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Magnetic nanosystem a tool for targeted delivery and diagnostic application: Current challenges and recent advancement

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ABSTRACT

Over the last two decades, researchers have paid more attention to magnetic nanosystems due to their wide application in diverse fields. The metal nanomaterials' antimicrobial and biocidal properties make them an essential nanosystem for biomedical applications. Moreover, the magnetic nanosystems could have also been used for diagnosis and treatment because of their magnetic, optical, and fluorescence properties. Superparamagnetic iron oxide nanoparticles (SPIONs) and quantum dots (QDs) are the most widely used magnetic nanosystems prepared by a simple process. By surface modification, researchers have recently been working on conjugating metals like silica, copper, and gold with magnetic nanosystems. This hybridization of the nanosystems modifies the structural characteristics of the nanomaterials and helps to improve their efficacy for targeted drug and gene delivery. The hybridization of metals with various nanomaterials like micelles, cubosomes, liposomes, and polymeric nanomaterials is gaining more interest due to their nanometer size range and nontoxic, biocompatible nature. Moreover, they have good injectability and higher targeting ability by accumulation at the target site by application of an external magnetic field. The present article discussed the magnetic nanosystem in more detail regarding their structure, properties, interaction with the biological system, and diagnostic applications.

1. Introduction

Magnetic nanosystem has been considered a potential tool for biomedical application. MNs have been widely used in various extraction processes, killing cancer cells, bioseparation, and drug delivery applications. It is also used in diagnosis and treatment; hence it is ideal for theranostic application. Furthermore, MNs are a fantastic alternative for targeted drug delivery systems due to their special magnetic features, which include minimal toxicity, high magnetic saturation, and stability in biological fluids. It has been an effective photodynamic treatment agent (Akbarzadeh et al., 2012).

Due to MNs' widespread use in several industries over the past 20 years, researchers have focused more on them. The antibacterial and biocidal qualities of metal nanoparticles make them an essential nanosystem for the biomedical industry and therapeutic applications. Moreover, the magnetic nanosystems could have also been used for diagnosis and treatment because of their magnetic, optical, and fluorescence properties.

MNs also have application in cancer therapy as it has to target ability using an external magnetic field. Because in cancer, the drugs get difficulty killing the cancer cells due to the non-specificity of the drug. As a result of this, it shows side effects lead to harmful effects on normal cells.

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The fabrication of a targeted drug delivery system could overcome this drawback of the anticancer agents. The magnetic nanosystems work under magnetic guidance, achieving high targeting and cell specificity (Nandwana et al., 2015). It could be used as an excellent drug delivery system due to its sustained release ability with higher encapsulation efficiency. The magnetic field's presence may alter the drug's biopharmaceutical parameters (Barreto et al., 2013).

This system shows good biocompatibility over the other type of nanosystems. Some in-vivo studies stated the safety and biocompatibility of MNs as they do not offer any accumulation in the organs or any part of the body; instead, they are prone to rapid elimination from the body.

With all the above advantages and efficient properties of MNPs researchers are facing many problems related with its biocompatibility, stability and targeting ability. Hence the current challenges also should be discussed while considering its efficacy for clinical therapy.

Particles possessing magnetic properties and falling within the nanoscale are known as magnetic nanoparticles. It is possible to communicate the magnetic properties of MNPs using a variety of metals; examples of such metals include nickel, cobalt, and iron. Coating the magnetic core with organic and inorganic polymers, such as fibronectin, dextran, and RGD peptides, can improve biocompatibility by shielding biological entities from harmful reactions. Surface charge modifications, protein-binding ability, and surface topography can all be used to tailor surface coatings to specific requirements. This improves the functionalization of the particles and promotes better interactions with biological entities while having the least amount of harmful effects. Concerns about toxicity play a significant role in the fields of tissue engineering and regenerative medicine. As was previously mentioned, MNPs are used in regenerative medicine when cells (the therapeutic agents) are labeled with MNPs so they can be implanted into the body. The therapeutic efficacy of cell-based therapy can be considerably reduced by using toxic particles for an extended length of time (Huang et al., 2008). Various studies revealed that initial assessment of toxicity of novel MNPs with the use of *in vitro* tests shows biocompatibility of MNPs (Sharifi et al., 2012b).

The stability of MNPs is the critical problem associated with the application of MNPs in clinical therapy. Various research groups have worked to solve this problem. Hg, Pb, Cd, and Cu were found to be effective adsorbents for Fe_3O_4 nanoparticles coated with humic acid in wastewater. The magnetic source for these adsorbents is Fe_3O_4 nanoparticle; however, it is susceptible to air oxidation, resulting in magnetization loss (Yantasee et al., 2007). Although coating the Fe_3O_4 with inorganic shells such as silica and carbon improved its chemical stability, the magnetic response of the adsorbent decreased after coating. To resolve the conflict between chemical stability and magnetic response, calcine Fe_3O_4 nanoparticles to obtain a good crystalline structure (Zhang et al., 2007; Lu et al., 2005; Q. Gao et al., 2009). For biomedical applications, MNPs' ability to retain their colloidal stability and dispersibility is crucial (Colombo et al., 2012). MNPs typically need to be smaller than 100 nm in mean size in order to display superparamagnetic characteristics. Furthermore, MNPs with a small mean size offer benefits in terms of pharmacokinetics. In fact, smaller-sized nanoparticles are less likely to be ingested by macrophages and show improved diffusion and distribution towards the intended sites (Hosu et al., 2019). Based on the previously mentioned, a large portion of MNP research is focused on designing and creating MNPs with a high magnetic power and an appropriate mean size while maintaining their superparamagnetic characteristics.

The present review discusses the magnetic nanosystem in more detail regarding their structure, properties, interaction with the biological system, and recent advancement in diagnostic applications and therapy.

1.1. Types of magnetic nanosystems

1.1.1. Magnetic nanofibres

Nanofibers (NFs) have received a lot of attention lately due to advances in fundamental research and technological applications in nanoscience and nanotechnology. Numerous benefits are associated with NFs, including their large specific surface area, high aspect ratio, and significant shape anisotropy. Furthermore, they offer the ability to precisely control bulk density, diameter, connectivity, and surface properties. By using nanotechnologies to dope NFs with magnetic nanoparticles (MNPs), MNFs can combine the benefits of MNPs and NF. Additionally, using this tactic could result in MNPs and magnetic powder working in concert. Electrospinning, phase separation method, template method, decomposition method, magnetic field assisted method, and decomposition method are some of these nanotechnologies. MNFs have a lot of potential for use in many different contexts (Chen et al., 2018).

The researchers have developed magnetic nanofibres using β-lactoglobulin (BLG) and magnetic glass ceramic nanoparticles (MGNPs) colloids. The electrospinning method was used to fabricate the magnetic nanofibres, and SEM and TEM evaluated their morphology. The average diameter of magnetic nanofibres was found to be 370 nm. The use of MGNPs in nanofibres leads to a decrease in the average diameter to 150 to 240 nm (see Fig. 1), resulting in decreased magnetization. As the concentration of MGNPs increases, magnetic properties like saturation magnetization (Ms) and remnant magnetization (Mr) also increase in polymer solution (Erfan et al., 2019).

Biomedical application: Biocompatible magnetic materials have many applications in the biomedical fields, including drug release, enzyme immobilization, biological separation and purification, and magnetic resonance imaging. These materials have the advantages of easy operation, easy separation, easy modification, and low toxicity or nontoxicity. The drug release systems can be divided into four categories based on the principle of controlled drug release: diffusion control systems, chemical control systems, solvent activation systems, and regulatory release systems. Because of their high transport efficiency, ability to target therapy, magnetic response, low toxicity, high specific surface area, controlled size, biocompatibility, biodegradability, and superparamagnetic qualities, magnetic nanomaterials are widely used in controlled drug release (Chang et al., 2021).

A type of MNFs segments for electrospinning and sonication cell manipulation was presented by Liu et al., 2012. The segments were made by MNP in a polymethylglutamic acid precursor solution. When NFs were segmented using ultrasound, the findings showed that as acoustic time is reduced, the length of the fiber segments also decreases (see Fig. 1).

The average fiber diameter was approximately 400 nm, as demonstrated by the SEM images, and the MNPs were evenly distributed throughout the nanofibers. Additionally, cells were cultivated in media containing fibers and the procedures of cell culture, digestion, and passage were monitored in order to assess the use of magnetic fibers in cell biology.

1.1.2. Multifunctional magnetic nanoparticles

Magnetic nanoparticles (MNPs) have particle size ranges between 1 and 100 nm. An external magnetic field can be used to accelerate these particles. Among the various MNPs, the nanoparticles with superparamagnetic properties have broad interest due to their strong magnetic interactions in the external magnetic field. The core containing Fe, Ni, or Co as the main component is responsible for the quantum effect, whereas the coating stabilizes and shields the core from the medium's chemical effects (Dürr et al., 2013). MNPs are most widely used for drug delivery applications due to their targeting ability. In a magnetic drug delivery system (MDDS), a superconducting magnet is used with a magnetic field to guide MNPs to a specific organ or tissue. This leads to administering a higher quantity of drugs and tends to lower the toxicity

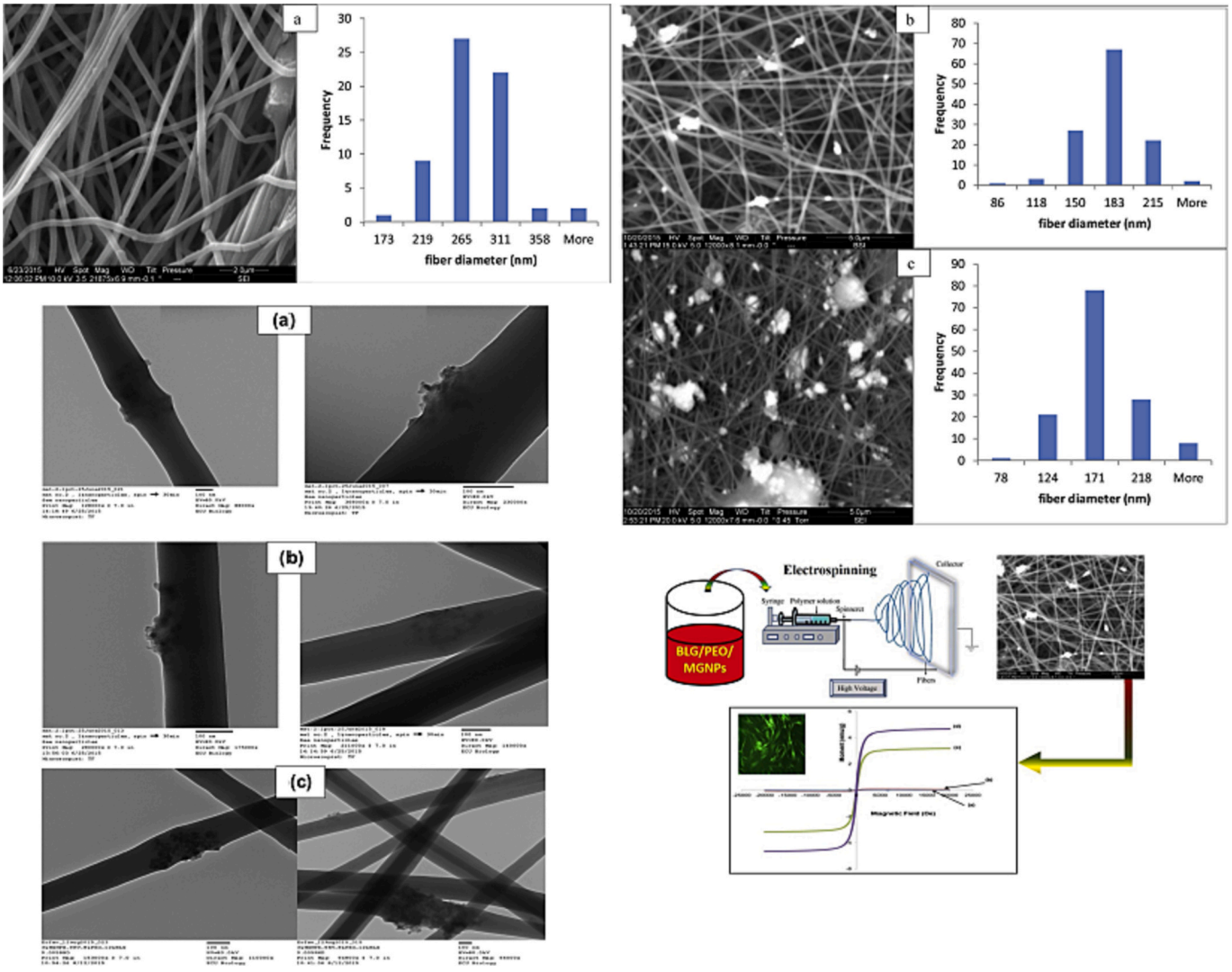

Fig. 1. Showing Magnetic nanofibres with various diameters and the effect of the addition of different concentrations of polymer solution (adapted from Erfan et al., 2019).

towards the normal cells (Flores-Rojas et al., 2022; Yoshida et al., 2007).

1.1.3. Magnetic nanocluster

Nanoscience is one of the most important fields of study in modern science. Thanks to nanotechnology, scientists, engineers, chemists, and medical professionals can now operate at the molecular and cellular levels, making major strides in the life sciences and healthcare. The application of nanoparticle (NP) materials offers a number of advantages due to their unique physicochemical properties and size. Due to the widespread applications of magnetic nanoparticles (MNPs) in the domains of biotechnology, biomedicine, material science, engineering, and the environment, there has been a great deal of interest in the synthesis of MNPs of different kinds (Tartaj et al., 2003). The biological sciences currently have few real-world uses for nanostructured materials. Nevertheless, the remarkable properties of these materials present a very promising future for their use in this sector. Nanoclusters are incredibly small particles with nanometer-scale dimensions, or micron size, between molecules and tiny structures. As materials, they can exhibit properties that are not present in larger structures, even 100 nm, but as molecules, their enormous size allows them to exhibit quantum behavior in previously undiscovered domains. Biology, chemistry, and physics have all made such significant strides recently. The preparation of these monodisperse-sized nanocrystals is important because their dimensions greatly influence their properties (Davaran and Entezami, 1996; Rye, 1996; Portet et al., 2001). Magnetic nanoparticles find extensive applications in industry, such as magnetic recording media, and in medicine, where they are used as cancer treatment agents and in magnetic resonance contrast media. For every potential application of magnetic nanoparticles, different characteristics are required. For example, in data storage applications, particles with a stable, switchable magnetic state are required to represent bits of information that are not affected by temperature fluctuations. For use in biological applications, particles with superparamagnetic characteristics at room temperature are preferred (Cabuil, 2004; Morcos, 2007; Ersoy and Rybicki, 2007). For use in therapy, biology, and medical diagnosis, the magnetic particles also need to be stable under physiological conditions and at pH 7 in water. The size of the particles—which should be small enough to avoid precipitation due to gravitational forces—as well as the surface chemistry and charge—which produce both steric and coulombic repulsions—will determine how colloidally stable this fluid is.

