

Review Article

Smart Magnetic Iron Oxide-Based Nanocarriers: A Transformative Paradigm for Targeted and Controlled Drug Delivery

Ayush A. Shinde, Mayur D. Nandeshwar, Aditya D. Deohans, Arti S. Shinde, Manasi M. Choudhari* , Swati P. Deshmukh

Shraddha Institute of Pharmacy, Kondala, Zambare, Dist, Washim-444505, India



Citation A.A. Shinde, M.D. Nandeshwar, A.D. Deohans, A.S. Shinde, M.M. Choudhari, S.P. Deshmukh. Smart Magnetic Iron Oxide-Based Nanocarriers: A Transformative Paradigm for Targeted and Controlled Drug Delivery. *J. Pharm. Sci. Comput. Chem.* **2026**, 2(1), 52-74.

 <https://doi.org/10.48309/jpscc.2026.571931.1037>

**Article info:**

Submitted: 2026-01-18

Revised: 2026-03-12

Accepted: 2026-03-22

ID: JPSCC-2601-1037

Article Podcast: [Click here](#)

Keywords:

Magnetic iron oxide nanoparticles, Smart nanocarriers, Targeted drug delivery, Stimuli-responsive drug release, Magnetic guidance and targeting, Nanomedicine and theranostics

ABSTRACT

Magnetic iron oxide nanocarriers (MIONs) have gained significant attention in drug delivery due to their unique magnetic responsiveness, biocompatibility, and ability to enable site-specific targeting. This review summarizes recent advances in the design and biomedical applications of MION-based drug delivery systems. Particular emphasis is placed on the structural characteristics of MIONs, including particle size, morphology, and surface chemistry, which critically influence magnetic behavior, biodistribution, and drug release performance. Common synthesis approaches such as co-precipitation, thermal decomposition, hydrothermal, and microemulsion methods are discussed, along with surface functionalization strategies using polymers, lipids, and targeting ligands to improve stability and targeting efficiency. Key mechanisms enabling targeted and controlled drug delivery, including magnetic guidance, magneto-thermal release, and stimuli-responsive systems (pH, temperature, and magnetic field), are also highlighted. The review further outlines major biomedical applications of MIONs in targeted chemotherapy, gene delivery, antimicrobial therapy, and theranostic platforms that combine diagnosis and treatment. Emerging applications in neurological and cardiovascular therapies are also discussed. Despite significant progress, challenges such as toxicity concerns, aggregation, and limited clinical translation remain. Future perspectives focus on the integration of artificial intelligence, magnetic biosensing technologies, hybrid nanopatforms, and green synthesis approaches to develop safer and more efficient magnetic nanocarriers for next-generation targeted drug delivery.

Introduction

Magnetic iron oxide nanoparticles (MIONs), typically composed of magnetite (Fe_3O_4) or maghemite ($\gamma\text{-Fe}_2\text{O}_3$), exhibit distinct superparamagnetic behavior when their size is reduced below a critical diameter. This property allows them to respond

dynamically to external magnetic fields without retaining residual magnetism once the field is removed a critical feature that prevents undesirable particle aggregation in physiological environments. The ability to manipulate these nanoparticles remotely using an external magnetic field has opened new avenues in site-specific drug delivery, hyperthermia therapy, biosensing, and magnetic

resonance imaging (MRI) contrast enhancement. Furthermore, their surfaces can be modified with various polymers, surfactants, or ligands to improve biocompatibility, enhance stability, and enable selective targeting to cancerous or inflamed tissues. These surface-engineered MIONs can encapsulate or conjugate drugs, peptides, or genes, enabling multifunctional systems capable of both therapeutic action and diagnostic imaging a cornerstone of nanotheranostics [1]. Their magnetic control provides an additional advantage of external modulation, allowing physicians to direct nanoparticles toward specific tissues, release drugs on-demand through heat induction, or monitor biodistribution in real time [2]. The concept of magnetic drug targeting originated in the 1970s when researchers first explored the potential of using magnetically responsive particles to localize drugs within tumor sites under an external magnetic field. Early formulations involved micron-sized ferromagnetic particles that suffered from rapid clearance by the reticuloendothelial system (RES) and poor tissue penetration. With advancements in nanotechnology, the synthesis of nanoscale iron oxide particles with controlled magnetic and physicochemical properties revolutionized the field. In the 1990s, SPIONs were first approved for clinical use as MRI contrast agents, paving the way for biomedical acceptance of magnetic nanomaterials. Over time, the development of surface modification techniques, such as coating with dextran, polyethylene glycol (PEG), or chitosan, significantly improved the biocompatibility and circulation half-life of MIONs. Concurrently, the integration of magnetic targeting with stimuli-responsive drug release mechanisms triggered by pH, temperature, or alternating magnetic fields expanded the potential of these systems beyond passive delivery [3]. Today, MIONs are being explored as multifunctional platforms capable of synergizing diagnostics, targeted therapy, and controlled release, representing a pivotal shift toward precision nanomedicine [4]. Remarkable progress, the clinical translation of MIONs faces challenges related to particle aggregation, immune recognition, biodistribution, and long-term toxicity. This review aims to provide a

comprehensive overview of the design principles, synthesis strategies, and biomedical applications of MIONs in therapeutic drug delivery [5].

The subsequent sections discuss in detail the physicochemical properties that govern their performance, including structure, surface characteristics, and magnetic behavior. Various synthesis and functionalization approaches such as chemical co-precipitation, solvothermal, and microemulsion methods are examined to highlight their influence on nanoparticle quality and functionality [6]. The mechanisms of magnetic targeting and controlled drug release are analyzed to elucidate how external magnetic fields and intrinsic stimuli can be leveraged for spatially and temporally controlled drug delivery. Furthermore, the review explores the biomedical applications of MION-based systems in targeted chemotherapy, gene delivery, antimicrobial therapy, and theranostics, alongside emerging roles in neurological and cardiovascular interventions. Finally, it addresses current challenges, regulatory hurdles, and translational perspectives, concluding with insights into future directions, including smart magnetic nanocarriers, hybrid nanoplateforms, and sustainable synthesis approaches [7]. MIONs represent a multifunctional and tunable platform with immense potential for advancing targeted and personalized medicine. Their ability to respond to magnetic fields and other physiological stimuli enables unprecedented control over drug biodistribution and therapeutic action. However, realizing their full clinical potential demands concerted efforts to optimize synthesis, improve stability, ensure safety, and develop standardized regulatory frameworks. This review thus endeavors to bridge the gap between fundamental understanding and translational application, providing a critical perspective on the evolving role of MIONs in the next generation of therapeutic drug delivery systems [8].

Physicochemical Properties of Magnetic Iron Oxide Nanoparticles

MIONs have emerged as one of the most versatile and multifunctional nanomaterials for

biomedical applications, especially in targeted and controlled drug delivery systems. Their unique physicochemical attributes including crystal structure, magnetic responsiveness, surface chemistry, biocompatibility, and size-dependent properties govern their interaction with biological systems and determine their therapeutic efficiency. Understanding these fundamental physicochemical properties is therefore crucial for designing MION-based nanocarriers that exhibit precise targeting, high loading capacity, and controllable drug release with minimal toxicity, as indicated in Table 1 [9].

