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MAGNETIC NANOPARTICLES FOR THEIR THERAPEUTIC APPLICATIONS

Divyani Singh * and Prashant Shukla

Department of Pharmaceutics, Hygia Institute of Pharmaceutical Education and Research Faizullahganj, Prabhandh Nagar, Lucknow - 226020, Uttar Pradesh, India.

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Correspondence to Author:
Divyani Singh

PG Scholar,
Department of Pharmaceutics,
Hygia Institute of Pharmaceutical Education and Research
Faizullahganj, Prabhandh Nagar,
Lucknow - 226020, Uttar Pradesh, India.

E-mail: divyani.singh0015@gmail.com

ABSTRACT: Magnetic nanoparticles are hugely used in hyperthermia, targeted drug delivery processes, diagnosis, extraction, and cellular imaging of biological molecules, which can be widely used in cancer treatment. The focus of attention is on formation, features, types, made work, coating material, and therapeutic application of magnetic nanoparticles. It also pivots in safety and biocompatibility in magnetic nanoparticles (MNPs). Particles within the size range of nanoscale exhibit magnetic properties and are known as magnetic nanoparticles (MNPs). The major advantage of magnetic nanoparticles is the targeting at the specific site. Various polymerization and coating of metals can be done, such as applying chemotherapeutic drugs to correct inherited diseases. The various process of Magnetic Nanoparticles formation through diagrammatical picture is also discussed in this article. This review discusses the therapeutic application, preparation method, features of magnetic nanoparticles, types, made work, surface coating, biocompatibility, and safety.

INTRODUCTION: Nowadays, Magnetic nanoparticles (MNPs) have been investigated and researched by scientists and researchers [1]. Magnetic nanoparticles include an immense range of applications in various fields like environmental correction, magnetic resonance imaging (MRI), magnetically fluid in biomedicine and biotechnology and also in data base storage [2]. A magnetic nanoparticle in a 1-100 nm size range which is used and is appropriate in science and technology fields.

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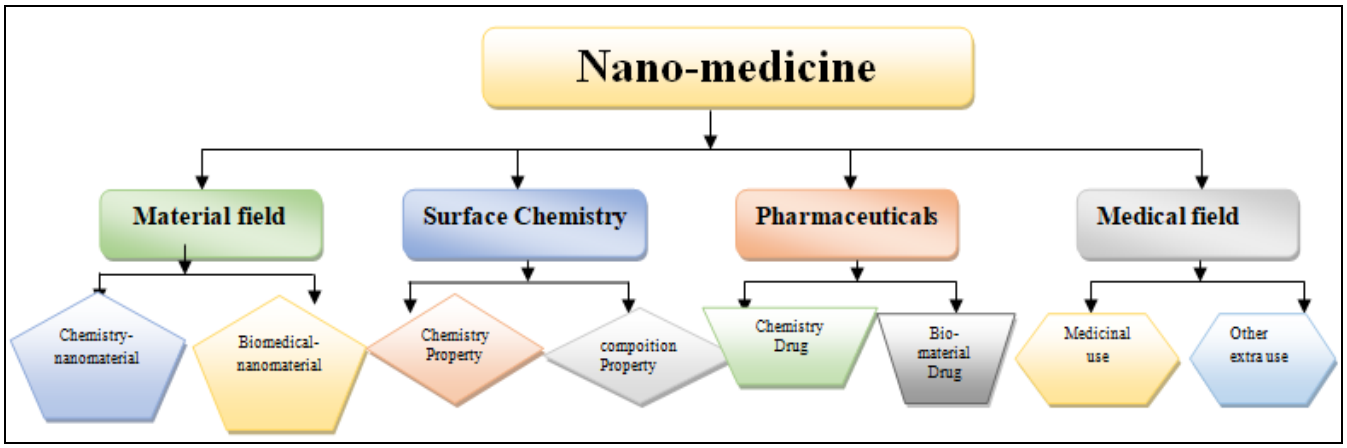
A magnetic nanoparticle (MNPs) contains distinctive property as the huge surface volume ratio, and the size dependency with its magnetic feature intensely change from its bulk material. Magnetic nanoparticles have been enormously used in catalysis, nerve stimulation, *etc* [3-22]. Magnetic nanoparticles perform finest when their dimension is below the critical value, around 10-20 nanometres, but it also depends upon the material. The tiny particles make the lump decrease the power of nanoparticles.

The application includes shielding methods to chemically stabilize the uncoated nanoparticles to protect it from decomposition at the time and after synthesis. The techniques include grafting or coating the nanoparticles using organic compounds like polymers and surfactants or applying the inorganic layer of carbon or silica *etc.* [23].

Magnetic nanoparticles (MNPs) have the finest magnetic inclination, biodegradable, and contain a small size effect and reactive function groups [24]. These are different from other because it gives a reaction to the external magnetic field used in various disease diagnosis and treatment. MNPs are also used *in-vivo* medicinal methods [25]. Specifically characterized nano-size particles are hugely used in bio-labeling, catalysis, and biological separation.

In the case of the catalytic reaction of the liquid phase, the tiny magnetic nano-size particles coordinates' quasi homogenous system, which includes an edge like high reactivity, high separation and huge scattering. This article includes preparation methods of magnetic nanoparticles will be discussed briefly. Also, the protective coating methods, features, application and advantage of magnetic nanoparticles will be discussed [26].



FLOW CHART OF NANO-MEDICINE

Devising of Magnetic Nanoparticles (MNPs): Magnetically induced nanoparticles are formulated by the two main methods- top-down and bottom-up methods. The illustrative diagram of the 2 methods is given below.