Paramagnetic nano-aAPC was encouraged to aggregate using a magnetic field, boosting T-cell activation. An external magnetic field stimulates paramagnetic nano-aAPC-linked T cells. To encourage TCR aggregation and aAPC-mediated activation, nano-aAPC is magnetized and pulled to the field source and surrounding nanoparticles in the field. Applying an external magnetic field on naive cells caused the

aggregation of nano-aAPC. Additionally, it aids in boosting T cell proliferation both *in vitro* and *in vivo* following adoptive transfer (Perica et al., 2014a, 2014b).

Artificial antigen presenting cells (aAPCs) are an effective tool for both adoptive and active immunotherapy because they provide stimulatory signals to cytotoxic lymphocytes. Until now, micron-sized beads have been combined with T cell activating proteins, like MHC peptide or CD3, to create aAPC. Because of their unique trafficking and biophysical interaction characteristics, nanoscale platforms may make it possible to develop novel immunotherapeutic approaches (Rhodes and Green, 2018). Various research groups have worked on the iron oxide and dextran based aAPCs. Surface-bound MHC Ig dimer signal 1 and anti-CD28 signal 2 were directly conjugated with iron-dextran nanoparticles to create reproducible magnetic aAPCs, which have also been applied in other investigations. While nano-aAPC can stimulate anti-tumor effector T cells *in vivo* from naive populations, its potential to mediate the rejection of established tumors in highly immunosuppressive microenvironments is not explored. Nanoscale iron-dextran aAPC has great potential tumor targeting hence could be used in cancer therapy (Perica et al., 2014a, 2014b). The ideal size of an aAPC for *ex vivo* cellular expansion may be particles with a diameter of 5 to 10 μm, but nanoscale aAPCs have shown better *in vivo* pharmacokinetic characteristics and are more appropriate for systemic injection. Compared to microscale aAPCs, nanoscale aAPCs are known to be less effective T cell activators because they have a substantially smaller surface area for contact with T cells (Mannix et al., 2008). Magnetic-field-induced nanoparticle clustering is another way to boost activation by increasing the surface contact area between nano-aAPCs and T cells (Giannoni et al., 2005).

Nano-aAPC-activated T cells under a magnetic field inhibited the growth of B16 melanoma, which indicate that this innovative approach may generate sizable numbers of activated antigen-specific T cells (see Fig. 2). Magnetic fields have been used to direct the *in vivo* movement of paramagnetic particles and particle-labeled cells. This technique may be combined with magnetic clustering to drive site-specific T-cell activation.

This work indicates a novel technique wherein nano-aAPC may be linked to magnetic field-enhanced activation of T cells to promote the generation and activity of antigen-specific T cells produced from naive progenitors. This will enhance cancer therapy using cells (Perica et al., 2014a, 2014b).

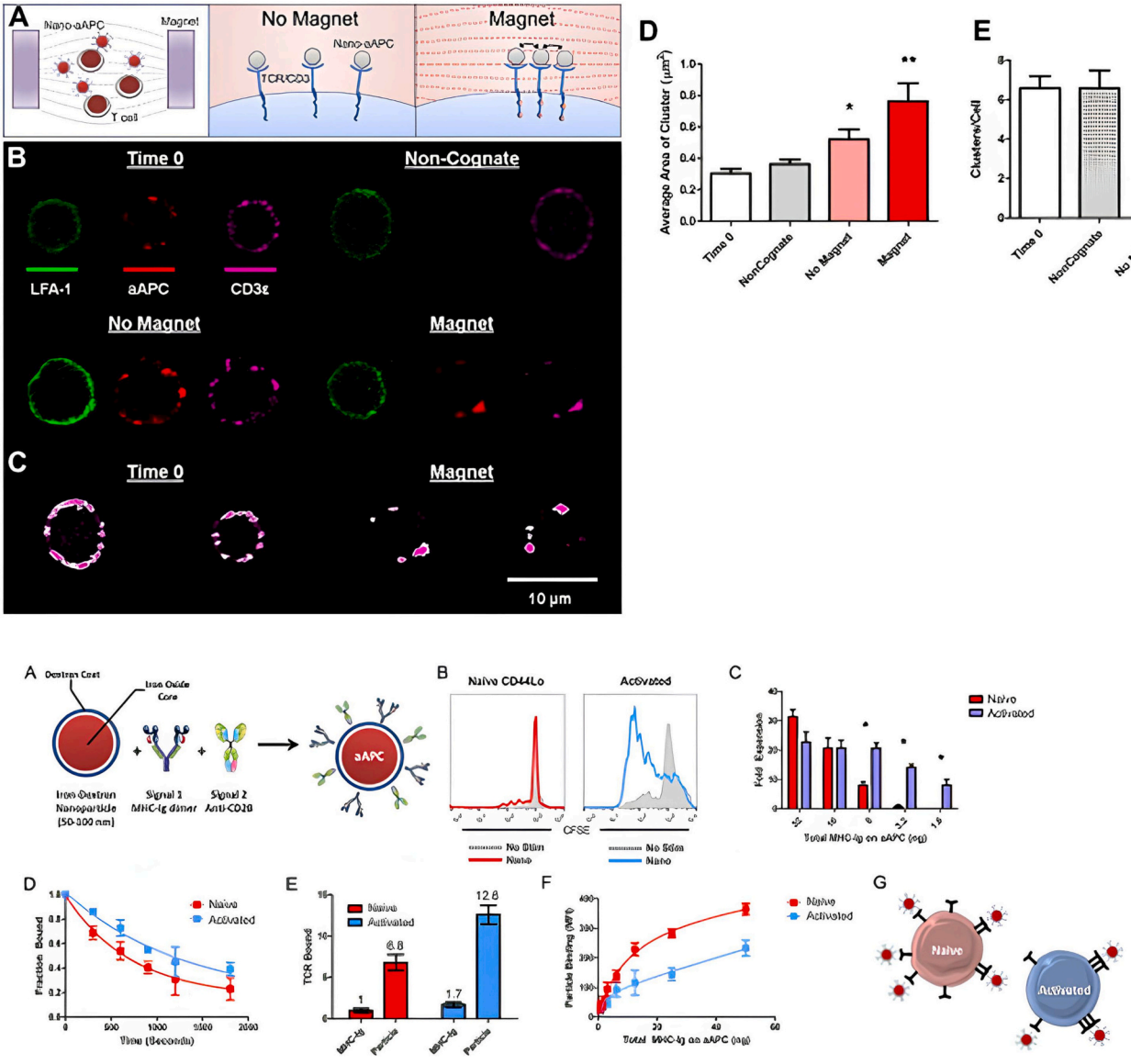

Fig. 2. Development and evaluation of magnetic nanoclusters (adapted from Perica et al., 2014a, 2014b).

1.1.4. Biomimetic magnetosomes

The delivery of many different medications and therapeutic substances is accomplished by using a wide variety of aAPCs. Biomimetic magnetosomes are one type of aAPC that may be produced using magnetic nanoclusters. In Fig. 3, we see a clustered structure whose surface may be covered by azide-leucocyte membranes after being functionalized by T-cell stimuli. Magnetism and superparamagnetism could be needed to use aAPCs for MRI purposes. However, these traits cannot coexist because of their inherent contradictions (Seo et al., 2006; Tian et al., 2011). The magnetism is reduced in nanoparticles that are almost 10 nm in size. The superparamagnetic-ferromagnetic transition and increased saturation magnetization can be brought about by merely increasing particle size (Lee et al., 2013; Nadaf et al., 2023). The preparation of biomimetic magnetosomes can overcome these drawbacks.

1.1.5. Magnetic hollow mesoporous silica (MHMS) nanospheres

MHMS nanoparticles are potential carriers for the targeted delivery of therapeutic agents due to the higher surface or tissue penetration (Liu et al., 2015). Magnetic mesoporous silica spheres receive a sizable cavity from the MHMS coupled with the mesopores. MHMS nanospheres were prepared by electrostatic self-assembly of magnetic Fe_3O_4 nanoparticles using various other components like surfactants, tetraethoxysilane (TEOS), and polystyrene (PS) (see Fig. 4). It showed good compatibility *in vivo* and lower toxicity towards the cells in in-vitro studies.

Researchers have devised a one-step fabrication process for MHMS nanospheres with a yolk-shell configuration. Compared to other MHMS, this one stands out due to its large cavity, ink-bottle-like pores, and high specific surface area. An in-vitro dissolution assay showed superior loading efficiency and regulated magnetization with the expected ("on-off") release pattern.

1.1.6. Bifunctionalized mesoporous silica yolk-shell magnetic nanostars

These magnetic nanostars were synthesized by biofunctionalization technology. These magnetic nanostars were prepared using dried β-Cyclodextrin, (3-isocyanatopropyl) triethoxysilane (IPTS), and *N*, *N*-dimethylformamide (DMF). The curcumin was then loaded in FMNS by vacuum pumping assisted recrystallization process in getting curcumin-loaded biofunctionalized magnetic nanostars (Cur@FMNS).

As the molecular structure of curcumin is unstable under numerous chemical or physical circumstances, there may be chances of reacting with $–NH_2$ groups. Hence, the specific binding site is needed to form a stable inclusion complex, which Peilin Huang et al. achieved with the help of biofunctionalization technology (Huang et al., 2016). This increased biocompatibility and lowered the toxicity towards normal cells. In contrast, it significantly increased the cytotoxicity to SK-HEP1 cells and HepG2 cells more than the pure curcumin solution was observed as shown in Fig. 5.

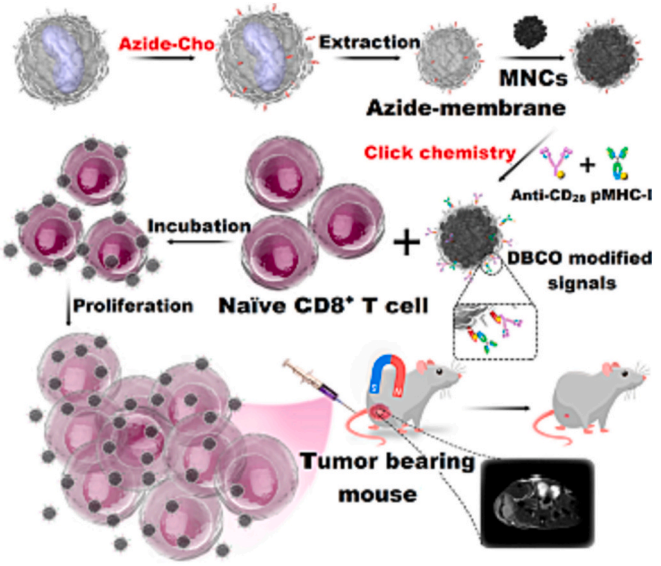

Fig. 3. Fabrication of magnetosomes and their application in cancer treatment (adapted from Zhang et al., 2017a, Zhang et al., 2017b).

1.1.7. Mesoporous cobalt ferrite nanosystems

Magnetic nanosystem in conjugation with the ferrite material is the topic of interest for various research groups working on developing magnetic nanoparticles (Pedrosa et al., 2016). Among these ferrite materials, cobalt ferrite ($CoFe_2O_4$) is the widely used component for the fabrication of MNPs due to their ability to provide semi-hard magnetic properties to cobalt ferrite. The higher magnetic anisotropy constant of cobalt ferrite than the magnetite could be the reason for its semi-hard property. Nanometer-sized crystallites serve as the foundation for mesoporous structures. The pH level significantly influences the crystallite size and phase purity. A parasitic hematite phase forms at pH levels under 7, whereas these mesostructures are constructed from 7.8, 9.6, and 9.0 nm crystallites, depending on the starting pH values. The surfactant-assisted hydrothermal method was used to fabricate mesoporous cobalt ferrite magnetic nanosystem using non-ionic block copolymer such as Pluronic® P123 (Palade et al., 2020).

The researchers used a co-precipitation-annealing process at 1000 °C to create the nanoparticles. With a length of 80–160 nm and a width of 43 nm, the produced NPs have an extended morphological structure. Georgiou et al. (2019) reported the fabrication of monodisperse mesoporous cobalt ferrite NPs using a ligand-exchange approach. But the hydrothermal surfactant-assisted method was superior to the other techniques for mesoporous Cobalt Ferrite Nanosystems formation at ambient temperature.

1.1.8. CRISPR/Cas9 complexed polyethyleneimine (PEI) magnetic nanoparticles

Magnetic nanoparticles (MNPs) made of polyethyleneimine (PEI) and CRISPR/Cas9 were developed previously (Ehrmann et al., 2021). They have evaluated the CRISPR/Cas9 complexed polyethyleneimine (PEI) magnetic nanoparticles for non-viral delivery of CRISPR/Cas9 and DNA template. Hence this study shows that the PEI-MNPs are a potential strategy for plasmid encoding CRISPR/Cas9 and DNA templates. It could be helpful for enhanced safety and the use of gene editing (Rohiwal et al., 2020).

1.1.9. Poly-allylamine-hydrochloride (PAAH) magnetic nanoparticles

The study was carried out to remove the pathogenic bacteria using electrostatic interaction and magnet capture. This study procedure introduced magnetic nanoparticles (MNPs) for PAAH (poly-allylamine-hydrochloride) stabilization. Escherichia, Acinetobacter, Pseudomonas, and Bacillus, four major pathogenic species related to diverse species, showed high eradication efficacy in the presence of MNPs. Because of processes involving the exterior cell structure and ion exchange capability, the MNPs exhibit distinct adhesion effects on bacterial cells, which are stronger for Acinetobacter and Pseudomonas (Ayeshamariam et al., 2021).