Structure, Composition, and Magnetic Behaviour

The structural framework of MIONs is predominantly derived from iron oxides such as magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$). These crystalline phases possess inverse spinel structures, where Fe^{2+} and Fe^{3+} ions occupy both tetrahedral and octahedral sites within an oxygen lattice. The presence of mixed valence states facilitates electron hopping, conferring intrinsic magnetic properties to the nanoparticles. Among these, magnetite is often preferred due to its higher saturation magnetization (92–100 emu/g) and superior magnetic susceptibility, which enable efficient manipulation under external magnetic fields [10]. The composition and crystal purity of MIONs significantly influence their physicochemical behavior. Slight deviations in stoichiometry, such as oxidation of Fe_3O_4 to $\gamma\text{-Fe}_2\text{O}_3$, alter the magnetic domain configuration and can reduce the magnetic response. Hence, precise control over synthesis conditions, including temperature, pH, and precursor ratios, is essential to maintain phase stability and prevent surface oxidation. X-ray diffraction (XRD), Mössbauer spectroscopy, and Raman spectroscopy are typically employed to confirm the crystalline phase and oxidation state of iron ions [11]. Magnetic behavior in MIONs arises from the alignment of magnetic moments within their domains. When exposed to an external magnetic field, MIONs exhibit magnetization proportional to field strength, which saturates beyond a certain limit known as the saturation magnetization (Ms). This property is central to

their application in targeted drug delivery, where magnetic guidance enables localized accumulation at specific disease sites. Moreover, the reversible magnetization behavior of MIONs ensures rapid demagnetization once the field is removed, minimizing the risk of aggregation or embolism in biological fluids [12].

Size, Shape, and Surface Characteristics

The physicochemical behavior and biomedical performance of MIONs are profoundly influenced by their size, morphology, and surface properties. Typically, nanoparticles ranging between 5 and 100 nm exhibit optimal magnetic and biological characteristics. Particles below 20 nm often display superparamagnetic behavior, while those larger than 50 nm may transition to a ferromagnetic state, leading to irreversible magnetic aggregation. Thus, precise size control is essential for achieving stable colloidal suspensions and efficient *in vivo* performance [13]. The shape of MIONs whether spherical, cubic, octahedral, or rod-like, affects their magnetic anisotropy, surface area, and cellular internalization. Studies have shown that cubic and octahedral morphologies offer higher magnetic moments due to more ordered surface spin arrangements compared to spherical counterparts. Moreover, anisotropic nanoparticles such as nanorods or nanowires exhibit direction-dependent magnetic behavior that can be exploited for enhanced magnetic responsiveness and improved penetration into tissue matrices [14]. Surface characteristics, including charge, functional groups, and roughness, play a vital role in determining the interaction of MIONs with biological environments. Bare iron oxide nanoparticles tend to aggregate due to high surface energy and magnetic dipole–dipole interactions. Therefore, surface modification with organic or inorganic coatings (*e.g.*, dextran, PEG, silica, or chitosan) is employed to enhance dispersion stability, biocompatibility, and drug conjugation capability. The surface charge, often represented by zeta potential, influences colloidal stability and cellular uptake [15]. Nanoparticles with moderate positive or negative zeta potential (± 20 –30 mV) generally exhibit good stability and lower nonspecific protein adsorption.

<https://doi.org/10.1016/j.ijpharm.2024.124799>

Atomic force microscopy (AFM), dynamic light scattering (DLS), and transmission electron microscopy (TEM) are essential tools for characterizing these morphological and surface parameters [16]. This figure highlights the key design attributes that influence the performance of MIONs. The surface can be functionalized with biomolecules such as proteins, antibodies, carbohydrates, or polymers to enhance biocompatibility and targeting efficiency. The characteristics, including size, stiffness, porosity, and topography determine biodistribution and cellular uptake.

Responsiveness to stimuli such as pH, temperature, light, and magnetism allows for controlled and site-specific drug release. The shape cube, rod, sphere, plate, ellipse, and star affects circulation and cellular internalization behaviour, while the material composition ranging from micelles, liposomes, nanogels, dendrimers, and polymers to inorganic structures like iron/silica, gold, or mesoporous systems, dictates stability, magnetic properties, and therapeutic potential. Overall, these integrated features enable the precise engineering of magnetic nanocarriers for efficient targeted drug delivery and diagnostic applications, as shown in Figure 1.

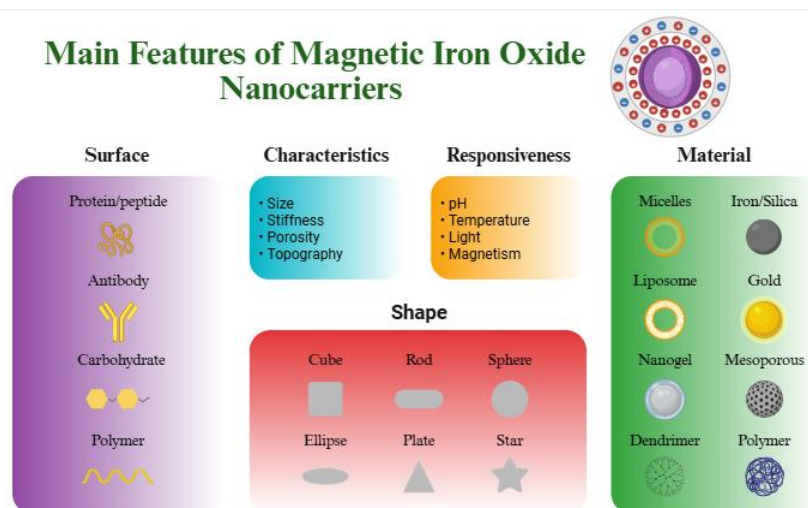


Figure 1. Main features of MIONs. The schematic illustrates the key structural and functional parameters that define MIONs for biomedical applications

Superparamagnetic and its Role in Drug Targeting

Superparamagnetic is a defining feature of ultra-small MIONs, typically below a critical diameter of 20 nm. In this state, each nanoparticle behaves as a single magnetic domain that can rapidly align with an external magnetic field but exhibits no residual magnetization when the field is removed. This unique phenomenon prevents particle aggregation and facilitates safe circulation within biological fluids [17]. In drug delivery, the superparamagnetic behaviour enables the application of external magnetic fields to direct MIONs toward a specific site, such

as a tumor or inflamed tissue. The absence of remanent magnetization ensures that once the external field is withdrawn, nanoparticles remain well-dispersed, reducing the risk of vascular blockage or immune clearance. The magnetic moment and susceptibility of MIONs directly influence the efficiency of magnetic targeting, as higher magnetization enhances responsiveness to external fields and improves drug accumulation at the desired location [18]. The magnetic relaxation mechanisms, Néel and Brownian relaxation, also play pivotal roles in modulating drug release and imaging efficiency. The balance between these relaxation processes dictates the magnetic heating capability (used in

hyperthermia therapy) and the stability of drug conjugates under oscillating fields. Superparamagnetic MIONs also find application in magnetically triggered release systems, where localized magnetic fields induce mild heating or structural deformation of coatings to control the release of encapsulated drugs. Thus, superparamagnetic is not only vital for targeted delivery, but also for controlled and responsive therapeutic action [19].