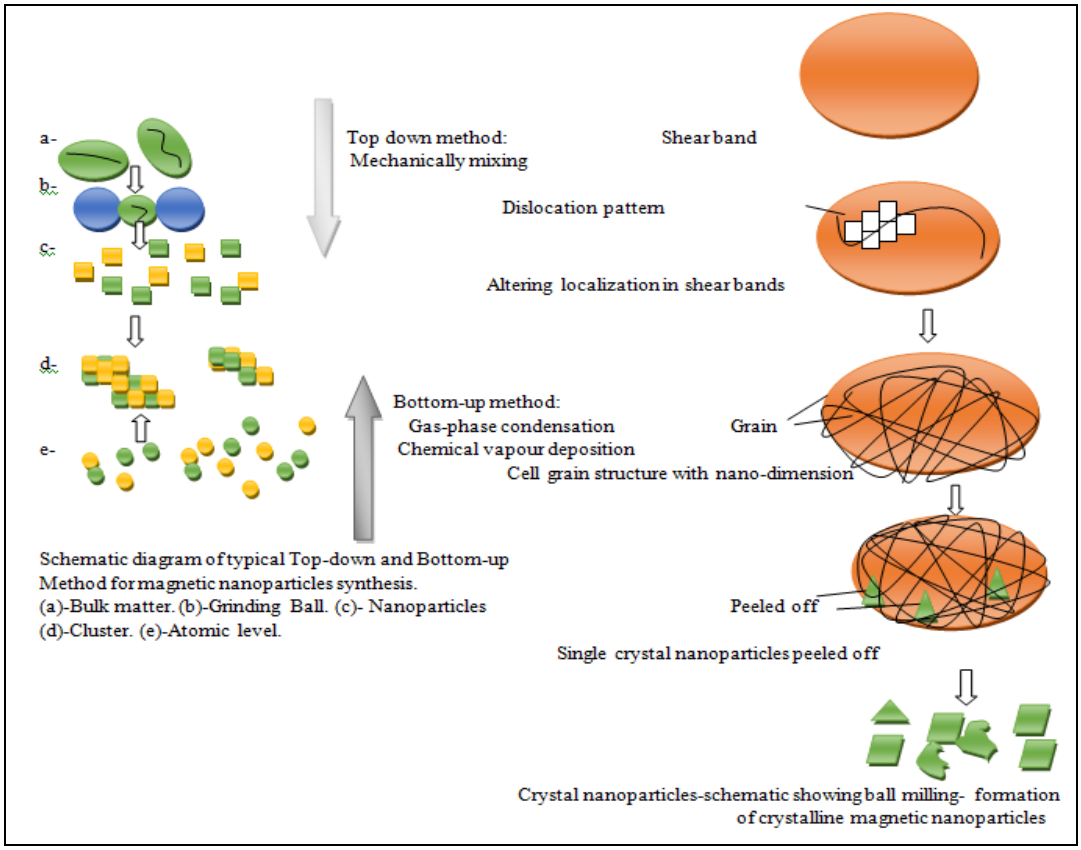


FIG. 1: METHOD OF PREPARATION OF MAGNETIC NANOPARTICLES

The top-down method includes ball milling, lithography, thin film or bulk material broken down into nanometre or micrometer size.

The bottom-up methods include magnetic nanoparticles formed by nucleation and growth process. Examples of bottom-up methods are GPC and wet chemical technique, and Sol-Gel method.

Ball Milling Method: John Benjamin developed the ball milling method in 1970 and used it to prepare reduced-size powders [27]. The working mechanism of the ball milling method is proposed by Fecht *et al.* [28].

Mechanical ball milling method is bifurcated into two types: High energy ball milling method [29] and ordinary ball milling method [30-31]. The high-energy ball milling method uses the ball mill's high energy to mechanically alloy the raw material and transform the raw material into nano-spinel type ferrite. The ordinary ball milling method mainly involves crushing iron oxide particles of huge size into very fine particles by force between the steel ball and the inner wall of the ball mill. The mechanical ball milling method is further bifurcated into dry and wet methods. The wet method is a very good option for getting crystal structure with high magnetization [32].

For the preparation of magnetic nanoparticles, there are three stages in ball milling method. The first stage includes deformations and dislocations of bulk material due to collision between ball and bulk materials. The second stage includes formation of small granules (nano size) due to accumulation, recombination, and rearrangement due to dislocation. The third stage includes granules orientation becoming random, and edges of bulk material are peeled off. In this way, the crystallized form of nanoparticles is obtained from bulk material [33].

In a recent experiment, the year 2020, the high-energy ball milling method was used for carbon encapsulated magnetic nanoparticles synthesis. In this experiment, carbon-encapsulated magnetic nanoparticles were manufactured using a high-energy ball mill working at an angular velocity of 1200rpm and having 100ml hardened stainless steel milling tanks. Ethylene glycol is used to reduce resistance, and dopamine drugs in various concentrations were added to the tank. Milling was stopped every 6 hours, and samples were collected from the tank. The sample was washed several times with deionized water and absolute ethanol, centrifuged and dried at 333 K in the air. Result found from this experiment includes- in the XRD pattern analysis, carbon encapsulation was found amorphous. The TEM observation found the average diameter as 13nm, 9nm, 7nm, and 6nm, respectively, for all samples. In magnetism analysis, smaller particles were found to have higher magnetic anisotropy constant because of various surface effects, and it contains larger coercive forces [130].

GPC Method: GPC is the bottom-up method in which particles are nucleated and grow to form magnetic nanoparticles. For many decades, scientists and researchers have tried hard to prepare magnetic nanoparticles using the gas-phase condensation (GPC) method. Granqvist and Buhrman prepared very fine nanoparticles using the GPC method in the year 1970s. Sputtering sources were not used, but instead, a thermal evaporation source was used. The particles were formed in the static, inert gas. But the size and crystallinity of the nanoparticles were uncontrollable.