2. Classification

The magnetic nanosystems can be classified into different classes based on the type of components used for preparation (organic or inorganic), accessory substance, structural modification done by functionalization, and application.

2.1. Organic and inorganic components

2.1.1. Superparamagnetic iron oxide nanoparticles (SPIONs)

The SPIONs are a particular class of magnetic nanoparticles used in

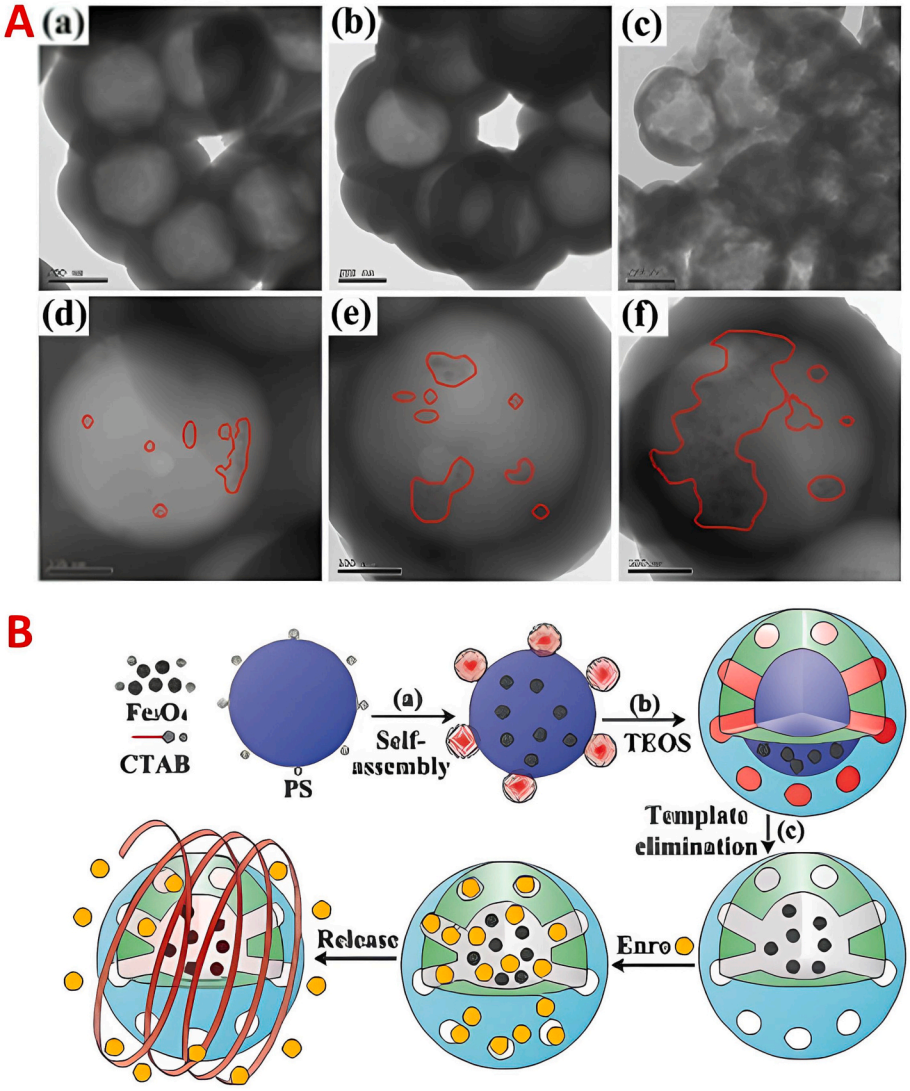

Fig. 4. Illustration of (A) TEM images of MHMS and (B) one-step synthesis of MHMS (adapted from David et al., 2015).

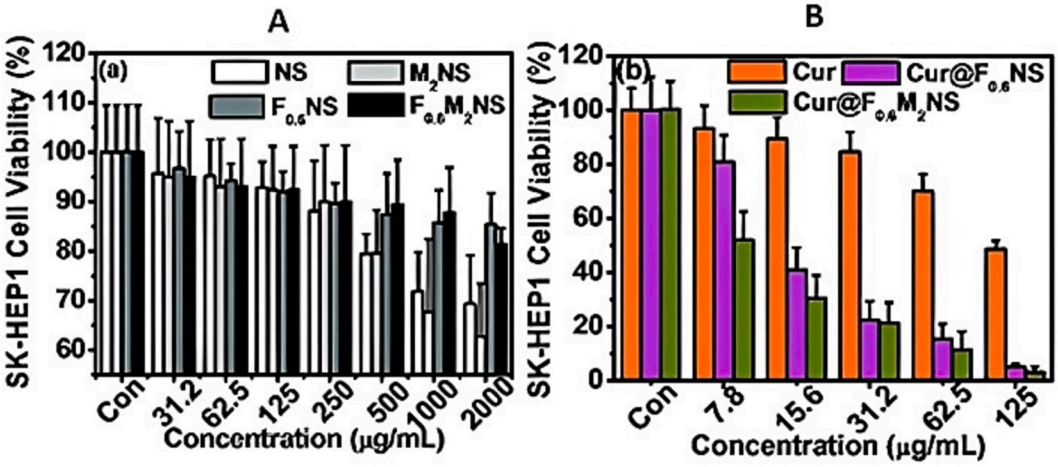

Fig. 5. Increased cytotoxicity towards (A) SK-HEP1 cells and (B) HepG2 cells (adapted from Huang et al., 2016).

diagnosing hepatocellular carcinoma by drug targeting approach (Sharkey et al., 2017). Hence, these are used for the theranostic application, surface functionalization or conjugation, as a highly efficient MRI contrast agent, and for imaging (Schleich et al., 2015). Recently it was used as the MRI-based cell tracking agent for in-vivo study and has proven its application in the demonstration of oxidative stress,

histopathology, and biodistribution studies (Sharkey et al., 2017). Therefore, it can be used for the controlled delivery of drugs and the effective delivery of vaccines (Reddy et al., 2017; Pusic et al., 2013).

The size of the nanoparticles primarily determines their magnetic characteristics; below ~15 nm, they are superparamagnetic, and above ~20 nm, they are ferromagnetic. Furthermore, different nanoscale iron oxide morphologies (shape-dependent properties), including plates, cubes, rods, and tubes, have been shown to exhibit improved magnetic properties. By assembling these low-dimensional nanoparticle building blocks into 1D, 2D, and 3D ordered nanostructures, more options for adjusting their physical characteristics and useful applications become available (Orza et al., 2017). Previously published report suggested that, superparamagnetic iron oxide nanoparticle clusters (SNCs) were simultaneously magnetically assembled as links to form core-shell iron oxide nanochains. The assembled SNCs could be fixed with a layer of deposited silica and which can be created using a sol-gel synthesis technique. The nanoparticles' permanent structure and morphology are provided by the layer of silica coating. Applications in biomedicine are made possible by the silica shell's large pore volume and pore size, as well as by the nanochains' strong colloidal stability and magnetic responsiveness. This work also presents a comparative study of the magnetic properties of anisotropic nanochains with random and parallel orientation (Tadic et al., 2019a, 2019b). Because of their stable morphology and structure, nanochains offer a straightforward method for adjusting magnetic properties through only nanochain alignment. To alter surface charge, Tadic et al. synthesized superparamagnetic iron oxide nanochains functionalized with amino (-NH_2) and carboxyl (-COOH) groups. These nanochain surfaces offer improved colloidal stability and have potential uses in the biomedical field. Zeta potential (ζ-potential) analysis confirms the surface modified nanochains' improved colloidal stability. Since the building blocks of the nanochains are tiny nanoparticles, their magnetic properties exhibit a superparamagnetic state at room temperature (Tadic et al., 2017).

2.1.2. Quantum dots (QDs)

The anticancer agents show severe side effects due to the non-specificity or lack of targeting ability with higher toxicity to the normal cells. Nano-carries such as quantum dots, liposomes, micelles, nanotubes, and metal oxides can target specific cells. The numerous advantages like optical properties, unique mode of drug release, and fluorescence make it a potential carrier for targeted delivery of anticancer drugs. Hence, the quantum dots were widely used for biomedical applications by lowering the side effects and sustaining the release of drugs with a particle size in the nanometer range (Zhao and Zhu, 2016; Sahoo et al., 2005).

2.2. Accessory components/ active targeting moieties (Antibodies and ligands)

2.2.1. Folic acid

There is a wide variety of food that contains folate, and it also takes part in metabolic processes. Study reveals that most tumor cells contain folate receptors (Rarokar et al., 2023a, 2023b, 2023c, 2023d). Folate receptor shows more affinity towards carboxyl deuterogenic modified folic acid complex. Moreover, folic acid complexes have a greater binding relationship than the original drug. The small size of folic acid makes it easier to enter the malignant cells through blood vessels. The radioactive elements coupled with folic complexes are used to treat ovarian cancer. The toxicity, stability, and functionalization are undetermined due to their absorption and excretion in-vivo as they are complex in structure and configuration. In addition, previous report stated that dissatisfaction with the release and efficacy of FA complex has been seen in tumor cells. Hence proper research on this topic should be done before its in-vivo diagnostic application. Also, fluorescent QDs, made by FA complex, are used for diagnosing tumor cells.

2.2.2. Hyaluronic acid

Hyaluronic acid is a naturally existing non-protein glycosaminoglycan with outstanding viscoelasticity, excellent biocompatibility, and adequate moisture retention capacity; it also has hygroscopic properties. These properties of HA make it countable for diagnostic applications. In addition, hyaluronic acid is vital in cell proliferation, malignant cell migration, and wound remedy. In cell selection applications, HA-modified nanoparticles are predicted to have higher affinity. Wan et al. stated that a high amount of aggregation was seen in HA-modified nanoparticles.

2.2.3. Arginine-glycine-aspartic (RGD) peptide

RGD can also be used as a moiety for functionalization of magnetic nanosystem for targeted delivery. It is possible to think of the therapeutic RGD peptide-modified magnetic mesoporous silicon nanosystem as a potentially successful method for the targeted treatment of hepatocellular cancer. Studies revealed that better antiproliferative effects had been seen due to RGD-modified paclitaxel and curcumin-weighted liposomes. The doxorubicin (DOX) chemotherapy medication was administered to human hepatocellular carcinoma HepG2 cells using the cyclic RGD peptide-conjugated magnetic mesoporous nanoparticles (RGDSPIO@MSN NPs), and their synergistic apoptosis-promoting effects were further investigated. The outcomes demonstrated that the RGDSPIO@MSN@DOX NPs could synergistically increase the death of HepG2 cells and had good stability, biosafety, and drug-loading capability. They also considerably boosted the absorption of DOX by HepG2 cells (Zhao et al., 2023).

3. Structure

Structurally, the magnetic nanosystems consist of a magnetic core at the center, surrounded by a lipid bilayer and therapeutic layer (see Fig. 6). Hence, the magnetic nanosystem's components are the magnetic nanosystem's magnetic core, lipid bilayer, therapeutic layer, biocompatible surface coating, functionalization, or ligand binding (Hosu et al., 2019; Dasari et al., 2020).

Magnetic core

Magnetic core is the central core of the magnetic nanosystem surrounded by therapeutic layer.

Therapeutic layer

It is the layer surrounds the magnetic core. It consist od drug molecules which can be release at the site of action and helps in targeted delivery.

Lipid Bilayer

This layer surrounds the therapeutic layer. It is made up of lipids. Lipids form bilayer structure similarly as present in th cell wall of the cells.

Biocompatible surface coating

Biocompatible surface coating consist of polymers (natural or synthetic) and metal. It surrounds the lipid bilayer.

Functionalized layer/functionalization

This layer consist of ligand/functionalization moiety which helps to target the desired receptor and helps for binding.

4. Magnetic properties

Magnetite and magnetite nanoparticles are widely used components for fabricating magnetor-responsive nanosystems. The functionalization of SPION lead to enhance magnetic and delivery properties with lower toxicity. Various research groups have proved this through in-vitro and in-vivo pharmacokinetic studies. The magnetic nanosystems engineered using Co, Fe, and Pt have been reported for potential magnetism, but the higher toxicity restricts their use in the biomedical field. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have accepted the clinical use of just a few iron oxide nanoparticle formulations, possibly because of the absence of typically

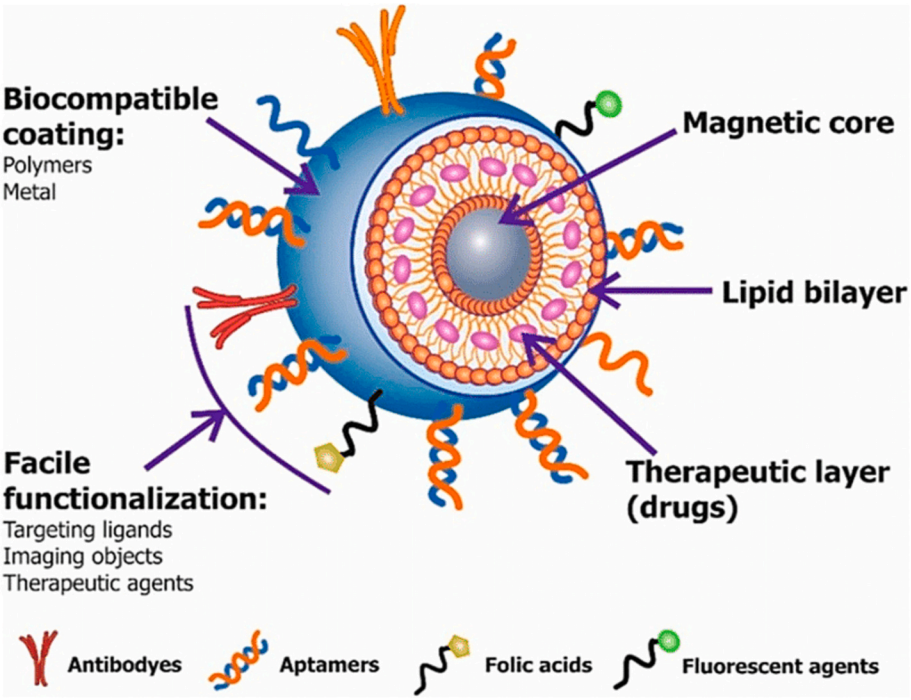

Fig. 6. Structure of Magnetic nanosystem.

widespread physicochemical exercise of particle layout and manufacturing in addition to qualifying criteria.