Biocompatibility, Biodegradability, and Stability Considerations

The biocompatibility and biodegradability of MIONs are of utmost importance. Although iron oxide itself is relatively non-toxic, its surface chemistry and degradation behavior can influence cellular interactions and biological responses. In physiological conditions, MIONs may undergo slow dissolution into Fe^{2+} and Fe^{3+} ions, which are naturally metabolized through the body's iron homeostasis pathways involving transferrin and ferritin. This biodegradation process ensures that the nanoparticles are ultimately eliminated or recycled, minimizing long-term toxicity [9]. However, uncoated or poorly stabilized nanoparticles can induce oxidative stress, membrane damage, or inflammatory responses due to the generation of reactive oxygen species (ROS) at their surface. Surface passivation using biocompatible polymers (*e.g.*, polyethylene glycol, dextran, chitosan) or inorganic shells (*e.g.*, silica and gold) effectively mitigates such effects by reducing direct contact between the iron oxide core and cellular components. These coatings also provide reactive functional groups ($-\text{COOH}$, $-\text{NH}_2$, and $-\text{OH}$) that facilitate further conjugation with therapeutic agents, targeting ligands, or stealth polymers [19]. The colloidal stability of MIONs in physiological media is another critical determinant of their pharmacokinetic behavior. Factors such as ionic strength, pH, and protein adsorption can destabilize nanoparticle suspensions, leading to aggregation or rapid clearance by the reticuloendothelial system (RES). Coatings that impart steric or electrostatic stabilization extend the circulation time and improve biodistribution profiles. Additionally,

crosslinking or grafting of hydrophilic polymers can enhance mechanical stability and prevent premature drug leakage during systemic transport [20]. Thermal and chemical stability are also essential for ensuring reproducible performance during synthesis, sterilization, and storage. MIONs with robust coatings retain their magnetic and structural integrity under physiological temperature and oxidative environments. Long-term stability testing, involving zeta potential and particle size monitoring, is crucial for predicting the shelf life of magnetic nanocarrier formulations [21].

Correlation Between Physicochemical Attributes and Biological Performance

The therapeutic performance of MIONs is intricately linked to their physicochemical characteristics. Particle size determines biodistribution and clearance pathways; nanoparticles below 10 nm are often cleared renally, whereas those between 20 and 100 nm exhibit prolonged circulation and enhanced permeation into tumor tissues via the enhanced permeability and retention (EPR) effect. Similarly, surface charge modulates opsonization and macrophage uptake, influencing immune evasion and targeting efficiency [22]. The crystallinity and magnetic strength dictate the efficiency of magnetic targeting and hyperthermic response. High-crystallinity magnetite cores ensure stronger magnetic moments and superior responsiveness to external fields. Conversely, amorphous or partially oxidized particles may show reduced magnetization, diminishing targeting precision. Coating chemistry influences not only stability, but also drug loading efficiency and release kinetics. Hydrophilic coatings enhance solubility, whereas hydrophobic layers allow encapsulation of lipophilic drugs, offering tunable drug-nanoparticle interactions [23]. Surface functionalization with targeting ligands such as folic acid, antibodies, or peptides confers active targeting capabilities, promoting receptor-mediated endocytosis at diseased sites. The synergy between physicochemical optimization and biological functionality underpins the success of MION-based delivery

systems in achieving site-specific, controlled, and efficient drug delivery [24].

Characterization Techniques for Physicochemical Evaluation

The comprehensive characterization of MIONs is essential for correlating physicochemical properties with biological outcomes. Structural characterization using XRD confirms crystalline phase purity, while TEM and scanning electron microscopy (SEM) provide insights into morphology, size, and distribution. DLS and zeta potential measurements evaluate hydrodynamic size and colloidal stability in physiological media. Fourier-transform infrared (FTIR) spectroscopy and X-ray photoelectron spectroscopy (XPS) identify surface functional groups and confirm successful coating or conjugation [25]. Magnetic characterization

using vibrating sample magnetometry (VSM) or superconducting quantum interference device (SQUID) magnetometry quantifies magnetic parameters such as coercivity, remanence, and saturation magnetization. These values are crucial for understanding superparamagnetic transitions and targeting efficacy. Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) assess thermal stability and coating composition, whereas inductively coupled plasma mass spectrometry (ICP-MS) determines elemental composition and iron content [26]. Collectively, these analytical tools provide a multidimensional understanding of the interplay between structural, magnetic, and surface properties, facilitating the rational design of MIONs optimized for biomedical applications [23].

Table 1. Characterization techniques for physicochemical evaluation of MIONs

Characterization parameter	Technique	Purpose information obtained	Relevance to drug delivery	Ref.
Particle size and distribution	DLS, TEM, SEM	Determines hydrodynamic size, morphology, and uniformity.	Influences circulation time, cellular uptake, and magnetic targeting efficiency.	[27]
Crystal structure	XRD	Identifies crystalline phase and purity.	Confirms spinel structure (magnetite/maghemite) crucial for magnetic properties.	[28]
Surface morphology	AFM	Visualizes particle shape and surface roughness.	Affects surface interactions, coating efficiency, and drug loading.	[29]
Magnetic properties	VSM, SQUID	Measures saturation magnetization, coercivity, and remanence.	Determines magnetic response for targeted delivery and hyperthermia.	[30]
Surface chemistry and functional groups	FTIR, XPS	Identifies functional groups, coatings, and chemical bonds.	Critical for ligand conjugation and drug binding efficiency.	[31]

Thermal stability	TGA, DSC	Evaluates thermal decomposition and stability of coatings.	Ensures stability under physiological and formulation conditions.	[32]
Zeta potential / surface charge	ELS	Measures surface charge and colloidal stability.	Predicts aggregation tendency, interaction with cells, and <i>in vivo</i> circulation.	[33]
Drug loading and release	UV-Vis Spectroscopy, HPLC	Quantifies drug encapsulation efficiency and release kinetics.	Essential for evaluating therapeutic potential and controlled delivery.	[34]

Tailoring Physicochemical Parameters for Optimized Therapeutic Efficacy

Rational engineering of MIONs involves the fine-tuning of physicochemical parameters to achieve the desired pharmacological performance. For instance, adjusting synthesis temperature or surfactant concentration allows precise control over particle size and shape, influencing biodistribution and magnetic response. Similarly, modifying surface coatings can optimize drug loading, release kinetics, and targeting specificity. By coupling magnetic control with biochemical targeting, hybrid magnetic nanocarriers can be designed to respond to multiple stimuli such as magnetic fields, pH, and temperature enabling on-demand drug release [35]. The integration of biopolymers and smart coatings enhances biocompatibility and introduces functionalities such as stimuli-responsiveness or enzyme-triggered degradation. The evolution of surface engineering strategies has thus enabled the transition of MIONs from simple magnetic carriers to intelligent, multifunctional nanoplateforms capable of performing diagnostic, therapeutic, and monitoring roles simultaneously [36].