Mainly two possible models are proposed for the growth of the magnetic nanoparticles prepared by the GPC system based on the overlap between the growth zone of magnetic nanoparticles and the plasma zone. In the first model, nucleation and growth of magnetic nanoparticles occur in the plasma region (also known as the hot region); in this, magnetic nanoparticles show good crystallinity being bigger. In the second model, the nucleation and growth zone of magnetic nanoparticles partially overlap within the plasma zone.

In this model, smaller-sized magnetic nanoparticles are obtained having poor crystallinity [34]. The merit of this method is that particle size and crystallinity are well-controlled, but the yield of it is generally low when compared with ball milling method. A sputtering source was adopted in 1991 for the GPC method, which made this method more effective for preparing magnetic nanoparticles [35]. The nanoparticle's yield and target utilization rate can be enhanced when compared with the conventional

planar targets. This can be done using a hollow tube cathode where three important factors for manufacturing were used. The first includes using sputtering pressure higher than a threshold pressure. The second includes the nucleation process to occur outside the tube target to separate nucleation and growth. The third includes setting extra plasma at the tube outlet targeting for better crystallinity of the nanoparticles [131].

Thermal Decomposition Method: For the preparation of magnetic nanoparticles, thermal decomposition is one of the simplest methods. The thermal decomposition method produces high-quality superparamagnetic magnetic nanoparticles [36-37]. Decomposition of the organometallic complex uses precursors like light, heat, or sound to prepare nanoparticles [38]. The disadvantage of the thermal decomposition method is that magnetite crystal size is difficult to adjust because the thermal decomposition temperature used to get decreased by the boiling temperature of any selected solvent. Solvent free thermal decomposition method can also be used to prepare magnetic nanoparticles in which the temperature and reaction time can easily be changed. Also, magnetic nanoparticles' particle size and crystallinity can be varied more efficiently [39]. Nowadays, the thermal decomposition of iron oleate complexes in the presence of oleic acid using a heating process is a much more convenient technique for producing large-scale nanoparticles [40-41].

An example includes preparing high-quality ferrofluid-based magnetite particles made using the thermal decomposition method where PMAO acts as the novel-phase transfer ligands. PMAO enhances the ferrofluid stability for as long as 6 months. At the concentration of approx. 5 mg/ml, SAR values are higher as 66.04 W/g measured at magnetic field amplitude of 80 Oe and frequency around 178 kHz. Manufactured ferrofluid gives readily available and cost-effective cancer treatment and diagnosis methods for future use [132].

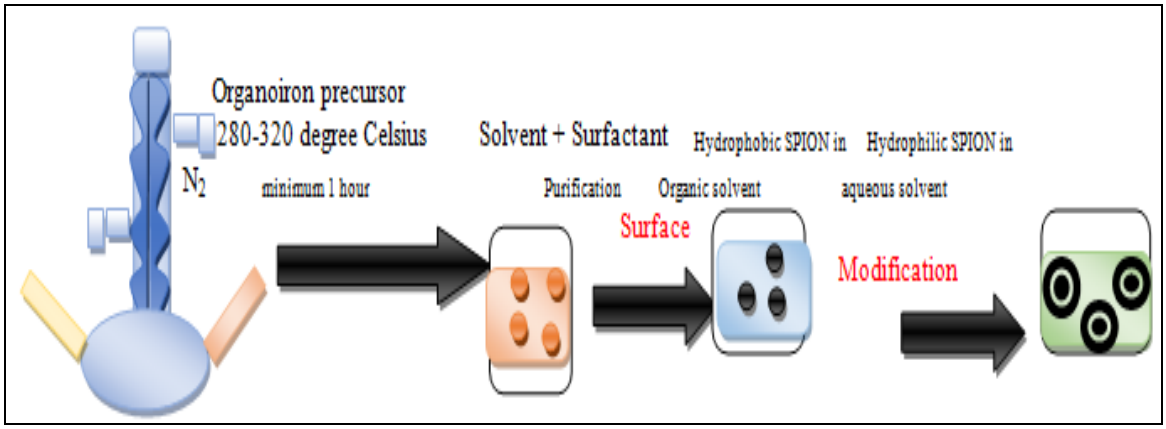


FIG. 2: EXAMPLE OF FORMATION OF HYDROPHILIC SPION IN AQUEOUS SOLVENT USING THERMAL DECOMPOSITION

Sol-Gel Method: The sol-gel method is a type of wet-chemical technique that is immensely used to prepare nanoparticles and thin films [42-44]. The use of polysiloxane layers with many functional groups (or a combination of them) has made it a way to use the sol-gel method in nanotechnology [45]. The sol-gel method contains various advantages over another, like it has good homogeneity, low cost, and is highly pure. The Sol-gel method is mainly used to prepare magnetic nanoparticles using metallorganic precursors [46-47]. Using the sol-gel method, ferric nitrate is reacted with ethylene glycol to produce iron oxides and a mixture of iron oxides. Still, pure magnetite cannot be produced using this method [48]. Magnetic nanoparticles can be easily synthesized using the sol-gel method combined with annealing under the vacuum using inexpensive, non-toxic ferric nitrate and ethylene glycol as initial materials. Magnetic nanoparticles can be obtained at a temperature range of at least 200-400 degrees Celsius. The size of obtained magnetic nanoparticles can be varied by varying annealing temperature, and magnetic properties can be easily evaluated [49]. In a recent experiment, a Mg0.5Zn0.5FenO4 magnetic nanoparticle, a novel catalyst, was efficiently synthesized using the green sol-gel process and worked as the magnetic photocatalyst for the fast decolorization of RB21

dye under encompassing conditions. This experiment is mainly performed to synthesize environmentally friendly, non-toxic, economical, easy to scale up, and free from volatile organic solvent, surfactants, *etc.* [133].