Magnetic nanosystems show various properties, but the most important properties are few, including the mechanism of magnetic relaxation, remanence, coercivity, saturation magnetization, magneto-crystalline anisotropy constant, and magnetic diameter. These properties mainly depend on the nature of the material used during the synthesis and coating process.

4.1. Ferromagnetism

In biomedical technology, ferromagnetism has become a topic of interest because of its wide application in cancer diagnosis. J.P. Liu stated that the coercivity of ferromagnets is the focused part of the research on the magnetic properties of the magnet (Liu et al., 2016). The size of these magnets plays a significant role in the coercivity of ferromagnetic materials resulting in size-dependent ferromagnetism. The coercivity enhances with decreasing in the atom size of the magnet. Moreover, the size reduction of metal oxides to 20 to 30 nm shows superparamagnetism at ambient temperature.

4.2. Superparamagnetism

Small ferromagnetic or ferrimagnetic nanoparticles exhibit superparamagnetism, a type of magnetism. Magnetization can randomly reverse direction in nanoparticles of a certain size when temperature is present. The Neel relaxation time is the typical interval between two flips. They are considered to be in the superparamagnetic state when their average value of magnetization appears to be zero in the absence of an external magnetic field and the measurement period is significantly longer than the Neel relaxation time. In this form, the nanoparticles can be magnetized by an outside magnetic field, acting as a paramagnet (Marghussian, 2015).

4.3. Magnetization

The IOMNPs' behavior in the presence of an external magnetic field is based on the degree of magnetic order and the temperature condition. The orbital energy of the dipole could help determine the magnetic moment per unit particle volume or magnetization. Dipoles stop the lowest energy state by forming a collection of several domains divided by a wall. The development of domain walls below a specific size, which results in single-domain nanoparticles, is energetically unfavorable (usually $<$100 nm).

4.4. Magnetic remanence and coercivity

Induced magnetization occurs when a magnetic field is present because the magnetic spins tend to align in its direction. Remnant magnetization is the phenomenon in which magnetization is still there even after removing a magnetic field. The extent of induced magnetization is called saturation of magnetization. The magnetic field is analogous to the coercive field which required to cancel magnetization. In nanoparticles having ferromagnetic and ferrimagnetic characteristics, hysteresis is commonly seen. Remanence and coercivity are insignificant for superparamagnetically charged nanoparticles (Nelea et al., 2003).

4.5. Magnetic anisotropy

The alignment of the magnetic dipoles has a special preference for nanoparticles known as magnetic anisotropy. Uniqueness in the shape of nanoparticles and crystal structure could be the reason for this phenomenon. The material itself may have this anisotropy. The magnetization arrangement in accordance with all feasible crystallographic directions is known as magnetocrystalline anisotropy (Lisjak et al., 2023; Brunner et al., 2019). At the same time, shape anisotropy is an orientation of polycrystalline material along the axis to get the desired shape.

Exchange anisotropy is a result of interactions between ferromagnetic and antiferromagnetic materials. How quickly the magnetic dipoles in the particles align to a particular direction of the applied magnetic field depends on the temperature of the system's "thermal energy." The degree of magnetocrystalline anisotropy may be estimated using temperature-dependent magnetization measurements, such as zero-field cooling (ZFC) or dynamic magnetic susceptibility curves (DMS) of materials (Massoudi et al., 2021) This results in the

suppression of the physical rotation of nanoparticles. When an external magnetic field is removed, colloidal suspensions of nanoparticles respond in one of two ways. In the first mechanism, the rotation of the liquid's physical particles causes the magnetic dipole to relax. The analogous characteristic rotational diffusion time (τB) is the Brownian relaxation time, which is given by;

$\tau B = 3Vh\ \eta\ /\ kT$ (1).

where η = viscosity of the carrier liquid.

Vh = hydrodynamic volume of the particle.

k = Boltzmann constant.

T = temperature.

4.6. Magnetic relaxation

The magnetization rotation inside the SPION's magnetic core causes Neel relaxation, which results in a relaxation period (Lin et al., 2020). The magnetic dipole within the particle also spins in the second process. The corresponding dipole rotation characteristic time τN is known as Neel relaxation time.

$$\tau N = \tau 0\ exp.(K\ V\ m/k\ T) \quad (2)$$

where τ0 = characteristic time of the approximation 10–9 s,

Vm = magnetic core volume.

K = anisotropy constant.

Colloidal suspensions of nanoparticles include both relaxation processes, but the faster method prevails. The carrier liquid's viscosity and the particles' hydrodynamic diameter impact the Brownian relaxation period. The Neel mechanism considers the material's anisotropy constant and magnetic core volume. Dynamic magnetic susceptibility investigations may be used to learn more about the magnetic relaxation features of nanoparticles in suspension. Additionally, data on typical magnetic relaxation durations are included.

4.7. Physical properties of magnetic nanoparticles

Magnetic effects are produced by the motion of particles that have both mass and electric charge. These particles include protons, electrons, holes, and both positive and negative ions. An electricly charged particle in motion produces a magneton, also called a magnetic dipole. Ferromagnetic materials are composed of a group of magnetons. A magnetic domain, also called a Weiss domain, is a volume of ferromagnetic material in which all magnetons are aligned in the same direction by the exchange forces. What distinguishes ferromagnetism from paramagnetism is the concept of domains. A ferromagnetic material's domain structure dictates how its magnetic behavior changes with size. Once the size of a ferromagnetic material is reduced below a certain threshold, it becomes a single domain. Fine particle magnetism originates from size effects, which are based on the magnetic domain structure of ferromagnetic materials. It is assumed that the state of lowest free energy for ferromagnetic particles smaller than a threshold size has uniform magnetization, and for larger particles, nonuniform magnetization. The former are referred to as single domain particles, while the latter are known as multidomain particles (Qu et al., 2001; Ersoy and Rybicki, 2007).

Materials are classified according to their response to an externally applied magnetic field. The orientations of the magnetic moments in a given substance allow one to distinguish between the various types of magnetism found in nature. Diamantism, paramagnetism, ferromagnetism, antiferromagnetism, and ferrimagnetism are the five basic forms of magnetism that can be described. In response to an applied magnetic field, the atomic current loops created by electron orbital motion act in opposition to it. All materials exhibit this type of mild resistance to a magnetic field, which is known as diamagnetism. However, because diamagnetism is so weak, any additional magnetic activity a material may have usually outweighs the effects of the current loops. When it comes to the electronic configuration of the materials, diamagnetism is observed in those with filled electronic subshells, where the magnetic moments are paired and eventually cancel each other out. One example of a diamagnetic material is quartz SiO_2, which has a negative susceptibility ($c < 0$) and weakly repels an applied magnetic field. The effects of these atomic current loops are avoided if the material has a net magnetic moment or a long-range ordering of its magnetic moments (Qu et al., 2001).

4.8. Influence of magnetic properties on their application

Based on whether they are used inside or outside of the body (*in vivo*, *in vitro*), magnetic nanoparticle applications in biomedicine can be divided into different categories. It is primarily used in the diagnostic domains of separation, selection, and magnetorelaxometry *in vitro*; *in vivo*, its applications can be further classified as therapeutic (drug targeting and hyperthermia) and diagnostic (nuclear magnetic resonance (NMR) imaging) (Hines and Guyot-Sionnest, 1996; Piao et al., 2008; Park and Cheon, 2001; Liu et al., 2005).

In vivo applications: The two main determinants of these particles' *in vivo* applications are their size and surface functionality.

Even in the absence of surface ligands, the diameters of superparamagnetic iron oxide nanoparticles, or SPIOs, have a major effect on *in vivo* biodistribution. Because ultra-small SPIOs and other particles with sizes between 10 and 40 nm can pass through capillary walls and are often phagocytosed by macrophages before being transported to the bone marrow and lymph nodes, they are essential for continuous blood circulation (Lu et al., 2007a, 2007b).

Therapeutic applications-Hyperthermia: Superparamagnetic iron oxide can be placed in varying current (AC) magnetic fields by arbitrarily flipping the magnetization direction between parallel and antiparallel orientations. This characteristic makes it possible for magnetic energy to be transferred to the particles as heat, which can be used *in vivo* to increase the temperature of tumor tissues and induce hyperthermia, which kills pathogenic cells. Tumor cells are more sensitive to temperature increases than normal cells (Mikhaylova et al., 2004; Kim et al., 2006). Prior studies have shown that tumor cell temperature can be effectively raised by dextran-coated magnetite (Wang et al., 2008) and magnetite cationic liposomal nanoparticles to treat hyperthermia during cell irradiation. This has been proposed as one of the most crucial approaches to creating future cancer treatments that work (Green, 2005).

Drug delivery: Drug targeting is one of the newest medical delivery technologies. Iron oxide magnetic nanoparticles have seen a sharp increase in potential applications for drug targeting in recent years. When paired with an external magnetic field and/or magnetizable implants, MNPs facilitate the delivery of particles to the targeted target area, fix them at the local site during the release of the medication, and act locally (magnetic drug targeting). Medication can be delivered to a designated site in order to reduce side effects and dosage needs. These particles' surfaces are frequently modified with organic polymers and inorganic metals or oxides in order to render them biocompatible and suitable for further functionalization through the attachment of various bioactive molecules.

Diagnostic applications: To begin with, NMR imaging. The advent of NMR imaging for clinical diagnosis has led to the need for new pharmaceuticals called magneto-medications. These drugs must be administered to the patient in order to: (1) increase the contrast between healthy and diseased tissue on imaging; and/or (2) display the organ functions or blood flow status.

In vitro applications-Separation and selection: Nowadays, there is a lot of interest in solid-phase extraction, or SPE, as a method for separating and preconcentrating desired components from a sample matrix. SPE is a popular extraction method used to find trace-level pollutants in environmental samples. Recent advances have led to the significant influence of nanoparticles, or particles smaller than a nanometer, on

sample extraction. SPE offers a great alternative to conventional sample concentration methods such as liquid-liquid extraction (Dubertret et al., 2002; Gao et al., 2004; Pellegrino et al., 2004). The magnetorelaxometer is item c. It was initially introduced as an immunoassay evaluation method (Murthy et al., 1999).

Magnetorelaxometry: When a magnetic field is removed, the relaxation of the net magnetic moment is used to determine the magnetic viscosity of the system of magnetic nanoparticles (Sun et al., 2008). There are two different ways to unwind. The internal magnetization vector of a nanoparticle first relaxes in the direction of the easy axis inside the core through a process known as Néel relaxation (White et al., 2006). Second, when particles perform rotational diffusion in a carrier liquid, a process known as Brownian relaxation takes place (Philipse et al., 1994a, 1994b). The distinctions between Néel and Brownian relaxation can be seen in the variations in their relaxation times (Caruso, 2001). Furthermore, Brownian relaxation can only take place in liquids, but Néel relaxation can happen regardless of the nanoparticles' dispersion.

5. Methods of preparation

Basically, it can be prepared by top-down and bottom-up approaches, as shown in Fig. 7.

5.1. Precipitation

Precipitation of product solutions is one of the earliest processes for creating nanoparticles. In precipitation reactions, a precipitating agent is introduced after the metal precursors have dissolved in a common solvent, such as water, to create an insoluble solid. Precipitation reactions' key benefit is the ability to produce enormous amounts of particles. Co-precipitation is a newly modified technique for synthesizing magnetic nanoparticles. This technique involves adding a base to aqueous salt solutions in an inert atmosphere at low or high temperatures to create MNPs. Alteration of standard co-precipitation procedure, cobalt ferrite ($CoFe_2O_4$) and zinc cobalt ferrite ($ZnCoFe_2O_4$) nanoparticles were produced to attain high Specific Loss Power (SLP) values. The specific loss power as a function of $CoFe_2O_4$ nanoparticles diameter (D) calculated at the magnetic field frequency (f) of 500 kHz (Darwish et al., 2019).

Co-precipitation effectively synthesizes monodisperse, functionalized, incredibly stable, and shape-controlled magnetic nanoparticles. Two processes are primarily involved in the production of magnetic nanoparticles by co-precipitation: (1) a brief burst of nucleation when the species concentration exceeds critical supersaturation; and (2) a steady development of the nuclei by diffusion of the solutes to the crystal surface (Gautam and Chattopadhyaya, 2016).

5.2. Microemulsion

A microemulsion is an isotropic dispersion of two immiscible water and oil phases in the presence of a surfactant. The hydrophilic head groups of the surfactant molecules are in the aqueous phase, and the hydrophobic tails of the surfactant molecules are dispersed in the oil phase, where they can form a layer at the intersection between the oil and water. Cyclohexane has been utilized as the organic phase and a non-ionic surfactant for fabricating iron oxide nanoparticles with magnetic properties (Lopez Perez et al., 1997).

A microemulsion is a single phase that is isotropic and thermodynamically stable and is made up of at least three components, two of which are immiscible and one of which, the surfactant, exhibits amphiphilic behavior (Klyachko et al., 1986). The microemulsion approach contrasted with a traditional co-precipitation method under the same circumstances. Lo'pezPe'rez. In order to control particle size, water nanodroplets are produced in an organic compound and used as nanoreactors in this microemulsion method. A surfactant coat surrounding these nanodroplets restricts their size and keeps them from organic molecules.