Mechanisms of Magnetic Targeting and Controlled Drug Release

MIONs, particularly magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$), have emerged as one of the most versatile and controllable nanocarrier systems in targeted therapeutics. Their unique magnetic responsiveness, combined with tunable surface chemistry and biocompatibility, enables precise control over drug localization and release kinetics. The mechanisms governing magnetic targeting and controlled drug release involve a synergistic interplay of physical forces, magnetic field manipulation, surface modification, and stimuli-responsive interactions. These processes collectively ensure enhanced therapeutic efficiency with minimal systemic side effects. This section elaborates on the underlying principles and mechanistic pathways that define the targeting precision and release control of MION-based nanocarriers, encompassing magnetic guidance, magneto-thermal effects, stimuli-responsive mechanisms, and mathematical models of drug release kinetics, as provided in Table 2 [37].

Table 2. Mechanisms of magnetic targeting and controlled drug release

Mechanism	Description & Strategy	Parameters	Advantages	Limitations and Challenges	Ref.
Magnetic Guidance and Targeted Accumulation	<ul style="list-style-type: none"> • External magnetic field directs MIONs to target tissue • Techniques: permanent magnets, electromagnetic coils, MRI-guided navigation 	<ul style="list-style-type: none"> • Field strength and gradient • Particle size and circulation time 	<ul style="list-style-type: none"> • Enhances site-specific delivery • Reduces systemic toxicity 	<ul style="list-style-type: none"> • Limited tissue penetration • Requires precise field alignment 	[38]
Magneto-thermal (Hyperthermia) Drug Release	<ul style="list-style-type: none"> • Alternating magnetic field induces localized heating • Drug released via temperature-triggered mechanisms • Acidic tumor/endosomal microenvironment triggers drug release 	<ul style="list-style-type: none"> • AMF frequency • Particle concentration • Thermal stability 	<ul style="list-style-type: none"> • On-demand release • Synergistic anticancer effect 	<ul style="list-style-type: none"> • Risk of overheating healthy tissue • Requires accurate calibration 	[39]
pH-Responsive Release	<ul style="list-style-type: none"> • Strategies: pH-sensitive polymers, lipid coatings, ligand conjugation • Drug release triggered by local temperature changes 	<ul style="list-style-type: none"> • Polymer pKa • Coating thickness • Release kinetics 	<ul style="list-style-type: none"> • Tumor-selective release • Reduces off-target effects 	<ul style="list-style-type: none"> • Potential premature release • Stability in systemic circulation 	[40]
Temperature-Responsive Release	<ul style="list-style-type: none"> • Thermoresponsive polymers (PNIPAM, PEG derivatives) • Particle structure or polymer coating changes under magnetic field to release drug 	<ul style="list-style-type: none"> • LCST (Lower Critical Solution Temperature) • Polymer composition • Drug loading 	<ul style="list-style-type: none"> • Controlled, localized release 	<ul style="list-style-type: none"> • Must match physiological temperature range 	[41]
Magnetic Field-Responsive Release	<ul style="list-style-type: none"> • Techniques: field-sensitive hydrogels, magnetic polymer composites 	<ul style="list-style-type: none"> • Field intensity • Particle anisotropy • Coating type 	<ul style="list-style-type: none"> • Non-invasive • Precise temporal control 	<ul style="list-style-type: none"> • Requires optimization of magnetic parameters 	[42]

Multi-Stimuli Responsive Systems	<ul style="list-style-type: none"> •Combines pH, temperature, and magnetic triggers• Hybrid coatings or multi-responsive polymer matrices 	<ul style="list-style-type: none"> •Trigger thresholds• Particle design• Release profile 	<ul style="list-style-type: none"> •Maximizes targeting specificity• Fine-tuned, controlled release 	<ul style="list-style-type: none"> •Complex synthesis• Reproducibility challenges 	[43]
----------------------------------	---	---	---	---	------

Magnetic Guidance and Targeted Accumulation

The concept of magnetic targeting capitalizes on the superparamagnetic nature of MIONs, which allows them to exhibit magnetization only in the presence of an external magnetic field, eliminating residual magnetism upon field removal. This property enables site-specific guidance of drug-loaded nanoparticles to desired tissues or organs using externally applied magnetic gradients [37]. *In vivo* studies demonstrate that local application of neodymium-iron-boron (NdFeB) permanent magnets or electromagnets near the target tissue substantially increases nanoparticle accumulation, achieving 5–10 times higher local drug concentration compared to passive targeting mechanisms such as the enhanced permeability and retention (EPR) effect. The ability to modulate the magnetic field strength and direction enables dynamic steering of the nanoparticles, even in deep-seated tissues [44]. Several parameters critically affect magnetic guidance efficiency, including particle size, magnetic susceptibility, blood viscosity, and the distance between the magnet and target tissue. Nanoparticles between 10 and 100 nm in diameter exhibit optimal circulation time and magnetic responsiveness. Additionally, surface functionalization with hydrophilic polymers like PEG or dextran reduces opsonization and RES uptake, prolonging systemic circulation and enhancing the likelihood of successful magnetic capture [45]. At the cellular level, the local magnetic field not only aids in accumulation, but also enhances cellular uptake through endocytosis driven by field-induced nanoparticle aggregation and membrane deformation. This magnetically induced localization allows for high local drug concentrations with reduced systemic toxicity especially vital for potent chemotherapeutic agents such as doxorubicin or paclitaxel [46].

Magnetic targeting provides a non-invasive, controllable, and reversible method of spatial drug localization, establishing the foundation for the next level of controlled release mechanisms under magnetic influence [47].

Magneto-thermal Drug Release Mechanisms

An equally critical mechanism in MION-mediated drug delivery is magneto-thermal activation, which relies on converting magnetic energy into localized heat upon exposure to an alternating magnetic field (AMF). This process, known as magnetic hyperthermia, induces localized heating typically in the range of 41–46 °C, which can both trigger thermally sensitive drug release and exert cytotoxic effects on tumor tissues [48]. The underlying principle of magneto-thermal conversion involves Néel and Brownian relaxation losses, where magnetic dipoles within the MIONs realign rapidly with the oscillating field, dissipating energy as heat. The specific absorption rate (SAR) a measure of heat generated per unit mass of nanoparticles is influenced by particle size, magnetic anisotropy, field frequency, and amplitude. Optimized MIONs with diameters of ~10–20 nm exhibit high SAR values suitable for localized hyperthermia [49]. Incorporated into polymeric or lipidic nanocarriers, this generated heat facilitates drug diffusion through carrier matrix softening, polymer swelling, or phase transition. For instance, thermo-responsive polymers such as poly(N-isopropylacrylamide) (PNIPAM) undergo a reversible volume phase transition at their lower critical solution temperature (LCST, ~32 °C). Under magnetic hyperthermia, the polymer matrix contracts, releasing the encapsulated drug in a controlled “on-off” manner [50]. Magneto-thermal therapy (MTT) achieves synergistic therapeutic effects when combined with chemotherapy. Localized heating not only promotes drug release, but also increases tumor perfusion, enhances cellular