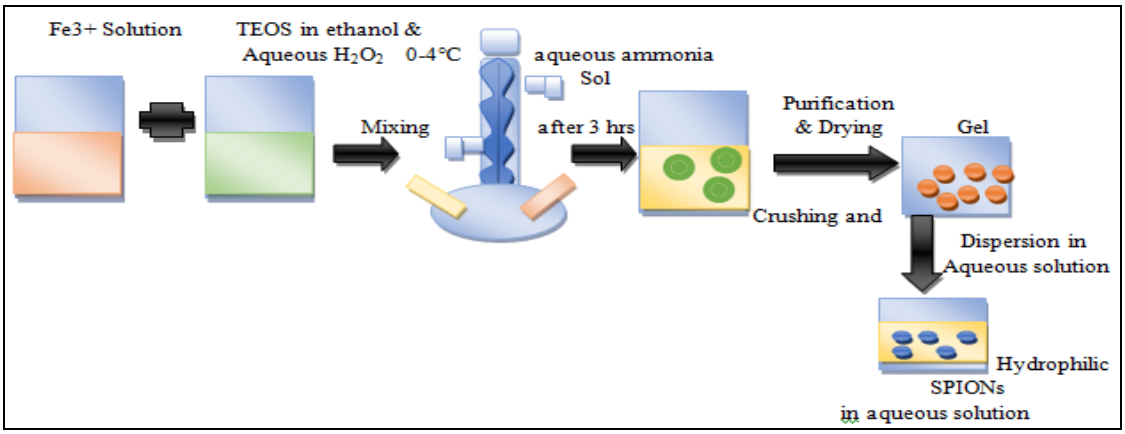


FIG. 3: EXAMPLE OF FORMATION OF HYDROPHILIC SPION IN AQ. SOLUTION USING SOL-GEL METHOD

Co-Precipitation Method: Co-precipitation is very effective and convenient way to formulate iron oxide from aqueous Fe_2+/Fe_3+ salt solution with the help of addition of base under ideal atmosphere at room temperature or elevated temperature [50]. In the homogenous aqueous solution, the hydrothermal condition was usually used to obtain ferrite nanoparticles by the co-precipitation of Fe^{3+} and Co^{2+} ions in the alkaline aqueous solution [51]. Rajendrain *et al*. demonstrated 6-20 nm sized cobalt ferrites prepared at room temperature in the aqueous solution by the oxidation of Fe^{3+} and Co^{2+} ions [52]. The size and magnetic properties of cobalt ferrite nanoparticles formulated by the co-precipitation method can vary greatly and depend upon the pH, salt concentration, counterion nature and stirring speed, etc. No systematic study has been done to study the effect of precipitation temperature on the synthesis of $CoFe_2O_3$ in a homogeneous aqueous solution prepared by the co-precipitation method [53]. Co1-xZnxFe_2O_4 nanoparticles having different x values were synthesized by the co-precipitation method. This nanoparticle possesses a single-phase cubic spinel structure confirmed by the XRD analysis method. Crystallite size increases with increasing Zn replacement in prepared samples, which was eventually confirmed by XRD study [134].

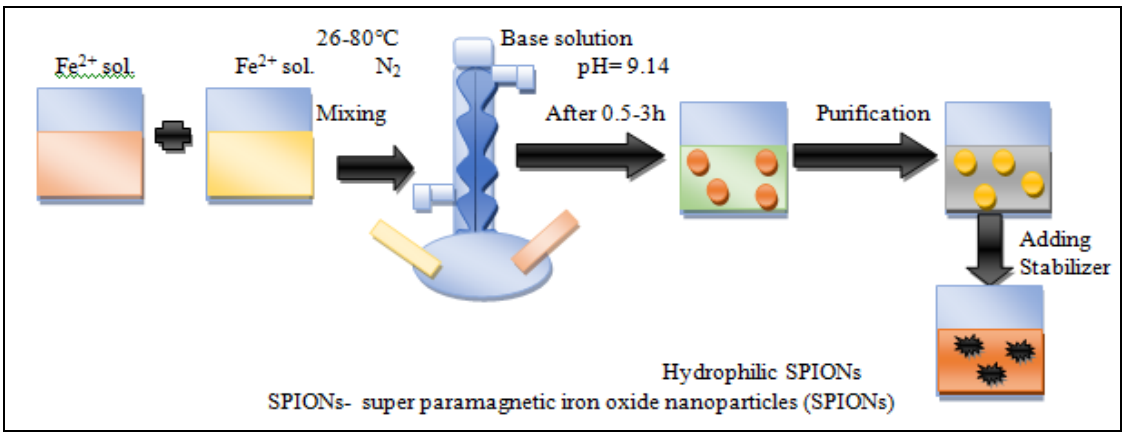


FIG. 4: EXAMPLE OF FORMATION OF HYDROPHILIC SPIONs

Microemulsion method and hydrothermal methods are also used to in the formation of magnetic nanoparticles. In the microemulsion method, a micro emulsion is thermodynamically stable isotropic dispersion of two immiscible liquids; the micro domain of both liquids is stabilized by interfacial film of surfactant molecule [54]. The hydrothermal method's hydrothermal synthesis system contains metal linoleate, ethanol-linoleic acid liquid phase, and water-ethanol solution at various reaction temperatures under hydrothermal conditions [55].