5.3. Thermal decomposition

The most effective techniques for producing magnetic nanoparticles with uniform particle size distribution and a high degree of size control are those using thermal decomposition (TD). Effenberger et al. prepared

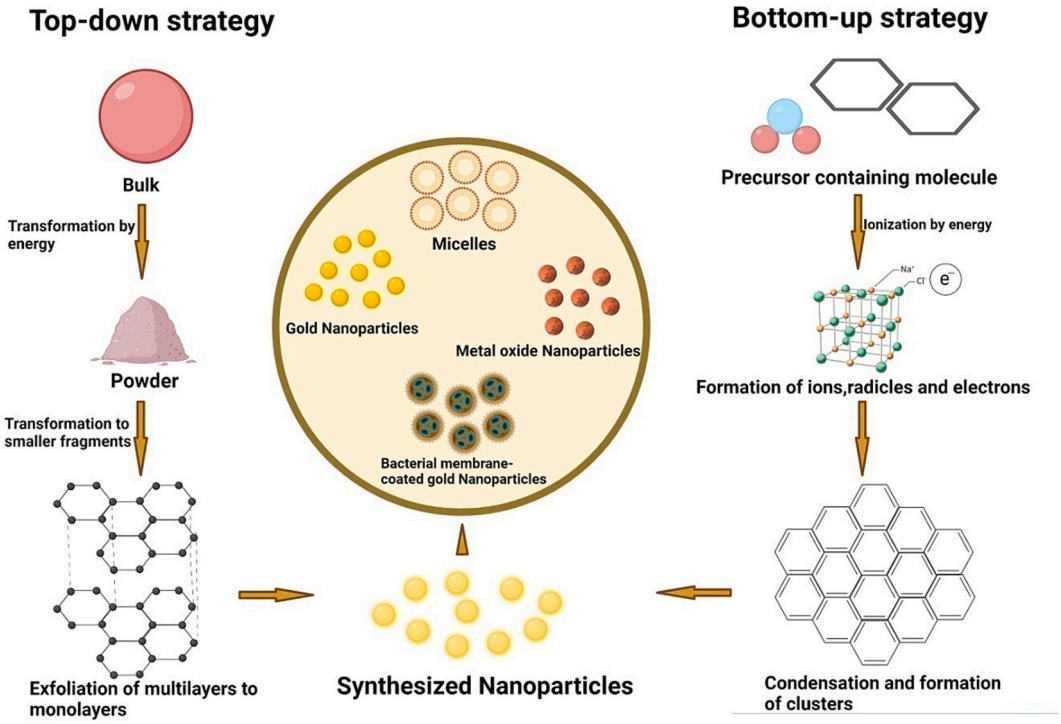

Fig. 7. Top-down and bottom-up strategy for preparation of magnetic nanosystems.

iron (III) acetylacetonate by thermal decomposed method to produce high-quality magnetic nanoparticles and alternatively used cheaper solvents such as 1, 2-octane diol, and cyclohexanol reduced the cost of nanoparticles (Effenberger et al., 2017). In thermal decomposition, materials with high boiling points are mainly used to synthesize nanoparticles. Nanoparticle in thermal decomposition especially possesses suitable crystal structures, which are preferentially combined with a good quality surfactant to get even nanosized particle. This method is used at high temperatures and high amounts of toxic material such as Chloroform, n-hexane, and metal oxides. However, this method is not as eco-friendly as other techniques. Oleic acid, oleyl amine, fatty acids, and hexadecyl amine are amphiphilic surfactants that enable fine-tuning of the nucleation and growth kinetics of the nanoparticles. The morphology and nanoparticle size when using the thermal breakdown approach to create SPION is highly dependent on the duration of the reaction, its temperature, and the ratio of precursor-to-surfactant (Sharifi et al., 2012a, 2012b). Researchers created Fe (III) glucuronate in monodisperse superparamagnetic Fe_3O_4 nanoparticles coated in oleic acid by thermal decomposition. The surface of the Fe_3O_4 nanoparticles was altered with poly (3-O-methacryloyl-D-glucopyranose)-terminated-carboxyl—bis(ethane-2,1-diyl)phosphonic acid (PMGP) to make them dispersible in water. The ability of a substance to be nontoxic is essential for practical biomedical applications in the future. Rat mesenchymal stem cells were used as a test subjects for the PMG-P and Fe_3O_4 nanoparticles to assess their toxicity and labeling potential. The PMG-P and Fe_3O_4 nanoparticles displayed high relaxation with minimal cellular uptake, according to MR relaxometry (Patsula et al., 2016).

5.4. Solvothermal

The solvothermal method used solvent and heating procedures to prepare magnetic particles for a particular size. Using a precursor made from e-waste (Copper acetate, iron acetate obtained as a by-product during gold recovery from electronic waste recycling process), the solvothermal decomposition process was used to create the magnetic copper ferrite that contains carbon (Muthukumar et al., 2018). The solvothermal method combines this material with the surfactant to give small particle sizes and desired morphological properties. In the solvothermal process, a solvent and its precursors are heated in a closed system to a temperature higher than the solvent's boiling point. The precursors are subjected to various influences under supercritical conditions, which leads to the production of the desired substance (Dinadayalane et al., 2022; Chaudhary et al., 2024). These influences include pressure increase, high temperature, and peculiar solvent behavior. Despite producing the finest results, the solvothermal method frequently necessitates using environmentally hazardous chemicals. However, the hydrothermal process is green because it uses water, the most eco-friendly solvent (González et al., 2021). Like the hydrothermal method, the solvothermal approach uses organic solvents during the synthesis process rather than water. If alcohols or glycerol are utilized as the reaction media, the reactions are referred to as alcohothermal and glycothermal, respectively. Mahajan et al. synthesized Fe_2O_3 Magnetic Nanoparticles for SiO_2 Coating by improved Solvothermal Synthesis sodium dodecyl sulfate. PEG 6000 was used as the double capping reagents to enhance one-pot solvothermal synthesis to produce monodisperse magnetic -Fe_2O_3 nanoparticles (MNPs). This double protective layer improved MNP uniformity (Z average 257 11.12 nm, PDI = 0.18) and colloidal stability. DLS, SEM, TEM, XPS, and XRD were used to characterize the materials. It was shown that these MNPs might be used to create core-shell structures with uniform and adjustable silica coatings. For use in various applications, such as magnetic separation and catalysis, silica-coated MNPs are essential (Mahajan et al., 2021). The solvothermal method can combine with other techniques, such as microwave-assisted sonochemical thermal decomposition, to achieve the desired magnetic nanoparticles.

5.5. Sonochemical

Chemical reactions result from acoustic cavitation, which is bubbles' formation, expansion, and implosive collapse in a liquid. This method is used for the comparative study of different magnetic nanoparticles. Ghanbari et al. have effectively synthesized ferric oxide magnetic nanoparticles in an inert atmosphere at room temperature. With a saturation magnetization of 66 emu/g and a coercivity of 39 Oe at ambient temperature, Fe_3O_4 nanoparticles display ferromagnetic activity. Furthermore, the polyvinyl alcohol matrix's thermal stability and fire-resistant properties can be improved by nanoparticles (Ghanbari et al., 2014).

Fuentes-García et al. described the development of a pH-triggered release system based on core@shell mesoporous magnetic nanoparticles (MNP@mSiO_2) that were produced quickly and easily with the use of ultrasound. $Fe_{2.9}Mn_{0.1}O_4$ magnetic cores with specific loss power levels suitable for hyperthermia (463 W/g) and a mesoporous silica shell with a large surface area (269 m^2g^{-1}) functionalized with hydroxyl groups are revealed by the characterization process (-OH). The aminosilane granules in MNP@mSiO_2 were loaded with DOX, allowing for pH-triggered DOX release in acidic settings (Fuentes-García et al., 2021).

5.6. Microwave-assisted synthesis

A microwave-assisted synthesis method is a practical approach with the advantages of narrow size distribution and high purity. As other processes are time-consuming, microwave synthesis requires less time and arrangements for the synthesizing MNPs. To synthesize homogenous Co_3O_4 nanoparticles with a limited size distribution, a microwave-assisted synthesis approach is used by Bhatt et al. and demonstrated that the experiment produced high-purity Co_3O_4 with ferromagnetic properties (Bhatt et al., 2011).

Microwave-assisted synthesis uses excitation by microwave electromagnetic radiations to align the material's dipoles in an external field (Hu et al., 2011). Internal heat may be produced during the process of arranging or orienting molecules by the external field, which decreases the processing time and energy requirement. The heating uniformity of microwaves is mostly caused. By using a microwave-assisted synthesis technique, the reaction time can be significantly shortened (Dahiya et al., 2018a, 2018b). Standard organic solvents can be used for microwave-assisted synthesis in either open or sealed vessels. The solvent's boiling point (as in an oil bath experiment) often determines the maximum reaction temperature that can be reached when solvents are heated by microwave irradiation at atmospheric pressure in an open vessel. The projected rate increases would be minimal if there were no particular or nonthermal microwave effects. High-boiling microwave-absorbing solvents, such as dimethyl sulfoxide, 1-methyl-2-pyrrolidone, 1,2-dichlorobenzene, or ethylene glycol, have commonly been utilized in open-vessel microwave synthesis to obtain still high reaction rates (Kappe and Dallinger, 2006). A microwave-assisted synthesis method is effective with the advantages of narrow size distribution and high purity. As other processes are time-consuming, microwave synthesis requires less time and arrangements for synthesizing magnetic nanoparticles. To synthesize homogenous Co_3O_4 nanoparticles with a limited size distribution, a microwave-assisted synthesis approach is used by Bhatt et al. The findings demonstrate that the experiment produced high-purity Co_3O_4 with ferromagnetic properties (Bhatt et al., 2011). Previous reports stated that different surface charges of superparamagnetic iron oxide nanoparticles (MNP) are investigated as nano sorbent for removing chromium (VI) in an aqueous solution. Using a microwave polyol-based technique, uniform magnetic nanoparticles with particle size 12 nm were created. Tetraethyl orthosilicate (TEOS) and (3-aminopropyl) triethoxysilane (APTES) were then grafted onto their surfaces to change the surface charge.

5.7. Chemical vapor deposition

In chemical vapor deposition, conditions are set for the vapor phase mixture to be thermodynamically unstable, forming the solid material as nanoparticles during the vapor phase synthesis of NPs. Alijani et al. gave a novel strategy for chemical vapor deposition-based one-step production of magnetic carbon nanotube/diatomite earth composite to apply lead ions removal (Alijani et al., 2014).

5.8. Laser pyrolysis

The absorption of laser energy is a different technique for heating the precursors to induce reaction and homogenous nucleation. By laser abrading the matching elemental target material in the necessary liquid, magneto plasmonic bimetallic alloy nanoparticles, magnetic oxide, or carbide can be produced immediately (Semaltianos and Karczewski, 2021).

5.9. Lithography

The combined benefits of top-down and bottom-up methods are shown by the same advanced technique known as nanosphere lithography (NSL). This technique is suitable for making nanoparticles (NPs). This preparation process of NPS by NSL is carried out in two separate steps. Firstly the method of coating with a suspension of nanosized polystyrene spheres could be used, and in the second step, chemical treatment is given to increase the hydrophilic nature. Finally, a hexagonal closed-pack structure is obtained called a colloidal crystal mask followed by sonication to get the crystallized form of NPs (Nur and Willander, 2020).

5.10. Magnetron sputtering technique

This is a technique of depositing various materials like metals and ceramics onto the substrate with the help of a magnetic field. It has many advantages over other methods. It allows a faster rate of deposition at lower pressure. It forms solid adhesive coatings even on heat-sensitive polymers or substrates (Wolke et al., 1994, Wolke et al., 1998a, 1998b, Wolke et al., 2003; Nelea et al., 2003; Porter et al., 2004; Chen et al., 2007; Nieh et al., 2001; Feddes et al., 2003, Feddes et al., 2004a, 2004b; Nakamura et al., 2007; Wan et al., 2007, Ozeki et al., 2007). These properties make it a more exciting area for many researchers working on metallic and non-metallic implants. It could be used for biocompatible coating on metals and non-metallic items (Juhasz and Best, 2011).

5.11. Surface functionalization of MNPs

MNPs are frequently coated with nonmagnetic or magnetic materials for three reasons: (i) to change the MNPs' magnetic properties; (ii) to give them a modified surface that can be further functionalized; or (iii) to make them chemically and colloidally stable. Inorganic materials like silica (SiO_2), gold, or gadolinium; nonpolymer organic stabilizers like phosphates, oleic acid, and stearic acid; and polymer stabilizers like dextran, polyethylene glycol, and polyvinyl alcohol are some of the most often used coating materials (Laurent et al., 2008). Alternatively, MNPs can be scattered and incorporated into a matrix to create composites (Fdez-Gubieda et al., 2012). However, in this scenario, the MNPs are stationary, which may not be ideal for some applications. Chemical synthesis frequently uses organic materials to coat MNPs. These organic coatings can be chemically anchored or physically absorbed onto the MNPs' surface, offering uniform single-particle coating with adjustable thickness and characteristics. They are also reasonably simple to obtain. These materials, however, can degrade at high temperatures and are not very suitable for highly reactive MNPs (like Fe MNPs), which limits the use of the MNPs. However, direct and uniform coating of MNPs with inorganic coatings can be very laborious, even though they can offer greater chemical stability than organic polymers (Lu et al., 2007a, 2007b). Because of their potential use in a number of applications, including the treatment of cancer, surface modification of MNPs with biocompatible materials like carbon, PEG, or Au has generated a lot of interest in recent years (Gupta and Gupta, 2005). Coating the MNPs can also be used to functionalize them using therapeutic medications, contrast agents, or specific targeting ligands.

In this manner, it will be possible to address some of the most prevalent drawbacks of MNPs, such as their nonspecificity or lack of biocompatibility, while also giving the MNPs new capabilities for multifunctional applications. The functionalization of MNPs has been the subject of extensive research, particularly in the field of biomedical applications. Chemotherapy drug molecules, such as doxorubicin, can be affixed to the surface of MNPs to function as magnetic drug carriers. This allows the drugs to be released locally and carry a large dose to the tumor site, thereby reducing their toxicity to the surrounding tissues (Hao et al., 2010). However, it has been demonstrated that MNPs functionalized with amine groups can bind to bacterial pathogens in the context of bacterial treatment, enabling their quick capture and removal (Pecharsky and Zavalij, 2005).

5.12. Colloidal chemical synthesis

5.12.1. Spray pyrolysis

Applying a solution to a series of reactors in a spray pyrolysis method allows aerosol droplets to evaporate the solvent, forming a solid as a result. The solute condenses inside the droplet as a result of the precipitated particle's molecules drying out and disintegrating at a high temperature. Studies show that employing this method has enhanced MNPs' photocatalytic degradation and magnetization capabilities (Majidi et al., 2016; Shatrova et al., 2017; Kaya et al., 2019).