membrane permeability, and sensitizes cancer cells to cytotoxic agents. For example, Fe_3O_4 -loaded liposomes containing doxorubicin exhibit accelerated release and enhanced tumor regression under AMF exposure compared to passive delivery [49]. The spatial confinement of thermal effects ensures minimal damage to surrounding healthy tissues, as the generated heat dissipates rapidly beyond the magnetic focus. Importantly, fine-tuning AMF parameters (100–500 kHz frequency; 10–30 kA/m field strength) allows precise control over both therapeutic temperature and release rate. Integration of magneto-thermal mechanisms with biodegradable nanocarriers thus represents a powerful platform for spatiotemporally controlled therapy [51].

Stimuli-Responsive pH, Temperature, and Magnetic Field Release Systems

Beyond magnetic guidance and hyperthermia, MION-based nanocarriers can be engineered for multi-stimuli-responsive drug release, leveraging variations in physiological microenvironments such as pH, redox potential, and enzymatic activity. This dual or triple responsiveness ensures release specificity tailored to pathological conditions [52]. Tumor tissues and intracellular compartments (endosomes/lysosomes) exhibit acidic microenvironments (pH 4.5–6.5). MIONs functionalized with pH-sensitive linkers (*e.g.*, hydrazone, imine, or ester bonds) or polymers such as poly(β -amino esters) or chitosan derivatives can exploit this gradient for targeted drug release [53]. Under acidic conditions, protonation of functional groups weakens electrostatic interactions or cleaves acid-labile linkers, leading to drug detachment. For example, doxorubicin conjugated to MIONs via hydrazone linkage remains stable at physiological pH (7.4) but rapidly releases in tumor-like environments, ensuring selective cytotoxicity [54]. In thermo-responsive systems, temperature variations induced by external stimuli (including magnetic hyperthermia) alter the physicochemical properties of the carrier matrix. Polymers such as PNIPAM or poly(ethylene glycol)-co-poly(ϵ -caprolactone) can undergo conformational transitions,

releasing encapsulated drugs at elevated temperatures [55]. The synergistic coupling of magnetic heating and thermal responsiveness allows programmable control of release kinetics. For example, Fe_3O_4 -PNIPAM nanocomposites demonstrate stepwise release of paclitaxel under alternating field exposure [56]. Apart from heat induction, alternating or pulsed magnetic fields can directly modulate drug release through mechanical deformation, vibration, or disruption of magnetic bonds. When MIONs are embedded within polymer matrices, field-induced oscillations cause structural rearrangements that open diffusion channels, enabling on-demand drug pulsation [57].

Magneto-mechanical actuation can stimulate cellular mechanotransduction pathways, enhancing endosomal escape and intracellular drug trafficking [58]. Advanced MION hybrids incorporate redox-sensitive disulfide linkers or enzyme-cleavable peptides that respond to elevated glutathione (GSH) or matrix metalloproteinase (MMP) levels in cancer cells. The combination of magnetic responsiveness with biochemical triggers provides multi-layered release control and improves therapeutic precision [59]. The integration of multiple stimuli magnetic, pH, and thermal within a single nanocarrier ensures adaptability to dynamic biological environments and significantly minimizes premature leakage [60]. Such smart nanocarriers enable sequential drug release, where initial magnetic accumulation is followed by localized, condition-dependent release, achieving superior therapeutic outcomes [61]. Figure 2 demonstrates the concept of stimuli-responsive drug delivery using magnetic nanocarriers. Upon exposure to a specific stimulus, such as a magnetic field, heat, light, ultrasound, or internal biological cues, the nanocarrier undergoes structural or chemical changes that trigger the release of the encapsulated drug molecules. External stimuli heat, light, magnetic field, and ultrasound, can be precisely controlled from outside the body, allowing spatial and temporal regulation of drug release. Meanwhile, internal stimuli pH variation, redox potential, and enzyme activity, exploit the unique microenvironment of diseased tissues, such as acidic pH or elevated

enzyme levels to induce targeted release. Dual-stimuli responsiveness enhances therapeutic efficacy while minimizing systemic toxicity,

making it a promising strategy for advanced, intelligent nanomedicine systems.

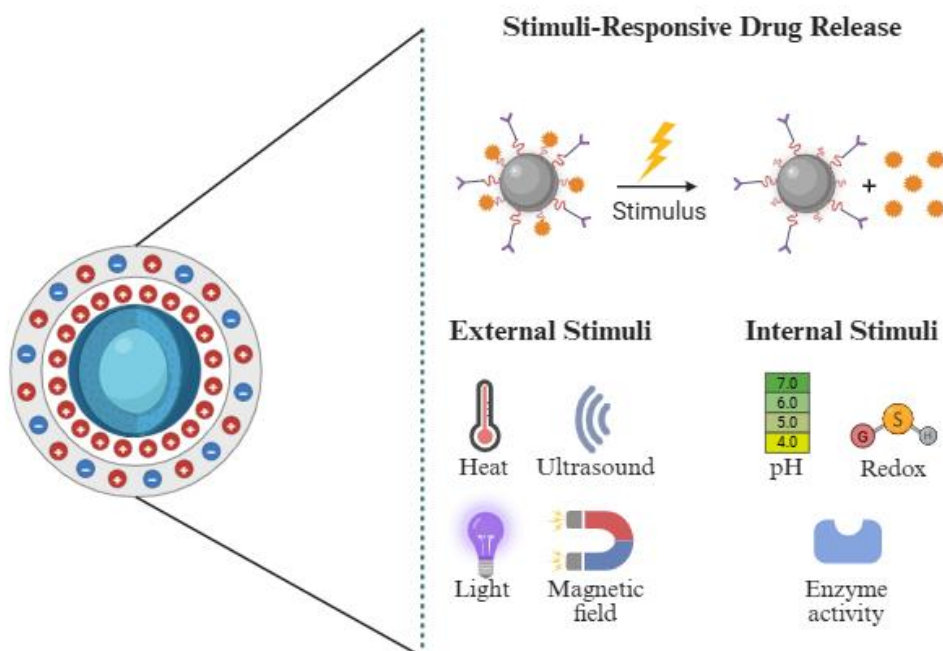


Figure 2. Mechanism of stimuli-responsive drug release from magnetic nanocarriers. The schematic illustrates how magnetic nanocarriers can be engineered to respond to various internal and external stimuli, enabling controlled and site-specific drug release.

Mathematical Models for Drug Release Kinetics

Understanding and predicting drug release kinetics from magnetic nanocarriers are crucial for optimizing therapeutic efficacy and designing controlled release systems. Mathematical modeling provides a quantitative framework to describe the mechanisms of drug diffusion, degradation, desorption, and external-field modulation. Several classical and advanced kinetic models have been applied to describe MION-mediated drug release [62].