TABLE 1: OUTLINE OF COMPARISON BETWEEN VARIOUS PREPARATIONS METHODS OF MNPs

Synthetic method	Synthesis	Reaction temp(°C)	Reaction period	Solvent	Surface capping agent	Size distribution	Shape control	Yield	Ref.
Co-precipitation [50]	Very simple	20-90	minutes	water	needed	Relatively narrow	Not good	high	53,80
Thermal decomposition [36, 37]	Complicated	100-320	Hours-day	Organic compound	needed	Very narrow	Very good	high	40, 41, 80
Microemulsion [54]	Complicated	20-50	hours	Organic compound	needed	Relatively narrow	good	low	54, 80
Hydrothermal synthesis [55]	simple	220	Hours-days	Water-ethanol	needed	Very narrow	Very good	medium	55, 80

TABLE 2: MERITS AND DEMERITS OF VARIOUS MANUFACTURING METHODS OF MNPs

Methods	Advantages	Disadvantages	Reference
Gas-phase deposition/condensation [34,35]	Easy to perform	Difficult to control particle size	34, 35, 94
Wet chemical preparation methods			
Sol-gel synthesis [42, 43]	Precisely controlled in size, aspect ratio, and internal structure	Weak bonding, low wear resistance, high permeability	44, 94
Chemical co-precipitation [50]	Simple and efficient	Not suitable for the preparation of highly pure, accurate stoichiometric phase	50, 94
Hydrothermal reactions [55]	Easy to control particle size and shape	High reaction temperature, high pressure	55, 94

Features Magnetic Nanoparticles: A physical and chemical features of magnetic nanoparticles mainly depends on their molecular composition, chemical structure, and synthesis route (preparation pathway). A magnetic nanoparticle shows superparamagnetic nature and ranges from 1 to 100 nm in size.

Surface Features:

Surface Charging: Veiseh *et al.* proposed that charged magnetic nanoparticles cause absorption of proteins into it, which is recognized by RES and removed from circulation (Duran, *et al.* 2008). A magnetic nanoparticle with a positive charge binds to non-specific cells, and magnetic nanoparticles with strong negative charge increase liver uptake.

This process gives an electric potential that provides the basis of electrophoresis, the movement of dispersed colloids relative to fluid on application of an external electric field. Duran *et al.* suggest examples of how this helps in the preparation and the use of nanoparticles, such as giving a coat and drug loading [56].

Surface Effect: On decreasing particle size, many nanoparticle atoms are surface atoms that indicate that surface and interfacial tension are essential. For example, for face-cantered cubic (fcc) cobalt with a diameter of approximately 1.6 nm, 60% of total spins is surface spins [57].

Size-dependent Magnetic Features: Magnetic nanoparticles exhibit very distinguished magnetic feature that differs from the bulk material. Features like coactivity (Hc) and susceptibility depend upon size, composition, and shape differences [58]. When the size of nanoparticles is reduced below the critical value (DC), individual nanoparticles become a single magnetic domain and exhibit superparamagnetic behaviour when the temperature is adjusted above the blocking temperature (Tb). These nanoparticles have a larger constant magnetic moment and exhibit gigantic paramagnetic atoms with a higher response speed when magnetic fields are applied with zero remanences (residual magnetism) and coactivity (the field required to bring magnetization [84] to zero). These properties make superparamagnetic nanoparticles very forceful against the magnetic resonance contrast agents. Another size-dependent feature of magnetic nanoparticles is super-paramagnetism. Magnetic anisotropic energy resists from spin-up form to spin-down form of magnet which is proportional to multiplication of

magnetic anisotropic constant(Ku) and volume of magnet (V) [135]. Bulk materials have anisotropic magnetic energies, which are much higher than thermal energies (kT); the thermal energy of nanoparticles inverts the magnetic spin direction, following magnetic fluctuation results in total zero magnetization, called superparamagnetism [136].

Types of Magnetic Nanoparticles:

Oxides:

Ferrite: Ferrite nanoparticles are so much researched magnetic nanoparticles till now. When the ferrite nanoparticles get less than 128 nm, they become superparamagnetic, preventing self-lumps as they display magnetic behaviour on an external magnetic field application. The remanence becomes zero when the external magnetic field is removed. Like the non-magnetic oxide nanoparticles, the surface of ferrite nanoparticles is often altered by silicones or phosphoric acid derivatives, surfactants, etc., to increase its stability in the solution.

Metallic Magnetic Nanoparticles: Metallic core of magnetic nanoparticles can be modified by surfactants, oxidation, precious metals, and oxidation. In the presence of oxygen, Co nanoparticles forms anti-ferromagnetism, CoO layer on Co nanoparticle's surface [59]. Nowadays, work has been done on producing Co core Co O shell nanoparticles with golden outer shells. Nanoparticles having a magnetic core made of basic iron or cobalt with a non-reactive shell made of grapheme is being synthesized recently. It consists of various merits as compared with ferrite or elemental nanoparticles like:

Higher stability in an organic solvent as well as in the acidic and basic medium. The chemistry of graphene surfaces uses many methods already known for carbon nanotubes. Higher magnetization.

Functionalization and Surface Coating of MNPs:

Polymeric Coatings: For biomedical applications, surface coating is essential for magnetic nanoparticles. Because of the superparamagnetic properties, nanoparticles are still inclined to form a lump due to their high surface energy. Colloidal electrostatic stabilization formed due to the repulsion of surface charges on nanoparticles is not correct to prevent lumps in biological fluids because salts or other electrolytes can neutralize this charge. Also, the evading uptake by RES and maintaining a lengthy plasma half-life is crucial for many MNPs application in medicine [60].