5.12.2. Laser pyrolysis

In order to initiate and sustain chemical reactions, the laser pyrolysis method applies heat to a mixture of gases continuously using a CO_2 laser. Because it promotes localized heating and cooling effects, this technique is effective for heating precursors to influence reactions and nucleation. The morphological and chemical characteristics are also improved by this process, such as the crystalline matrix, high surface area, electrical conductivity, coercivity, and magnetic saturation of up to 70 emu/g (Alonso et al., 2018; Siddiqui et al., 2018; Dumitrache et al., 2015).

5.12.3. Co-precipitation

This method is said to yield the most accurate and successful results when used to create superparamagnetic iron oxide nanoparticles (SPIONs) with a mean diameter of $<$50 nm. It includes all chemical reactions occurring in an aqueous monophasic liquid medium where it is necessary to regulate the growth and nucleation of coherent iron hydroxide nuclei. The magnetization of MNPs is largely dependent on the annealing temperature; the most encouraging results have been found in the 900–1000 °C range (Darwish et al., 2019; Albalah et al., 2020).

5.12.4. Thermal decomposition

The application of thermal breakdown is now widely accepted thanks to the synthesis of superior MNPs. It mostly entails breaking down metal precursors, like oleates, acetylacetonates, etc., at very high temperatures (150–300 °C) while organic solvents, like benzyl ether or octadecene, are present and have high boiling points (250–300 °C) (Anderson et al., 2019).

5.12.5. Sol-gel method

The sol-gel method is one of the most studied and widely applied techniques for producing nanoparticles because it offers a suitable wet route for the synthesis of metal oxides. A "sol" of nanoparticles is

produced by hydroxylation and condensation of a molecular precursor in an aqueous solution. To attain the intended crystalline structure, wet gel—a three-dimensional network of metal oxides produced by additional condensation and polymerization—needs a few more heat treatments. This approach has certain advantages over the others, such as lower operating temperatures and greater control over the kinetics of the reaction through ingredient manipulation (Alagiri et al., 2012).

5.12.6. Polyol method

The use of surfactants in the Sol-Gel production process is associated with the problem of changing the surface charge and surface geometry of nanoparticles (NPs). Therefore, an alternative method called the Polyol Method makes use of polyols, such as polyethylene and propylene glycol, to prevent inter-particle aggregation, maintain a high degree of crystallinity in freshly formed NPs, and regulate particle growth. It appears that this synthesis method is highly popular, especially in the biomedical sector (magnetic resonance imaging). By precipitating metals following the reduction of dissolved metallic salts, this synthesis method yields fine metallic particles directly. The polyol approach is quite effective for the synthesis of nanocrystalline alloys and bimetallic clusters (Vega-Chacón et al., 2016; Hsu and Tao, 2018).

6. Characterization of MNPs

6.1. Measurement of particle size (DLS) and zeta potential

The particle size, size distribution, and zeta potential (ζ) of MNPs can be determined using dynamic light scattering techniques on Nano Brook 90 Plus Zetasizer (Brookhaven Instruments Corporation). The steps could be as follows: add 100 µL of a sonicated MNP suspension containing 1 mg/mL to 3 mL of ultrapure water, vortex the mixture, and use the result to determine the particle size. Three runs of three minutes each will yield the mean diameter (Rarokar et al., 2016, 2019, 2021). The polydispersity index (PDI) can show the sample's particle size distribution. The zeta potential, a measure of charge on the surface of nanoparticles, determines the stability of formulation and interaction with cellular membranes. Utilizing the idea of electrophoretic mobility in an electric field, the zeta potential of nanoparticles is determined. It is possible to report the average of three readings (each reading equals 30 runs). When taking measurements, the temperature must remain at 25 °C (Rarokar et al., 2019).

6.2. Differential scanning calorimetry

DSC would be used to characterize the physical states of individual drug and excipients alone and in combination for compatibility study. It could also be used to characterized the physical state of magnetic nanoparticles. These thermal characteristics of each powder sample can be determined by heating a sample at a specified temperature range and a heating rate (Rarokar et al., 2021).

6.3. Fourier transform infrared spectroscopy

The spectra of the MNPs would be recorded at room temperature with the KBr pellet technique using an FT-IR spectrometer with IR microscope infinity (having focal point at infinity for higher precision), ATI Mattson, resolution 1 cm^{-1} (Rarokar et al., 2022). The FTIR spectrum of other components would be measured to study the compatibility of those excipients with the drug molecules to be loaded in MNPs.

6.4. X-ray diffraction

The MNPs and their formulations are analyzed to study the comparative crystalline status of these samples using a powder x-ray diffractometer. The operational procedure for PXRD analysis has been reported previously by Rarokar et al. in 2022 (Rarokar et al., 2022).

6.5. Drug loading

In addition to the drug itself, the concentration of the drug at the target site also affects how it works. The drug loading in the MNPs must therefore be determined. A solvent evaporation method is preferred for drug loading. In a nutshell, 100 mg of MNPs and 10 mg of the drug are combined for hours at 37 °C with stirring at 100 rpm in a closed container containing 4 mL of ethanol. A further drug concentration gradient between the MNPs and the external solution may result from allowing the solvent to evaporate to 1 mL, producing a loaded drug concentration that gradually increases. The drug-loaded MNPs samples will then be centrifuged, collected, cleaned with the loading solvent, and dried in a moisture analyzer. The equation would be used to determine the drug-loaded content.

6.6. Determination of the content

A UV–Vis spectrophotometer is used to analyze drug content by examining a solution containing 10 mg of MNPs-drug dissolved in 10 mL of a suitable solvent.

6.7. Field emission-scanning electron microscopy (FE-SEM)

A cover slip mounted on a specimen tab would hold a suspension of MNPs of about 5 g/mL. At room temperature, the samples would be allowed to dry. The formulation's particles will then be examined and captured using scanning electron microscopy. Using a vacuum evaporator to coat the particles in platinum, the coated samples can be seen and caught on camera in a field emission SEM.

6.8. The field-dependent magnetization

The physical property measuring system will perform field-dependent magnetization and zero field cooled-field cooled measurements. Magnetic Nanoparticles (MNPs) can be utilized to target a specific area of the body. When an externally applied alternating magnetic field (AMF) is used, heat is generated. The magnetic nanoparticles in the drug carriers align with the direction of the magnetic field, producing heat. When an external magnetic field is applied, all the magnetic moments align with its direction until magnetisation saturation is achieved. After removing the magnetic field, a remnant magnetisation is left, indicating that a specific magnetic field called the coercivity field, is required to restore the system to its initial state. However, magnetisation does not return to its initial value immediately. Observing a hysteresis loop in the magnetisation cycle, in which there is a delay in the magnetic response and the inability of the magnetic moment direction under AMFs to shift immediately with the AMF.

Magnetic Hyperthermia (MHT) uses AMF to generate heat by inducing MNPs at a specific frequency (f), amplitude (A), and magnetic field (H) based on the Néel-Brown relaxation mechanism. This is achieved by using superparamagnetic nanoparticles. The rate of temperature increase is determined by the specific absorption rate (SAR) of the MNPs and the composition of the biological medium. A detailed explanation of this complex heating system is available. Using MNPs for MHT has the advantage of producing heat in deep tumor tissues. Furthermore, if $H \times f \leq 5 \times 108\ A\ m - 1\ s - 1$, the applied AMF is safe for human health.

Particle imaging technologies such as Magnetic Particle Imaging (MPI) are essential for using MHT in clinical settings. Magnetic Resonance Imaging (MRI) can be performed in real-time with magnetic nanoparticles (MNPs) due to their excellent magnetic properties and biocompatibility. Nevertheless, the primary disadvantage of MHT is that it requires a significantly higher dosage of MNPs, usually around 1 to 2 mg, which is much more than what is needed for MRI. For MNPs to be approved for use in biomedical applications, they require specific properties. These properties include minimal protein adsorption,

biocompatibility, nontoxicity, and the ability to evade the reticuloendothelial system (RES). In addition, the theragnostic capacity, which integrates both therapeutic and diagnostic capabilities, plays a critical role in nanomedicine. MNPs are considered a state-of-the-art tool for nanomedicine due to their ability to be functionalised and guided by a magnetic field.

6.9. Particle binding assays

Cells will be cultured at 4 °C at 107 cells/mL in FACS wash buffer for equilibrium particle binding (PBS with 2% FCS or 0.05% sodium azide). For 60 to 90 min, aliquots (30 μL) of cells will be combined with different doses of nanoparticles containing fluorescently tagged MHC-Ig dimer. After washing, mean channel fluorescence (MCF) was calculated using FlowJo, and cell-bound fluorescence could be measured using a flow cytometer.

6.10. Targeting of cells by magnetic nanoparticles

Effective cell transport to the target region is crucial for the efficacy of cell-based treatments. Since some lesions are located in difficult-to-access locations, new strategies to find the position of curative cells are needed. Magnetic vectorization of cells is a novel approach with the potential for cell therapy, regenerative medicine, and tumor treatment (Garello et al., 2022). In a nutshell, MNPs mark therapeutic cells before they are introduced into the bloodstream of living things. The cells are kept inside particular body regions using a static magnetic field. Magnetic cell targeting is an appealing method to enhance the localization of cells since it is compatible with usage in biological systems and allows for non-intrusive control of cells *in vivo*. Moreover, the advantages of immune cells used for tumor therapy and stem cells employed for tissue regeneration.

Following some common findings, cells must be loaded with MNPs for *in vivo* cell targeting. The labeling process must ensure sufficient particle internalization while maintaining cell survival and functionality. Macrophages quickly ingest big MNPs (>200 nm in diameter) and are neutrally charged. Small (<200 nm in diameter), positively or negatively charged particles can be easily absorbed by non-phagocytic stem cells. Researchers reported that when positively charged, bigger MNPs (with a diameter exceeding 0.9 m) can also be efficiently absorbed by endothelial cells and cardiac-derived stem cells, which can be used for magnetic targeting *in vivo* (Garello et al., 2022).

6.11. Role of organ-on-a-chip for toxicological evaluations of magnetic nanosystems

An organ chip is a microfluidic cell culture apparatus made using techniques specific to the manufacturing of microchips. It consists of one or more continuously perfused chambers that are populated by living cells arranged to mimic the physiology of tissues or organs. In particular, by tackling the problems that slow down the clinical translation of nanomedicine, Organ Chip offers a novel platform for more accurate predictive testing of nanotherapeutics (Zhang and Khademhosseini, 2015). One promising application of organ-on-a-chip technology is drug toxicity evaluation. The ability to combine drug metabolism and drug toxic processes into a single device, organ-on-a-chip offers a unique advantage in that it makes toxicity assessment of drug metabolites easier. Drug toxicity has been evaluated using a human organ-on-a-chip that has data correlated with a clinical trial (Cong et al., 2020). The nanomedicine community is gradually embracing a new paradigm that has emerged in the last ten years for modeling biological systems on microfluidic chips. These systems replicate organs, tissues, and illnesses such as cancer on tiny, intricately shaped devices (Stavrou et al., 2023). An artificial spleen with microfluidic properties has been developed to remove pathogens from sepsis patients' blood. The device used magnetic nanoparticles functionalized with mannose-binding lectin (MBL), a human blood opsonin that binds a wide range of pathogens, including bacteria, viruses, parasites, fungi, and toxins, to remove pathogens from blood (Chen et al., 2021b).

7. Interaction with the biological system

The ROS-based mechanism of the magnetic nanosystem is illustrated in Fig. 8. It shows the interaction of the magnetic nanosystem with the biological system. The interactions between MNPs and biological systems are influenced by a variety of factors. Mathematically speaking, the forces that exist between MNPs and biological membranes can be described in terms of particle "wrapping time."

Particle size, shape, membrane surface energy, and elasticity all affect wrapping time. Variations in cellular uptake according to multiple MNPs' physical characteristics, such as size and shape, in several cell lines (A549, HeLa, and MDA-MB 435). A protein "corona" effect, wherein MNPs exposed to serum or extracellular environments develop a protein coat around them. Such biological coatings give nanomaterials biological characteristics while hiding their synthetic nature. The process by which magnetic nanoparticles exhibit antimicrobial activity entails the production of reactive oxygen species (ROS) and subsequent disruption of bacterial electron transport leading to the oxidation of NADH. The enhanced production of ROS by MNPs coated with LL-37 or CSA-13 is most likely related to the mechanism of action of CAPs, which causes pore formation in cell membranes and aids in the transport of nanoparticles into Candida cells. The redox state of cells is altered by magnetic nanoparticles, which intensifies the production of reactive oxygen species.

7.1. Bio-distribution, toxicity and side effects

Nanoparticle biodistribution is a problem since metal-containing particles are swiftly removed from the circulation by the reticuloendothelial system but stay for a long time in organs like the liver and spleen. Additionally, the physical properties of nanoparticles, such as size, shape, and surface coating agents, notably the coating chemistry, determine opsonization, which in turn controls uptake by the reticuloendothelial system. When compared to the kidney, the liver and spleen had higher levels of iron accumulation. When compared to the control, chronically exposed animals' liver samples had an increased level of iron. Additionally, high-dose-treated animals had more iron in their kidneys than control animals did.

Nanoparticle toxicity is influenced by a number of factors, including administration technique, surface chemistry, biodegradability, etc. In order to show that nanoparticle toxicity can also depend on concentration, no cytotoxic effects were seen in various cell lines at nanoparticle concentrations <100 g/mL. As with any breakthrough biomedical discovery, the risk-benefit ratio for nanoparticles must be examined to see whether the risks are acceptable (Alromi et al., 2021). The composition, shape, surface area, size, and coating of a nanoparticle are typically the most important factors to take into account when determining its cytotoxicity. To ensure that the hazardous effects are kept to a minimum, the surface of the nanoparticle must be modified.