Zero-Order and First-Order Kinetics

In zero-order models, the drug release rate remains constant over time, ideal for maintaining sustained plasma concentration. Such behavior is observed in magnetically modulated systems where field-triggered diffusion dominates. The first-order model, conversely, implies concentration-dependent

release, common in systems governed by dissolution or desorption processes [63].

Higuchi Model

The Higuchi model ($Q = k_H t^{1/2}$) describes drug diffusion from homogeneous matrices, assuming a concentration gradient-driven mechanism. It has been widely used for polymer-coated MIONs, where drug diffusion occurs through a semi-crystalline or porous matrix. Magnetic or thermal stimulation alters the diffusion coefficient (D_{eff}), leading to deviations from purely Higuchi behavior [64].

Korsmeyer-Peppas Model

For systems exhibiting anomalous (non-Fickian) diffusion, the Korsmeyer-Peppas model ($M_t/M_\infty = k t^n$) is applied, where the exponent n distinguishes between Fickian diffusion ($n \leq 0.45$), anomalous transport ($0.45 < n < 0.89$), and case-II transport ($n \geq 0.89$). Magnetic and thermo-responsive systems often show n values

in the anomalous range due to combined diffusion and relaxation effects [65].

Weibull and Hixson–Crowell Models

The Weibull model offers a flexible empirical approach that captures the sigmoidal release behavior observed in multi-layered MION composites. The Hixson–Crowell cube-root model is suitable for systems where drug release is governed by matrix erosion or degradation, relevant for biodegradable MION–polymer hybrids [66].

Magnetic Field-Dependent Kinetics

Recently, modified models incorporating magnetic field strength (B) and frequency (f) terms have been proposed to capture magneto-thermal contributions. The effective diffusion coefficient D_{eff} can be expressed as a function of field parameters: $D_{\text{eff}} = D_0 \exp(\alpha B + \beta f)$, where α and β are empirical constants reflecting the system's responsiveness. These models enable real-time control of release kinetics through external modulation.

Computational and Machine Learning Models

Advancements in computational modeling have introduced finite element simulations and machine learning algorithms to predict drug distribution and magnetic response in heterogeneous tissues. Such predictive models consider nanoparticle dynamics, magnetic field gradients, and tissue permeability, enabling personalized treatment optimization. Integrating experimental kinetic data with computational tools can refine nanocarrier design parameters, offering precise control over dose delivery and minimizing adverse effects [67].

Biomedical Applications of Magnetic Iron Oxide Nanocarriers

MIONCs, particularly magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$), have emerged as transformative tools in biomedical sciences due to their distinctive magnetic, physicochemical,

and biocompatible properties. Their capability for external magnetic field modulation, surface functionalization, and controlled drug release has expanded their application across multiple therapeutic domains, including targeted chemotherapy, gene and protein delivery, antimicrobial therapy, imaging-guided treatment, and regenerative medicine. MIONCs integrate therapeutic and diagnostic modalities in a single nanoplatform, marking a pivotal step toward precision and personalized medicine. The following sections discuss in detail the multifaceted biomedical applications of MIONCs in modern healthcare systems [68].

Targeted Chemotherapy and Cancer Treatment

One of the most extensively explored applications of MIONs is in targeted chemotherapy, where they address the limitations of conventional anticancer drug delivery such as systemic toxicity, nonspecific biodistribution, and poor tumor accumulation. MIONCs enable magnetic targeting, wherein an external magnetic field guides drug-loaded nanoparticles to the tumor microenvironment, thereby enhancing local drug concentration while minimizing adverse effects on healthy tissues. MIONCs are often encapsulated with biocompatible polymers (*e.g.*, PEG, chitosan, PLGA, dextran) or lipids to improve circulation time and reduce opsonization by the reticuloendothelial system (RES). The surface modification with targeting ligands such as folic acid, transferrin, or antibodies further enhances selective recognition of cancer cells through receptor-mediated endocytosis. For instance, doxorubicin-loaded Fe_3O_4 @chitosan nanoparticles have demonstrated superior cytotoxicity against breast and liver cancer cell lines under a magnetic field, with enhanced intracellular uptake and apoptosis induction compared to free drug administration [69]. MIONCs can serve as multifunctional theranostic platforms that integrate drug delivery with magnetic hyperthermia. Under an alternating magnetic field (AMF), these nanocarriers generate localized heat (42–46 °C), inducing tumor cell apoptosis and enhancing the permeability of tumor vasculature, which in turn

facilitates drug diffusion. This synergistic chemo-hyperthermic effect significantly enhances therapeutic efficacy. Clinical trials of NanoTherm®, an aminosilane-coated Fe₃O₄ nanoparticle formulation, have shown promising outcomes in treating recurrent glioblastoma through hyperthermia-based adjuvant therapy. MIONCs have demonstrated the potential to overcome multidrug resistance (MDR) by facilitating endosomal escape and bypassing efflux transporters. Their use in co-delivery systems combining chemotherapeutic agents (*e.g.*, paclitaxel, cisplatin) with siRNA or miRNA enables simultaneous gene silencing and drug action, thereby enhancing treatment efficacy. These advancements underscore the growing prominence of MIONCs in targeted and combination cancer therapy [70].

Gene delivery and Nucleic Acid Transport

MIONs have shown remarkable promise in gene delivery due to their ability to protect nucleic acids from enzymatic degradation and to direct their transport via magnetic guidance. Traditional viral vectors pose immunogenicity and mutagenesis concerns, whereas MIONCs offer a safer, controllable, and non-viral alternative for gene transfection. Surface-modified MIONCs can complex with nucleic acids such as plasmid DNA, siRNA, miRNA, or CRISPR/Cas9 constructs through electrostatic interactions or covalent bonding. Positively charged polymers such as polyethylenimine (PEI) or chitosan are often used to enhance loading efficiency and promote cellular uptake via endocytosis. Once internalized, endosomal escape mechanisms facilitated by proton sponge effects or external magnetic pulses enable the release of genetic material into the cytoplasm or nucleus [71]. A notable example is the Fe₃O₄-PEI/siRNA complex, which has demonstrated effective gene silencing of oncogenes such as Bcl-2 and survivin in breast and prostate cancer models. The application of a magnetic field significantly increases transfection efficiency by promoting nanoparticle accumulation at the target site a phenomenon termed magnetofection. Furthermore, magnetic nanoparticles conjugated with CRISPR components have been explored for precise

genome editing, allowing targeted gene repair and disease correction with high spatial control. Beyond cancer, MIONCs have been applied in gene therapy for neurological and cardiovascular disorders. For instance, magnetofection-based delivery of neurotrophic factors has been used to promote neuronal regeneration in Parkinson's disease models, while angiogenic gene delivery using Fe₃O₄ nanoparticles enhances vascular repair in ischemic tissues. These studies emphasize the versatility of MIONCs as platforms for safe and effective genetic modulation [72].