To prevent formation of lumps and opsonisation, the polymeric coating is done over nanoparticles which gives a steric barrier to nanoparticles. Also, these coating provides surface charge and chemical functionality to the nanoparticles. Due to coating, some variation occurs in the nature of the chemical structure of the polymer (ex-hydrophilic/hydrophobic, biodegradability etc), length or molecular weight of polymer, and manner in which polymer is attached (ex-electrostatic or covalent bonding), the conformation of the polymer and amount of surface covered. Monomeric species like biophosphonates [61], dimercaptosuccinic acid (DMSA) [62] and alkoxysilanes [63-64] are checked and its coating on magnetic nanoparticles.

Liposome and Micelles: Liposome drug delivery carrier is one of the oldest forms of nanomedicine. Liposomes are the phospholipids bilayered membrane carrier system ranging from 100 nm to 5 micrometers in size and are used in the delivery of proteins, peptides, small molecules, DNA, and MR imaging contrast agents [65].

The merit of liposomal encapsulation is its *in-vivo* nature and also to determine PEGylation processes, which gives wider circulation times. Liposomes can also encapsulate a larger number of magnetic nanoparticles core and deliver all at a time, avoiding dilution at the targeted site. Combining therapeutic agents in payloads enhances the multifunctionality of the vehicles. Multifunctional micelles forms amphiphilic block copolymer that entrapped magnetic nanoparticles for various applications [66-67]. Martine *et al.* formulate magnetic-loaded liposome (MFLs) by encapsulating maghemite nanocrystal within unilamellar vesicles of phosphatidylcholine and DSPE-PEG_{2000} [68].

Core-shell Structures: Core-shell structures use biocompatible silica or gold to encapsulate the magnetic nanoparticles, which is very much used for developing MRI contrast agents or MTCs for

drug delivery. MRI is free from radiation technique which is used to study clinical-based diagnosis [102]. The non-reactive coating protects against chemical degradation of magnetic core and prevents the release of potentially toxic chemicals. Specialization chemistry is generally established between these materials and those made of magnetic nanoparticles.

Silica shells are a very beneficial option to be used as protective coating on magnetic nanoparticles due to its stability within aqueous conditions and easy synthesis. The sol-gel process uses tetraethoxysilane (TEOS) to produce a coating of measured thickness [69-70]. Using functional groups like alkoxysilanes, 3-aminopropyltriethyoxysilane (APS) allows for reactive surface groups, which should add to core-shell structures. Also, the potential to encapsulate functional molecules like changing images or therapeutic agents within the protective matrix is unique property and potential to these nanostructures [71-72].

Functional Ligands: Ligands like the targeting agents, permeation enhancers, optical dyes, and the therapeutic agent's conjugate on the surface or incorporates within nanostructures. To perform nanoscale engineering, bio-conjugation chemistries utilized for protein coupling have been studied [73-74].

Actions like avidin-biotin binding, use of heterobifunctional linkers from amide, ester, or disulfide bonds, and click chemistry [75-76] are the latest and exhibit are attaching ligands to magnetic nanoparticles. Those using magnetic nanoparticles may find it helpful to view the basic concept of colloidal science to prevent unwanted flocculation or lumping during the processes [77].

Biocompatibility and Safety of Magnetic Nanoparticles: Toxicity is a very serious problem and an important factor in regenerative medicine and tissue engineering.

MNPs in regenerative medicine needs the labelling of cells that are implanted within the body. Using particle which is toxic can significantly diminish the therapeutic efficacy of cell-based therapy. Toxicology studies the adverse effects of chemical, physical and biological agents on people, animals, and the environment. When MNPs are incorporated into therapy and transplanted within the body, the risk of MNPs accumulating inside the organ is a major problem. This could cause an immunological or inflammatory response by the body. The above are hugely undesired scenarios.

Applications: A huge type of application is present for this type of particle which mainly includes:

Medical Diagnosis and Treatments: Cancer can also be treated by attaching magnetic nanoparticles to free-floating cancer cells, capturing and carrying them out of the body. Magnetic nanoparticles are used in experimental cancer treatment called magnetic hyperthermia, where the heat of MNPs is used when they are placed in a different magnetic field. Magnetic nanoparticles are coated using antibodies targeting cancer cells or proteins. For the detection of cancer also, magnetic nanoparticles are used.

***In-vivo* Applications:** For the *in-vivo* studies, two major factors are very important including:

Size and Surface Functionality: Particles with a diameter of 10-40 nm including ultra-small SPIOs play an essential role in prolonging blood circulation. Superparamagnetic iron oxide nanoparticles (SPIOs) diameter affects the *in-vivo* distribution without targeting surface ligands [78].

Therapeutic Application:

Hyperthermia: When placing super para magnetic iron oxide in altering current (ac), magnetic field randomly changes the magnetization direction between parallel and anti parallel orientation, helps to transfer heating magnetic energy to particle. This property is used in vivo to increase temperature of tumour tissues to destroy pathological cells by hyperthermia. In the past studies, magnetic cationic liposomal nanoparticles and dextran-coated magnetite increases the temperature of tumour cell very effectively for hyperthermia treatment in cell irradiation.

Diagnostic Applications:

NMR Imaging: The formation of NMR imaging technique created a new class of pharmaceuticals called magneto-pharmaceuticals. When administered to patients, these drugs enhance the image contrast between normal and diseased tissue and tell the organ function status and blood flow. Also, it can be used to develop the new imaging

method [85]. The combination of magnetic particles with florescent dyes or both is used, and radioactive tracers etc are under investigation [86].

Genetic Engineering: Magnetic nanoparticles are used in various types of genetic applications. It is used for the separation/isolation of messenger RNA. It can be quickly done within 15 min. Magnetic bead is attached to a poly T tail. When mixed with mRNA, the poly-A tail of mRNA is attached to bead's poly T tail, and separation occurs at the side of the tube and the liquid is poured out.

