate ($\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$) and cobalt acetate tetrahydrate ($\text{Co}(\text{CH}_3\text{COO})_2 \cdot 4\text{H}_2\text{O}$). Following are the steps for polyol nanoparticle synthesis-

- Certain amount of precursor salts- iron chloride tetrahydrate ($\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$) and cobalt acetate tetrahydrate ($\text{Co}(\text{CH}_3\text{COO})_2 \cdot 4\text{H}_2\text{O}$) along with ethylene glycol to make up a specific volume are employed for the synthesis of Fe₅₅Co₄₅ magnetic nanoparticles.

- One homogenous solution was obtained, and further 6 M of NaOH was added to the solution, until it reached a pH of 11.68.
- This mixture is then heated to 116 °C, and subjected to continuous stirring at 1500 rpm for a period of 2 hours.
- Once the reaction was complete, the final product was magnetically separated. Also, this obtained product was washed multiple times using ethanol and distilled water in order to remove excess of chlorine and sodium impurities.
- The sample was dried in an oven at a temperature of 80 °C; subsequently, it was calcined at 600 °C for 3 hours.
- The same procedure was performed with a different pH, which was 11.15; the mixture was stirred at 400 rpm and the calcination time was 5 hours. (instead of 3)

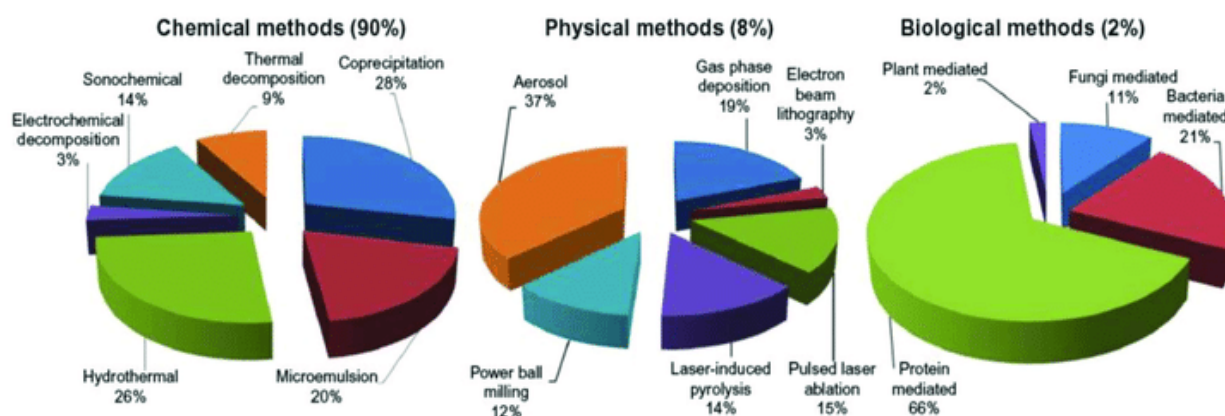


Fig. 3: Comparative pictorial representation of various synthesis methodologies of IONPs.

Methods	Evaluation
X-ray Diffraction	Size and crystal habit
Infrared Spectroscopy	Surface functionalisation
Mass Spectroscopy	Molecular weight analysis
Nuclear Magnetic Resonance Spectroscopy	Longitudinal and transverse relaxivity; structure conformation

Fig. 4: Methods of Characterisation for the evaluation of certain properties of iron oxide nanoparticles.

Applications

1. **MRI contrast agents:** The IONPs label has been approved for clinical use. Owing to high sensitivity to MR detection and non-toxicity, it can be used in Magnetic Resonance Imaging as a blood pool agent, i.e., angiography contrast agents that remain within the vascular space for longer time period, thereby extending the window for imaging. Superparamagnetic MR agents cause strong T₁ and T₂ (characterises RF-induced NMR spin polarisation) shortening and have a large magnetic moment. They comprise of miniscule ferromagnetic crystals. The crystalline symmetry, size of the core, and nature of the coating determine the T₁ and T₂ net magnetisation of these agents.

2. Magnetic nanoparticles can bind to drugs, proteins, enzymes, antibodies, or nucleotides, and can be directed to an organ, tissue, or tumour using an external magnetic field, or can be heated in alternating magnetic fields in the production of **localised hyperthermia** in tumours, via maximum power deposition. This can selectively kill cancer cells and improve the impact of radiation and chemotherapy, while safeguarding healthy somatic cells. Owing to numerous challenges
3. Iron oxide nanoparticles are potentially helpful in **wastewater treatment** when used as nano

absorbents and photocatalysts, attributing to their super para-magnetism, high adsorption potential, and chemical inertness. Also, owing to their outstanding surface and quantum size effects, they can execute microbial metabolism and immobilisation.

4. For **in vitro applications**, composites comprising of superparamagnetic nanocrystals dispersed in submicron diamagnetic particulate matter with prolonged sedimentation times (in the absence of a magnetic field) can be employed because the size restrictions are not so stringent, in contrast to vivo applications.
5. **Electronics:** Magnetic, electric, and optoelectronic materials and devices can be synthesised via nanoparticles of particle size less than 100 nm. Ultra-high density magnetic storage devices can also be formulated with numerous methodologies, such as extensive reduction and thermal decomposition of metallic pre-cursors.

Authors' Contributions

Abstract, Introduction, Brief on IONPs, Applications, Editing, Citations, and Proof-reading: Jena M.

Types of NPs, Methods of Synthesis, Citations: Patil S.

Declaration of Competing Interest

The authors hereby declare that they possess no competing financial fascination, or any personal relationships that could have appeared to impact the work reported in this paper.

Funding

This review work did not inherit any particular grant or funds from funding agencies in the public, commercial, or non-profit sectors.

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