Antimicrobial and Antiviral Applications

The rise of multidrug-resistant pathogens has necessitated the exploration of novel antimicrobial strategies. MIONs possess inherent antimicrobial activity attributed to reactive oxygen species (ROS) generation, membrane disruption, and metal ion release, which can be synergistically enhanced through drug loading or photothermal effects. MIONCs can act as nano-antibiotic carriers, facilitating the controlled release of antimicrobial agents (*e.g.*, vancomycin, gentamicin, ciprofloxacin) directly at infection sites. For example, Fe₃O₄ nanoparticles functionalized with silver ions or quaternary ammonium compounds have exhibited potent bactericidal activity against Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus* and *Escherichia coli*. Their magnetic responsiveness allows guided targeting to biofilm-infected areas, enabling localized disinfection and minimizing systemic side effects [73]. Magnetically responsive nanocarriers have demonstrated antiviral efficacy by disrupting viral membranes or inhibiting replication mechanisms. Fe₃O₄ nanoparticles conjugated with antiviral agents (*e.g.*, ribavirin or remdesivir) or functionalized with surface ligands (*e.g.*, heparin) show enhanced viral inhibition through targeted delivery and improved cellular uptake. Magnetic hyperthermia can further inactivate viruses by denaturing viral proteins, suggesting potential applications in antiviral coatings and disinfectants. The ability to combine magnetic targeting, antimicrobial drug loading, and photothermal or photodynamic actions

positions MIONCs as next-generation antimicrobial systems, particularly valuable in combating resistant infections and supporting wound healing applications [74].

Theranostic Systems: Dual Role In Therapy and Imaging

The integration of therapy and diagnostics, termed theranostics, represents one of the most transformative applications of MIONs. Due to their superparamagnetic properties, MIONCs function as excellent contrast agents for MRI while simultaneously serving as drug delivery vehicles or hyperthermia agents. MIONCs act as T_2 -weighted MRI contrast agents, producing signal hypointensity (darkening) in target tissues. Surface modification with biocompatible polymers and targeting ligands allows precise imaging of tumors, inflamed tissues, or atherosclerotic plaques. The dual-functionality of Fe_3O_4 -based nanoplatforms enables real-time monitoring of drug biodistribution, therapeutic response, and clearance pathways facilitating personalized treatment regimens. An exemplary system is PEGylated Fe_3O_4 -doxorubicin nanocarriers, which exhibit strong MRI contrast enhancement and magnetic field-controlled drug release [75]. Moreover, coupling MIONCs with fluorescent dyes, quantum dots, or radionuclides yields multimodal imaging platforms capable of MRI-optical-PET or MRI-CT hybrid imaging. This multimodal capability enhances diagnostic accuracy while reducing the need for multiple imaging agents. The theranostic potential of MIONCs extends to magnetic hyperthermia therapy, where the nanoparticles generate heat under alternating magnetic fields to induce cancer cell death while MRI simultaneously monitors treatment progress. MIONCs are also being engineered for photo-magnetic therapy, combining photothermal or photodynamic effects with magnetic targeting for enhanced spatiotemporal control. These developments underscore the promise of MIONCs in achieving personalized, image-guided, and minimally invasive treatment modalities [76].

Emerging Applications in Neurological and Cardiovascular Disorders

Beyond oncology and infectious diseases, MIONs are gaining recognition in the treatment of neurological and cardiovascular disorders, where targeted delivery and real-time monitoring are crucial yet challenging. Crossing the blood-brain barrier (BBB) remains a formidable challenge in neuropharmacology. The small size, modifiable surface chemistry, and magnetic guidance capabilities of MIONCs enable them to traverse the BBB efficiently. When guided by an external magnetic field, these nanoparticles can deliver neuroprotective drugs, anti-inflammatory agents, or gene therapies directly to the brain. For example, Fe_3O_4 nanoparticles coated with PEG or polysorbate 80 have been shown to deliver dopamine or neurotrophic factors in models of Parkinson's and Alzheimer's diseases, significantly improving neuroregeneration and cognitive function [77]. Magnetic nanoparticles have also been used for magnetothermal neuromodulation, where localized heating triggers neuronal activity, offering potential applications in controlling epilepsy, depression, or chronic pain. Their dual imaging and therapeutic functions facilitate precise localization and minimally invasive treatment of neurodegenerative disorders. In cardiovascular medicine, MIONCs contribute to targeted thrombolytic therapy, angiogenesis induction, and vascular imaging. Magnetic guidance allows site-specific delivery of thrombolytic agents (*e.g.*, streptokinase, urokinase) to occluded vessels, minimizing systemic bleeding risks [78]. Fe_3O_4 nanoparticles loaded with vascular endothelial growth factor (VEGF) or nitric oxide donors have been utilized to promote angiogenesis and tissue regeneration in ischemic myocardium. MIONCs also serve as effective contrast agents for magnetic resonance angiography (MRA), offering high-resolution visualization of vascular architecture and plaque characterization. The development of biodegradable magnetic nanocomposites has further enabled safe long-term use in cardiovascular diagnostics and therapy. Emerging studies have integrated MIONCs into scaffold materials and stem cell-based therapies,

enhancing cell proliferation, alignment, and differentiation under magnetic stimulation. Magnetic hydrogels and polymeric composites embedded with Fe_3O_4 nanoparticles have been designed for guided tissue regeneration, especially in bone and neural repair. The magnetic responsiveness aids in spatial control of cell growth and accelerates healing processes, indicating a promising future for MIONC-based regenerative medicine [79].

Challenges and Limitations

The application of MIONs in drug delivery systems has opened remarkable avenues in nanomedicine due to their unique physicochemical properties, magnetic responsiveness, and biocompatibility. However, despite extensive research and preclinical promise, several critical challenges and limitations impede their successful translation into clinical practice. These challenges span across material synthesis, surface functionalization, stability, biodistribution, toxicity, regulatory barriers, and large-scale manufacturing. This section delineates the multifaceted challenges that need to be addressed to harness the full therapeutic potential of MION-based nanocarriers. The therapeutic efficacy of MION-based drug delivery systems largely depends on their magnetic behavior, particle size, shape, and surface characteristics. Controlling these parameters with high precision during synthesis remains a major challenge. SPIONs exhibit size-dependent magnetic properties: particles below a certain size threshold (~ 20 nm) display superparamagnetic, while larger particles show ferromagnetic or ferrimagnetic behavior. Achieving narrow size distribution and uniform morphology is difficult in large-scale synthesis, resulting in inconsistent magnetic responses and reduced targeting efficiency under external magnetic fields. Colloidal stability of MIONs in biological fluids is a critical prerequisite for safe and efficient drug delivery. Nanoparticles often undergo aggregation due to van der Waals and magnetic dipole attractions when introduced into physiological environments. Serum proteins readily adsorb onto the nanoparticle surface, forming a “protein corona” that alters