Industrial Applications: Magnetic encapsulation is very important in many areas of life and also in different branches of industry. Magnetic iron oxides and metallic iron [83] are very commonly used as a man-made pigments in ceramics, paints, and porcelain. These materials are useful for the fundamental study of material science and its application also [79].

TABLE 3: APPLICATIONS OF MNPs

Application	Active ingredient	Polymer	Organic phase	MNPs	Reference
Magneto-chemotherapy	Doxorubicin, Paclitaxel	PVA	Chloroform	Iron oxide	[81], [87], [105]
Theranostics	Stilbene (hydrophilic drug), Doxorubicin	PCL, Mpeg-PPSu, FA-PEG114-PLAx-PEG46-acrylate and MPEG114-PLAx-PEG46-acrylate	Dichloromethane, Chloroform	Iron oxide	[81], [87], [106],[107], [108]
Drug delivery	Cisplatin	PLGA, PEG, mPEG-PPSu-mPEG	Dichloromethane	Iron oxide	[81],[109]
Hyperthermia	Doxorubicin, Paclitaxel	PLGA, PVA	Ethyl acetate, Chloroform	Iron oxide	[81], [87], [105]

TABLE 4: CLINICAL STUDIES OF MAGNETIC NANOPARTICLES

Types of magnetic nanoparticles	Target disease	Application	Intervention	Status	Reference
Ferumoxytol	Brain glioblastoma, Multiple Sclerosis	Imaging in patient with glioblastoma multiforme and sclerosis	National Institutes of Health Clinical Center, 9000 Rockville Pike Bethesda, Maryland, United States	Completed	[88], [110]
Ferumoxytol	Brain neoplasm, cancer of lymph node	Imaging of metastatic brain tumour, Magnetic Resonance Imaging	University of Texas MD Anderson Cancer Center Houston, Texas, United States	Completed	[89], [110]
Ferumoxytol	Brain glioblastoma, Myocardial Infarction	Steady-state blood volume maps in glioblastoma, Magnetic Resonance Imaging.	Royal Infirmary of Edinburgh Edinburgh, Midlothian, United Kingdom University of Edinburgh Edinburgh, Midlothian, United Kingdom	Completed	[90], [110]
Nano Therm	Brain glioblastoma	Intratumoral therapy	-	-	[91]
Ferumoxtran-10 (dextrane coated)	CNS inflammatory disease	Imaging of CNS inflammatory disease	-	-	[92]
Ferumoxtran-10	Multiple sclerosis, Prostrate cancer, Metastasis, Prostatectomy	Imaging of multiple sclerosis and cancer	Charité- Universitätsklinikum Berlin Berlin, Germany Vivantes Klinikum Am Urban Berlin, Germany Universitätsklinikum Bonn Bonn, Germany	Recruiting	[93], [111]
Super paramagnetic Iron Oxide	Pancreatic cancer	Magnetic Resonance Imaging	Massachusetts General Hospital Boston, Massachusetts, United States	Completed	[111]
Feraheme	Renal Transplant Rejection	MRI-GE Healthcare 3 Tesla magnet	Lucile Packard Children's Hospital Stanford, California, United States.	Completed	[112]
Ferumoxytol	Papillary Carcinoma of Thyroid Gland	MRI	Massachusetts General Hospital Boston, Massachusetts, United States	Completed	[113]

Metastatic Medullary Thyroid Cancer	
Follicular Thyroid Cancer	
Lymph Node Metastasis	