Due to MNPs building up in organs, the side effects of MNPs may result in decreased therapeutic efficacy as well as the activation of inflammatory or immunological responses. If MNPs infiltrate cells, their harmful effects could interfere with nuclear functions or lead to leakage or obstruction of the cell membranes, which would have a negative impact on metabolic activity, cell proliferation, and viability (Alromi et al., 2021). For instance, nickel nanoparticles may cause oxidative stress to cause the death of A549 cells and HepG2 cells, ultimately inhibiting cells in the subG1 phase. For all manufactured MNPs, toxicological assessments are therefore required. Since many industrial nanoparticles are non-biodegradable and there is a good chance that they will accumulate for an extended period of time in tissues, long-term research is essential because some nanoparticles' harmful effects may

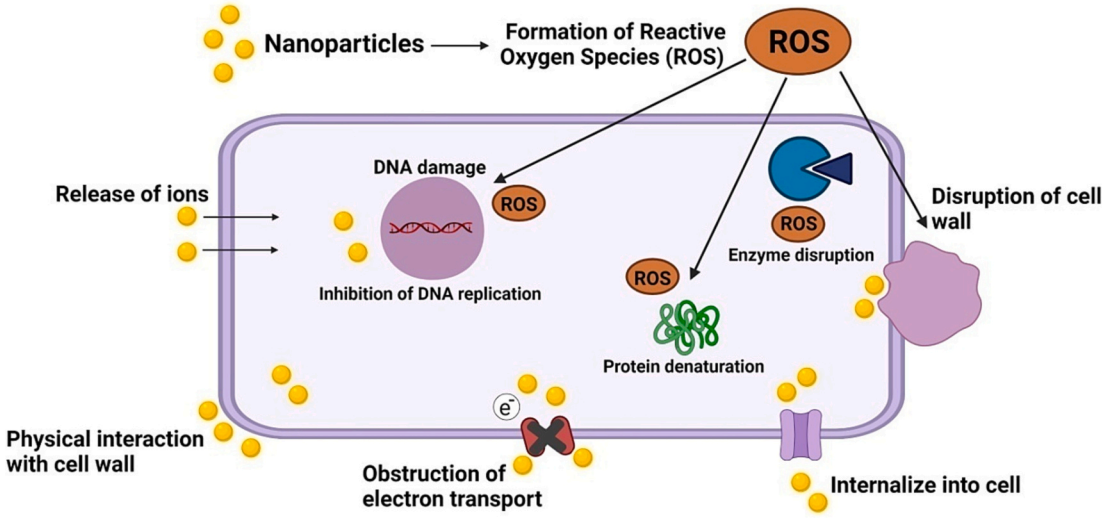

Fig. 8. Schematic presentation of ROS mechanism of nanoparticles and interaction with the biological system.

not be apparent until long-term exposure.

7.2. Magnetic field exposure

Known as magnetofections (MF), MNPs could be employed as efficient gene transfection methods when functionalized with DNA vectors. Modern magnetic polycation polyethylenimine-coated MNP and equivalent conventional gene vectors were directly compared, and the results showed a significant improvement in transfection effectiveness for both viral and non-viral vectors in permissive and non-permissive cells (Shubayev et al., 2009). Using antisense oligonucleotide delivery both *in vivo* and *in vitro*, MF effectively enhanced the efficiency of the luciferase reporter in endothelial cells by 360 times. Creating magnetic lipoplexes and polyplexes, preparing them for magnetofection, verifying their ability to attach intact DNA with MNP cores, and data processing are some phases in a magnetic nonviral gene transfer technique.

8. Biomedical and diagnostic applications

8.1. Antimicrobial

After the discovery of antibiotics, infections are generally treated by antibiotics. Furthermore, encapsulating antibiotics in metal nanoparticles could be a better option for treating infections (Anderson et al., 2019). Silver metal was also used to design nanowires as a antibacterial agent. These silver vanadate nanowires with a size of about 60 nm were functionalized with silver nanoparticles (1–20 nm). These are hybrid materials made by hydrothermally treating ammonium vanadate and silver nitrate precipitation reaction. Previously published a study on the preparation of silver nanoparticles for infection caused by the fungus *Candida albicans*, *Escherichia coli*, and *Pseudomonas fluorescens* (Fujimori et al., 2012).

Moreover, smaller sizes and high magnetism of iron oxide nanoparticles with lower toxicity were widely used in biomedical applications. The iron oxide nanoparticles were studied for various activities like antibacterial and antimicrobial. These activities solely depend on nanoparticle size, concentration, and stability. The magnetic iron oxide nanoparticles were prepared by laser ablation method and evaluated for the actions by carrying out the diffusion assay in an agar medium (Ismail et al., 2015; Iwamoto and Ishigaki, 2013). The activity assay against the bacteria (gram-positive and gram-negative) demonstrated their antimicrobial activity. Overall results of the study reported by Wang et al. show the direct interaction of nanoparticles with lower diameters between 1 and 10 nm, which was found to be a size-dependent phenomenon (Wang et al., 2017; Loo et al., 2018).

8.2. Antiviral

Various metal nanoparticles have been used for the delivery of antiviral agents. The silver nanoparticles encapsulating antiviral agents could be a promising therapy to inhibit hepatitis B virus replication. It is also helpful in producing HBV RNA and extracellular virions. Researchers hypothesized the direct interaction between metal nanoparticles and HBV double-stranded DNA. This interaction may lead to showing the antiviral mechanism.

Moreover, the antibacterial activity against various microbes has been previously reported by different research groups. They have worked on methicillin-resistant *Staphylococcus aureus* (MRSA), *Escherichia coli*, *Pseudomonas aeruginosa*, *Vibrio cholera,* and *Bacillus subtilis* for activity demonstration. The concentration-dependent activity was also studied, which showed inhibitory activity at lower concentrations (Lu et al., 2008). The study on the synergistic effect of silver or zinc nanoparticles encapsulated with various antibiotics (ampicillin, penicillin G, amoxicillin, kanamycin, erythromycin, clindamycin, chloramphenicol, and vancomycin) was demonstrated and published in previous studies (Lu et al., 2008; Ratan et al., 2021). In another study by Elechiguerra et al., silver nanoparticles' antiviral potential depends on the size of nanoparticles and their interaction for the removal of various kinds of viruses from both surface and groundwater sources is interestingly crucial for maintaining social health. However, the metal oxide nanoparticles like TiO_2 were found to be ideal photocatalysts for water treatment because of their benefit of non-toxicity after consumption. Additionally, the combination of titanium dioxide with silver nanoparticles showed a synergistic effect by enhanced photocatalytic inactivation of viruses (Ratan et al., 2021; de Dicastillo et al., 2020).

8.3. Drug or gene delivery

Despite the potential of nanocarriers like self-assembled nanocarriers, mesoporous silica nanoparticles for gene or drug delivery have some problems (Rarokar et al., 2021). The problems associated with targeting, accumulation, BBB penetration, circulation time, and stability-related issues should be resolved for better treatment. These problems could be solved by incorporating magnetic nanoparticles of different nanocarriers. The nanocarriers attached with magnetic nanocomposites (MNCs) drug/gene molecules can deliver the drug at the target site. It can be achieved by using an external magnetic field to guide the drug to attain the desired site of action and control its release

(Anik et al., 2021).

8.4. Hydrogel

Magnetic hydrogel nanocomposites consisting of magnetic nanoparticles encapsulated with anticancer agents could be prepared and evaluated for biomedical applications. It was used for wound healing, nerve repair, and controlled delivery with low biotoxicity. Moreover, the hydrogel containing magnetic nanoparticles was proven cargo for the drug. This hydrogel tends to release the drug at a specific site, followed by retrieval of magnetic particles. (Sun et al., 2008).

8.5. Liposome

The potential of liposomes as a carrier for the delivery of drug molecules can be used in combination with magnetic nanoparticles for efficient therapeutic delivery. The drawbacks associated with liposome delivery could be overcome by combining magnetic nanoparticles. In addition, it will improve its efficiency by increasing encapsulation and thermal disruption. (McNamara and Tofail, 2015).

The combined effect of MNPs with liposomes showed the benefits of improved biocompatibility and non-toxicity. The conjugation of biocompatible polymers and protein-resistant polymers showed other advantages like non-aggregation and increased uptake of nanoparticles by the RES, with increased stability in an internal physiological environment (McNamara and Tofail, 2015; Ali et al., 2021).

8.6. MRI

The MNPs also have some diagnostic applications because of their structural properties. MRI can be used to develop MRI reagents and for drug delivery applications. These are demonstrated for theranostic application in the management of solid tumors. The MNPs were efficient in treatment and MRI contrast agents in clinical practice (Ali et al., 2021). In the influence of the external magnetic field, protons of hydrogen aligned and based on low as well as high energy spin could form the images at different bangles. (Onishi et al., 2022). MNPs were proven a potential carrier for MRI because of their excellent contrast agents property and target-specific ability. It could help diagnose inflammatory diseases and cancer at the primary level. Furthermore, their size-dependent properties make them more promising magnetic contrast agents because of the ease of accumulation in specific organs or tumor cells.

8.7. Molecular diagnosis

Molecular detection is the most common application of magnetic nanoparticles. The surface modification and alteration of magnetic properties can be helpful in the development of an efficient analytical method. This technique can detect and separate DNA and RNA, cell separation, and protein purification. They are crucial to the development of biosensors that can identify particular biomarkers of cancer or inflammation as well as the magnetic separation of biomolecules for the purpose of molecular diagnosis (Hola et al., 2015). With just one milliliter of whole blood, microarray chips composed of MNPs produced via chemical vapor deposition technique may make it simple and effective to identify cancer cells (Li et al., 2016). Because MNPs can function as ferromagnetic labels and their surface can be readily modified with a variety of receptors, they are well suited to serve as platforms for biosensors. They can also be scattered throughout the sample and applied to the biosensor's active detection surface. Multifunctional nanoparticles, or MNPs, have been used extensively in sensing-related applications. MNPs, for instance, have been directly applied to the sensor to tag supports associated with the materials of the transducer. The cytosensor offers a lot of promise for investigating novel uses in the identification of numerous separation products based on MNPs (Rocha-Santos, 2014; Ferain and Legras, 2009).

8.8. Nucleic acid separation and detection

Nucleic acid is important functional material of our body that actively participates in the various biological processes of storage, copying, and transmission of genetic information. Therefore the imbalance or deficiency of such material may result in the development of multiple diseases, including type 1 (T1D) and type 2 diabetes mellitus (T2D), Alzheimer's dementia, and cystic fibrosis. Moreover, cancer can develop due to the increase or decrease in the level of nucleic acid (Ali et al., 2021; Onishi et al., 2022). Hence, measuring the nucleic acid level may give an idea about the development of deadly diseases in the primary stage. So it could be helpful for the detection or diagnosis of diseases. Various biomedical and diagnostic applications are quoted below in Table 1.

9. Cancer nanotheranostics

The field of nanotheranostics integrates three primary research domains: therapeutics - drug/molecular delivery; diagnostics - imaging/detection for early diagnosis, treatment, and prognosis for a particular disease type, including cancer/tu; and nano-particle/structure - organic and inorganic (Wong et al., 2020; Jagtap et al., 2017). Therefore, by delivering therapeutic molecules and offering early disease diagnosis and progression for future treatment profiles, nanotheranostics offers benefits over traditional treatments. Targeted delivery also reduces socioeconomic burden, exponential drug use and overdose, and allows for real-time patient monitoring of payload delivery, bioavailability, and biodistribution (Mura and Couvreur, 2012;Kumar et al., 2023). The magnetic properties of iron (Fe) were utilized by the hybrid iron-platinum (FePt) nanoparticles for the purpose of magnetic field-guided targeting of glioblastoma and hepatocellular carcinoma (Chen et al., 2020). As a chemotherapeutic and MRI diagnostic agent, 100 nm FePt NPs killed HepG2 cells with DOX delivery (Chan et al., 2019; Chan et al., 2021; Chen et al., 2020) and Mahlava and SK-Hep1 hepatocellular carcinoma cells with mitoxantrone (MIT) delivery (Chan et al., 2021) in two separate studies. This research group delivered DOX-conjugated FePt NPs magnetically using a different method utilizing PEGylated lipid nanobubbles. In addition to producing chemotherapeutic effects by delivering the drug DOX across the blood-brain barrier (BBB), the formulation allowed for the production of high-resolution MRI imaging for glioblastoma in an *in vivo* model.

10. Clinical trials

Because of their targeted approach, early clinical results have demonstrated that nanoparticle therapies can significantly reduce negative adverse effects and demonstrate increased efficacy when compared to conventional therapies. The FDA (Food and Drug Administration) requires a thorough and rigorous trial before approving nanoparticles and medications. A clinical trial cannot begin until the therapeutic agent has undergone testing on animals following its development in the laboratory. For about 20 years, iron-based nanoparticles with different surface ligands have been used in clinical settings as T2 contrast agents in magnetic resonance imaging (MRI) after receiving clinical approval. Known as Ferucarbotran, these 60 nm carboxydextran-coated iron oxide nanoparticles were licensed for use in hepatocellular carcinoma and cell labeling under the trade names Resovist in the United States and Europe and Cliavist in France. Under the trade names Endorem in England and Feridex in the USA, 80–150 nm dextran coated iron oxide nanoparticles known as Ferumoxide were authorized for the imaging of mononuclear phagocyte systems and cell labeling. Under the brand names Combidex in the USA and Sinerem in the European Union, smaller dextran coated magnetic nanoparticles measuring 20–40 nm were authorized for perfusion and lymph node

Table 1
Biomedical and diagnostic applications of different types of magnetic nanosystem.