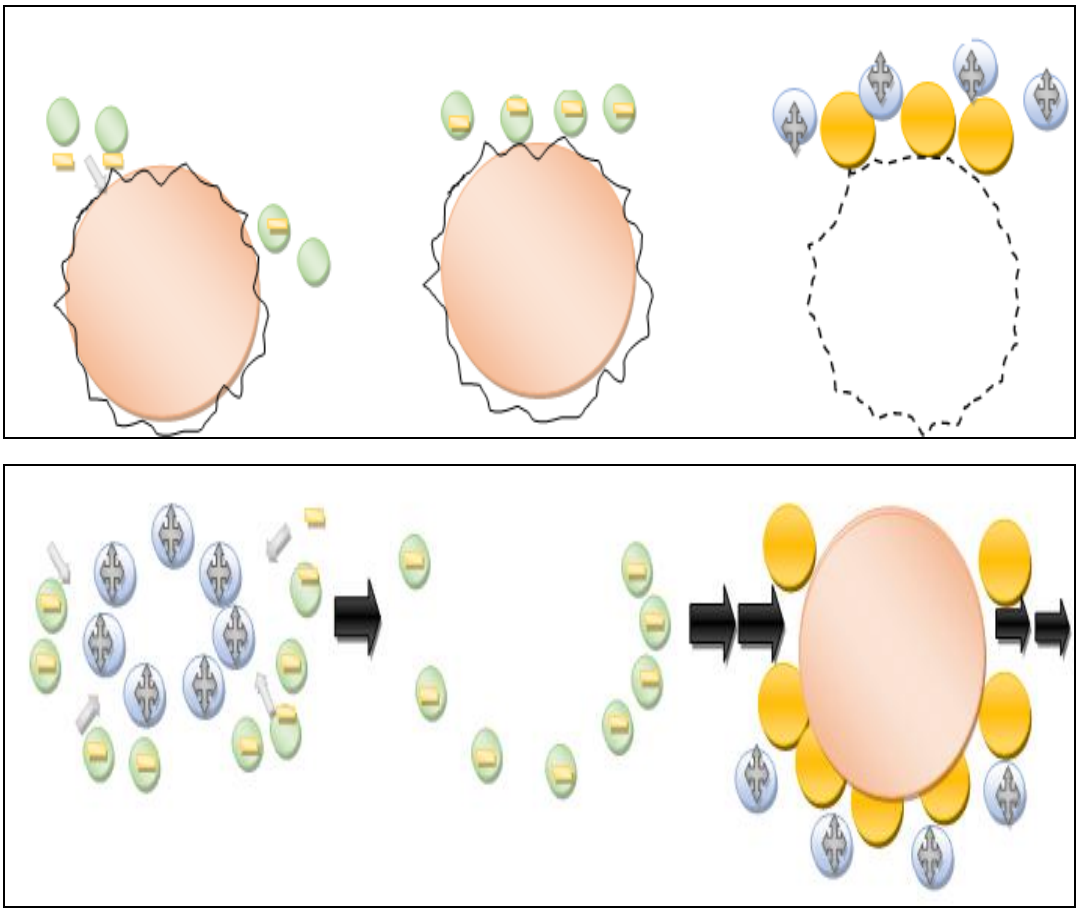


FIG. 5: MAGNETIC NANOPARTICLES ENCAPSULATION USING LAYER-BY-LAYER METHOD {MODIFIED FROM 103

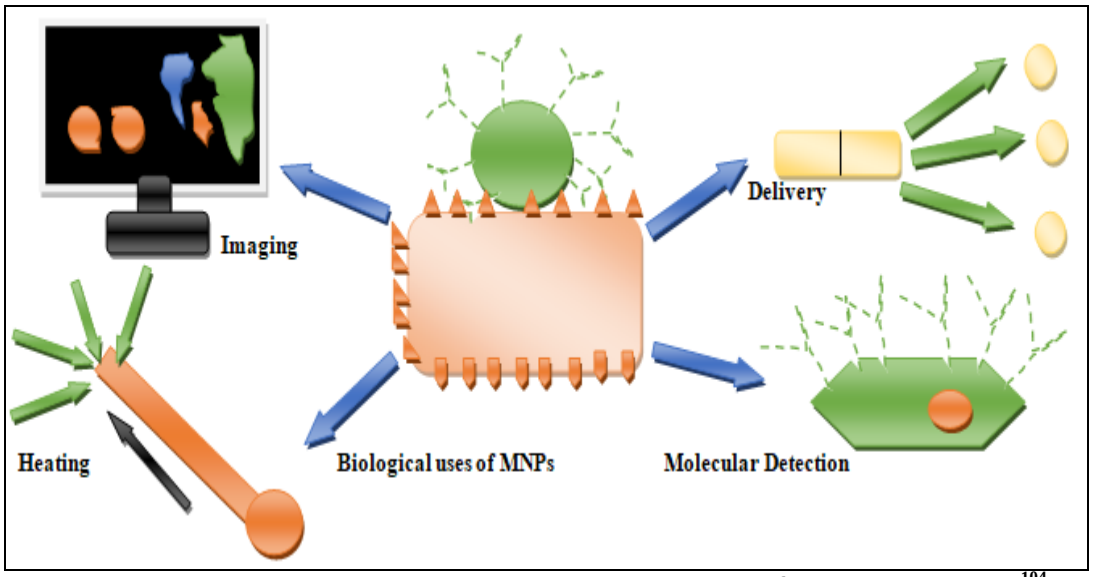


FIG. 6: VARIOUS USES OF MAGNETIC NANOPARTICLES {MODIFIED FROM [104]

TABLE 5: LIST OF RECENT PATENTS FOR PREPARATION METHOD OF LIPID-BASED MAGNETIC NANOPARTICLES

S. no.	Patent No.	Status	Title	Reference
1	US20080102127	A1	Hybrid lipid-polymer nanoparticles delivery composition	[95]
2	WO2011116963 US20130017239	A3 A1	Lipid nanoparticles capsules	[96],[97]
3	WO2008149215	A3	Method for the preparation of solid lipid micro- and nanoparticles.	[98]
4	US20130011339	A1	Nanoparticles compositions comprising a lipid bilayered and associated method.	[99]
5	CN102048697	A	Method for preparing solid lipid nanoparticles of water-soluble anti-tumour medicine	[100]
6	CN101972229	B	Preparation method of catalyse solid lipid nanoparticles preparation	[101]
7	US20090214633	A1	Pharmaceutical compositions suitable for the treatment of ophthalmic diseases	[114]
8	US20100104522	A1	Composition for skin external use containing omega-3 fatty acid	[115]
9	WO2006068890	A3	Lipid particles comprising bioactive agents, methods of preparing and uses thereof	[116]
10	US20130037977 (EP-2558074)	A1 A1	Preparation of lipid nanoparticles	[117], [118]
11	WO2010080724 WO2011149733 WO2011153120 WO2012044638 WO2012061259 US20120149894 WO2012162210	A1, A3, A1, A1, A3, A1, A1	Various patents on novel cationic lipids for oligonucleotides delivery	[119], [120], [121], [122], [123], [124], [125]
12	US20130035279	A1	Method and a system for producing Thermolabile nanoparticles with controlled properties and nanoparticles matrices made thereby	[126]
13	WO2007000531	A3	Method for preparing solid lipidic particles using a membrane reactor	[127]
14	WO2007028421	A1	Process for the production of nanoparticles	[128]
15	US20080286365	A1	Method for producing solid-lipid composite drug particles	[129]

CONCLUSION: Rapid development in the preparation of magnetic particles has allowed the use of new chemicals and compounds for more efficient targeting of the drug molecules to the targeted site, and many novel techniques are developing for applying a magnetic field, which can be used to treat a disease like cystic fibrosis and localized cancerous tumors. Very less clinical trials are done regarding magnetic nanoparticles, but their results are promising. Magnetic targeting is not useful in all cases but is still an effective tool as a biomedicine [82] used to treat different types of diseases and conditions.

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