S·No	Nanosystem	Findings	Biomedical Application	Reference
1.	Iron Oxide Nanoparticles	The role of IONPs in biomedical research was reported. This research aimed to reduce the drug concentration, lower the toxicity, and minimize other side effects. It also helps to increase the efficacy of IONPs-in cancer therapy.	Cancer Therapy	Montiel Schneider et al., 2022
2.	Iron oxide nanoparticles	These were fabricated for use in MRI as a contrast ingredient. The study showed that their photothermal and magneto thermal properties might be applied to mouse tumor ablation. Additionally, it illustrated the strong optical absorption over a wide spectral range in the near-infrared area. Hence it could also be used for tracing photoacoustic imaging.	MRI, Photoacoustic Imaging	Martins et al., 2021
3.	CRISPR/Cas9 complexed polyethylenimine (PEI) magnetic nanoparticles	This study shows that the PEI-MNPs are a potential strategy for plasmid encoding CRISPR/Cas9 and DNA template. It could be helpful for enhanced safety and the use of gene editing.	Gene editing	Ehrmann et al., 2021
4.	Superparamagnetic iron oxide nanoparticles (SPIONs)	SPIONs were investigated for model biological membranes within the Langmuir-Blodgett technique. This work showed that the modified SPION interacts with biological membranes efficiently. The study of magnetic hyperthermia confirmed it's used in cancer therapy.	Hyperthermia	Nieciecka et al., 2021
5.	Fe3O4 magnetic nanoparticle	Delivery of siBIRC5 and AS-ODN and radiation therapy improved by Fe_3O_4 magnetic nanoparticles for lung cancer.	Radiotherapy	Chen et al., 2021a
6.	Manganese oxide nanoparticles	Mn-based CAs with high biocompatibility and clear pictures are thought to be the best option for MRI. Due to the Mn(II) ion chelate's rapid circulation, MONs, such as MnO, MnO_2, Mn_3O_4, and MnOx have gained interest as T1-weighted magnetic resonance CAs. The average particle size is responsible for the circulation time of colloidal nanoparticles.	Multimodal contrast agents for MRI-CT imaging for tumor detection and diagnosis	Anik et al., 2021
7.	Iron oxide nanoparticle (IONP)	This study reveals the interaction between the iron oxide nanoparticle (IONP) and bacteria. The co-precipitation approach created the IONP with a negative surface potential (n-IONP). The prepared IONPs were evaluated for BacLight fluorescence assay, bacterial growth kinetic, and colony-forming unit studies. The results of this study demonstrated insignificant antimicrobial activity of n-IONP (<50 μM) against *Bacillus subtilis* and *Escherichia coli.*	Antimicrobial Agent	Abbas and Krishnan, 2020
8.	Magnetic Nanoparticles	The MNPS demonstrated up to 94% protein binding when cellulase was immobilized on nanoparticles. Fourier transform infrared spectroscopy was used to verify that the binding was successful. The optimal pH values for the free and immobilized enzymes were both 4.0, but the optimal temperatures were 50 °C and 60 °C, respectively.	Enzyme Immobilization	Darwesh et al., 2020
9.	Poly-allylamine-hydrochloride (PAAH) magnetic nanoparticles	This study procedure introduced magnetic nanoparticles (MNPs) for PAAH (poly-allylamine-hydrochloride) stabilization. *Escherichia*, *Acinetobacter*, *Pseudomonas*, and *Bacillus*, four major pathogenic species related to diverse species, showed high eradication efficacy in presence of MNPs.	Water Purification	Ayeshamariam et al., 2021
10.	Magnetic nanoparticle	The key characteristics of magnetic nanoparticles are excellent dispersion, a large surface area, low cost, Buffer systems, simplicity in separation, and signal detection. In this study, magnetic nanoparticles were developed for nucleic acid detection.	Nucleic Acid Separation and Detection	Tang et al., 2020
11.	Magnetic nanoparticle	Magnetic nanoparticles combined with different proteins provide a flexible method for creating biosensors, especially in biomedical applications. The application of magnetic nanoparticles in the detection of marine toxins is discussed. Magnetic Janus nanoparticles combine the dual-functioning properties of Janus particles. A single particle with magnetic characteristics makes it possible to manipulate them remotely and allow for headed movement and direction.	Biosensor	Zhao et al., 2020
12.	Silver Nanoparticle	AgNPs, or silver nanoparticles, are thought to have the potential to eradicate certain diseases. This work created and assessed a new magnetic hybrid colloid (MHC) containing micrometre-sized AgNPs. These particles can be easily collected from environmental media utilizing their magnetic characteristics after being used to disinfect, and they continue to be efficient at inactivating viral pathogens.	Antiviral	Katz, 2020
13.	MagR-MazE fusion protein-conjugated MNPs	In order to facilitate sensitive detection, this work presents a general and straightforward detection technique that uses magnetic nanoparticles (MNPs) and unique MagR-MazE fusion protein for molecular diagnostics. The new MNP compound created in this work can be produced quickly and with minimal chemical reagents.	Molecular Diagnosis	Anderson et al., 2019
14.	Iron oxide-based MNPs	Using iron oxide-based MNPs, bacterial biofilms may be made inactive *in vitro*.	In the treatment of infectious diseases	Chircov et al., 2019

(*continued on next page*)

Table 1 (*continued*)

S·No	Nanosystem	Findings	Biomedical Application	Reference
15.	Magnetic nanoparticle	There are several ways to create and modify magnetic nanoparticles, and interactions, when biomolecules bind to magnetic nanoparticles, are also reported. To demonstrate the effectiveness of the magnetic Bioseperation technology, certain real-world instances of magnetic bioseperation procedures are also addressed.	Bioseperation	Williams, 2017
16.	iron oxide, coated with poly(ethylene glycol), and conjugated through avidin-biotin	Poly(ethylene glycol) was used to coat iron oxide nanoparticles. Then avidin-biotin chemistry was used to include an antibody directed against the epithelial cell adhesion molecule (EpCAM). When targeted nanoparticles were exposed to tumor cells, EpCAM-expressing tumor cells (such as BxPC3, a pancreatic cancer cell) specifically absorbed the particles. Still, cells with low EpCAMexp hardly absorbed the particles. This brought to a close the enormous potential of magnetic nanoparticles for cancer prognosis and tumor cell counting.	Cell Isolation and Enrichment	Fatima and Kim, 2017
17.	Magnetic nanoparticle	The creation of premium magnetic nanoparticles coated with anti-carcino-embryonic antigen (CEA) antibodies. Particle size, particle suspension, and bioactivity were then assessed. Additionally, the stability of bio-magnetic nanoparticles suspended in liquid was studied, which shows the formation of stable MNPs. These MNPs could have the potential to use in immunotherapy.	Magnetic Immunoassay	Plouffe et al., 2014
18.	Polyethyleneimine-coated magnetic	Polyethyleneimine-coated magnetic nanoparticle was designed and evaluated *in vitro* as a carrier for drug and gene delivery. It could also be used in magnetic nanoparticle-mediated non-viral gene delivery.	MNPs as Carriers for Drugs and Genes	Gao et al., 2014; Adams et al., 2013
19.	Magnetic Fe_3O_4 nanoparticles	Superparamagnetic nanoparticles may be helpful when employing the somatic cell nuclear transfer method for reproductive cloning. Magnetic Fe_3O_4 nanoparticles are used as gene carriers to create a reliable, convenient, and targetable approach for delivering numerous genes into the nucleus of pig somatic cells. The spherical magnetic Fe_3O_4 nanoparticles showed a sizable attraction for DNA plasmids harboring the genes for a green fluorescent protein (DNAGFP) or red (DNADsRed) fluorescent protein after surface modification by polyethylenimine.	Gene delivery	Kami et al., 2011
20.	Magnetic Gold Nanoparticle	For the precise detection of HPA by MRI, researchers have created a tailored probe based on magnetic gold nanoparticles linked with an antiHPA antibody.	Labeled cell detection by MRI	Johnson et al., 2011
21.	Iron oxide	Development and advancement in the design of MNPs suggest using magnetic material-based biosensors.	Sensor	
22.	Amino-magnetic nanoparticles (NH2-MNP)	They claimed to employ functionalized magnetic nanoparticles (MNPs) for the real-time RT-PCR detection of COVID-19. This is based on an earlier method of extracting and purifying RNA from nasopharyngeal cells.	Isolation of viral RNA and analysis using the polymerase chain reaction (PCR) method	Koh and Josephson, 2009

imaging (Anderson et al., 2019). Combidex is one of the most widely used MNPs and has been used in several clinical trials for the imaging of lymph node metastases (Canfarotta and Piletsky, 2014).

11. Current challenges in delivery of MNPs

As the conventional chemotherapy is administered systemically, it often causes considerable adverse reactions such as nausea, hair loss, and bone marrow suppression, as well as liver and kidney toxicity. These aspects determine the dose of the chemotherapeutic agents and limit their effects on the tumor. Therefore, in the recent years, it has been a trend in cancer pharmacotherapy to identify substances with higher specificity. Although considerablesuccess has already been achieved (e.g., Herceptin), the limits of this strategy have become clear. The targeted blockage of a specific signaling pathway has led to the emergence of genetically mutated cancer cells that are able to circumvent this blockage by upregulation of an effective parallel, alternative, or overlapping pathway. That leads to broad-spectrum medicinal products being used again. The biodistribution of these substances is of particular relevance to targeted therapy. This is where nanotechnology comes in. It can be used to transport medicinal products very precisely to the intended site of action. Magnetic nanoparticle drug delivery opens the possibility of using local enhancement methods, so that the drug can accumulate and act in a previously determined area. This method was first described in 1978. It is based on the usage of three elements: iron (Fe), cobalt (Co), and nickel (Ni). Mostly, they are used as hybrids with other metal ions, oxygen, or carbon dioxide. There are innumerable possibilities for such combinations. The iron compounds are predominantly used because of their biocompatibility. They show the lowest toxicity and are even used therapeutically for iron substitution. The nanoparticles are coated in order to prevent agglomeration, ensure stability, and provide a positive effect on biodistribution. A wide variety of materials, including fatty acids, polyethylene glycol (PEG), dextran, and chitosan may be used. Magnetic nanoparticles can transport various different substances and molecules, such as chemotherapeutic agents, antibodies, nuclear acids, radionuclides, etc. In principle, this approach can be used for any tumor, irrespective of its size, differentiation, or site (Dürr et al., 2013).

12. Effect of MNPs on immune system

Local magnetic hyperthermia immunotherapy has a variety of modes of action, some of which have been previously examined in depth. The ability to achieve powerful immunomodulation without the use of drugs, which frequently cause adverse reactions, is a benefit of further developing these techniques; however, hyperthermia is still most frequently used as a supplementary form of treatment to chemotherapy or radiotherapy rather than as a primary one.This may be partly because repeated therapy is challenging and there is a dearth of knowledge regarding the best treatment parameters for clinical use across tumor types.

In the past, placing the tumor location in a hot water bath or

inserting a metallic probe to transfer microwaves across the tumor were two ways to cause local heating of tumor cells.In a manner similar to tumor excision, hyperthermia aims to remove tumor cells along with a margin of healthy cells from the tumor site, but heat-induced cell death is preferred to physical removal. By using this technique, cell debris is produced, which macrophages and other phagocytes remove to make room for new, healthy tissue. Unlike an insertable probe or a hot water bath, which have location and temperature accuracy flaws.

Magnetic nanoparticles have the ability to deliver accurate and uniform heating over a wider temperature range while noninvasively penetrating solid malignancies. Through a number of ways, targeted heating using magnetic nanoparticles can trigger immunogenic cell death (ICD) or other long-lasting anticancer immune responses. Cellular stressors like heat can trigger ICD, a unique apoptotic pathway that releases molecules known as DAMPs (damage-associated molecular patterns). The processing of tumor-associated antigens produced during cell death is made possible by the immunostimulatory and danger-signaling functions of DAMPs (Day et al., 2021).

13. Magnetic hyperthermia

The progressive rise in temperature to 40–43 °C is known as hyperthermia. It causes cancer cells to be destroyed and enhances the effects of radiation and chemotherapy. This method's incapacity to locally heat cancer cells is a drawback. Nevertheless, this problem can be avoided by injecting MNPs that are directed towards particular locations and using an external magnetic field to produce localized heat. Since this targeted method doesn't harm nearby healthy tissues, it may improve the safety and effectiveness of hyperthermia (Anik et al., 2021). Cancer therapy can be applied non-invasively using magnetic hyperthermia. This method provides an alternative for some cancers that might be challenging to remove surgically and for those that are located close to important organs. Treatment options may expand beyond specific tumors because magnetic hyperthermia addresses the problem of nonselective ionizing radiation linked with conventional radiotherapy. Treatment with hyperthermia causes specific biological effects in cancer cells, such as increased lysosomal permeability, which ultimately leads to an increase in oxidative stress because reactive oxygen species are produced. Increased lysosomal permeability also results in decreased tumor cell viability via increased cathepsin D activity within the cytoplasm. Moreover, the instability of the lipid membrane may be disturbed by the rotation of SPIONs brought on by dynamic magnetic fields, which could affect lysosomal permeability and trigger apoptosis (Egea-Benavente et al., 2021). For magnetic hyperthermia, a team of researchers used superparamagnetic iron oxide nanoparticles coated with carboxydextran. An alternating magnetic field was applied for 20 min to BALB/c nu/nu athymic mice that had been injected with A549 cells, a cell line used to treat non-small cell lung cancer. It was reported that the tumor size had significantly decreased. In order to replicate pancreatic cancer tissue, researchers injected mice with the murine pancreatic carcinoma cell line Pan02 cells. After the tumor grew, the mice were injected with iron oxide nanoparticles that were loaded onto monocyte/macrophage-like cells. When the MNPs in the cancerous tissue were exposed to an alternating magnetic field for three days, they began to produce heat. After some time, there was a noticeable decrease in the size of the tumor (Farzin et al., 2020).

13.1. Advantages and risks associated with magnetic hyperthermia

Treatments using hyperthermia have been discovered to be very effective against a wide range of aggressive cancers and have a number of advantages over traditional cancer therapies. Glioblastoma multiform is one example. Additionally, compared to more traditional methods of producing hyperthermia like ultrasound and radiofrequency radiation, this technique has a number of advantagees (Jose et al., 2020). For instance, the target depth, backscattering, or heat-sink effects of big blood arteries do not limit the application of magnetic hyperthermia, which is far more precise than these more traditional thermal approaches.

14. Conclusion

The present review enlightens the advantages of magnetic nanosystems in biomedical and clinical applications. Various research groups have also evaluated them for diagnosis purposes; therefore, they could be used for the theranostic application. Furthermore, the conjugation of the MNPs with various polymers and biochemical materials like amino acids and nucleic acids makes it a potential strategy for targeting the organs and the tumor site in cancer therapy.

CRediT authorship contribution statement

Nilesh Rarokar: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Formal analysis, Data curation, Conceptualization. **Sakshi Yadav:** Writing – original draft, Investigation, Formal analysis, Data curation. **Suprit Saoji:** Writing – review & editing, Supervision, Investigation. **Pratiksha Bramhe:** Investigation, Data curation. **Rishabh Agade:** Writing – original draft, Data curation. **Shailendra Gurav:** Writing – review & editing, Resources, Formal analysis, Data curation. **Pramod Khedekar:** Writing – review & editing. **Vetriselvan Subramaniyan:** Writing – review & editing, Supervision, Funding acquisition. **Ling Shing Wong:** Writing – review & editing. **Vinoth Kumarasamy:** Resources, Funding acquisition, Data curation.

Declaration of competing interest

Authors declared no conflict of interest.

Data availability

Data will be made available on request.

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