surface charge, hydrophobicity, and targeting ability. This corona can trigger immune recognition, opsonization, and rapid clearance by the reticuloendothelial system (RES), leading to poor bioavailability and non-specific biodistribution. Surface modification using polymers such as polyethylene glycol (PEG), dextran, or chitosan improves stability; however, achieving reproducible coating uniformity is difficult. Over time, coatings may degrade or desorb under physiological stress, exposing the iron oxide core and potentially leading to toxicity. Additionally, polymer-coated nanoparticles may still face aggregation issues under varying ionic strengths, pH conditions, or in the presence of divalent cations. Maintaining colloidal stability over extended periods, especially under magnetic field application or during storage, remains a persistent limitation for MION-based formulations. The toxicity profile of MIONs is highly dependent on size, surface charge, coating materials, and administered dose. Positively charged particles can interact strongly with negatively charged cellular membranes, leading to membrane disruption and apoptosis. Uncoated or inadequately coated nanoparticles may also induce hemolysis, platelet aggregation, and complement activation. Long-term exposure raises concerns about chronic inflammation, immune activation, and potential genotoxicity. Although biodegradable coatings can mitigate these risks, their degradation rate and by-products also require careful evaluation to ensure systemic safety. Targeting efficiency *in vivo* is often lower than expected from *in vitro* studies due to complex biological barriers such as the mononuclear phagocyte system, endothelial permeability, and interstitial pressure within tumors. The “enhanced permeability and retention” (EPR) effect, which is often exploited for passive targeting, is highly variable across tumor types and not consistently reproducible in human cancers. Consequently, even with ligand-mediated targeting, only a small fraction of systemically administered MIONs reach the intended site. The loss of targeting specificity and reduced accumulation at the disease site remain significant bottlenecks for effective therapeutic outcomes. Achieving optimal drug loading efficiency while

maintaining stability and controlled release is another challenge. The drug loading capacity depends on surface area, porosity, and interaction between drug molecules and nanoparticle coating materials. Inadequate loading leads to sub-therapeutic concentrations, while excessive loading may cause premature leakage or destabilization. Ensuring controlled and stimuli-responsive release particularly under magnetic, thermal, or pH triggers requires precise material engineering. Thermal or magnetic field-induced release mechanisms can cause non-uniform heating, leading to unintended tissue damage or unpredictable drug diffusion rates. Additionally, magnetic hyperthermia-based release systems face limitations in controlling local temperature gradients, which can influence drug stability and bioavailability. The reproducibility of release profiles across different physiological environments remains inconsistent, thereby limiting their translational potential. Understanding the biodistribution and clearance pathways of MIONs is essential for predicting therapeutic efficacy and safety. Most MIONs are rapidly sequestered by macrophages in the liver and spleen following intravenous administration, resulting in low accumulation at target sites. Their fate is influenced by particle size, surface charge, and coating composition. Particles smaller than 10 nm may undergo renal clearance, while those larger than 200 nm are more likely to be taken up by the RES. Achieving an optimal balance between circulation time and clearance remains difficult. Nanoparticles inevitably interact with the immune system, and MIONs are no exception. Recognition by macrophages, dendritic cells, and complement proteins can activate innate immune pathways, resulting in inflammation or hypersensitivity. The protein corona formed in the bloodstream alters the biological identity of MIONs, influencing immune recognition. Some coatings, such as PEG, have been shown to reduce immune clearance, but repeated administration may lead to “anti-PEG” antibody formation, reducing therapeutic efficacy over time. Inflammatory responses are not only dose-dependent, but also vary based on surface composition and particle morphology. Chronic exposure or accumulation in tissues can lead to granuloma formation or

fibrosis. Furthermore, magnetic field exposure itself may modulate immune cell activation, although data on this aspect remain limited and sometimes contradictory. Comprehensive immunotoxicological profiling is therefore required before clinical applications can proceed safely. One of the most prominent advantages of MIONs is their ability to be guided by external magnetic fields; however, magnetic targeting faces fundamental physical limitations. The strength of the magnetic field decreases rapidly with distance from the source, making it difficult to achieve effective targeting in deep-seated tissues or organs such as the brain or liver. Clinical-grade magnets can generate field strengths sufficient only for superficial targets or small animal models. For human applications, achieving adequate magnetic gradients for precise targeting without causing tissue heating or discomfort remains a technical challenge. Scalability and reproducibility are major barriers in translating laboratory-scale MION formulations into clinically viable products. Laboratory synthesis methods like co-precipitation or thermal decomposition allow fine control over particle size and morphology, but scaling up these methods often results in batch-to-batch variability. Parameters such as temperature, pH, reaction kinetics, and surfactant concentration significantly influence product quality and are difficult to control uniformly in industrial settings. The integration of drug molecules and targeting ligands introduces additional complexity, requiring multi-step synthesis and purification. Ensuring consistency in particle size distribution, surface charge, drug content, and magnetic properties is essential for regulatory approval but challenging to achieve. The lack of standardized protocols for characterization and quality control further hampers reproducibility across research groups and industrial batches. Developing cost-effective and scalable synthesis methods with high reproducibility remains a pressing need for commercialization.

Extensive preclinical research, only a limited number of iron oxide-based nanocarriers have been approved for clinical use, primarily as imaging agents rather than drug delivery vehicles. The regulatory landscape for nanomedicines is still evolving, and the absence

of specific guidelines tailored for magnetic nanocarriers poses a challenge. Regulatory agencies such as the FDA and EMA require comprehensive data on pharmacokinetics, toxicity, immunogenicity, and manufacturing consistency, which are often difficult to generate due to the complex nature of nanoparticle systems. Ethical considerations related to long-term safety, potential bioaccumulation, and patient consent also play a role in delaying clinical adoption. Moreover, the cost of extensive preclinical and clinical testing, coupled with uncertainties regarding intellectual property and environmental impacts of nanoparticle disposal, adds further complications. The establishment of harmonized global regulatory frameworks and standardized evaluation metrics is imperative for accelerating the clinical translation of MION-based therapies. While MION-based systems have demonstrated impressive results *in vitro* and in small-animal models, their translation to human clinical scenarios has been limited. The primary reasons include differences in physiological barriers, tumor microenvironment, immune responses, and magnetic field accessibility between humans and animals. Preclinical models often overestimate targeting efficiency and therapeutic response, leading to discrepancies in clinical outcomes. Furthermore, the long-term fate of MIONs in the human body especially regarding biodegradation, accumulation, and potential neurotoxicity remains insufficiently understood. Clinical studies have also reported variability in biodistribution and imaging contrast among patients, reflecting the need for patient-specific optimization. The inability to predict *in vivo* performance reliably hinders regulatory approval and commercialization. Thus, improved translational models and advanced computational simulations are required to bridge the gap between preclinical promise and clinical success. Effective translation of MION-based drug delivery requires convergence across multiple disciplines chemistry, material science, pharmacology, bioengineering, and clinical medicine. Lack of interdisciplinary coordination often limits progress in developing clinically relevant systems. For example, chemists may optimize particle synthesis without considering

pharmacokinetic behavior, while clinicians may face challenges interpreting magnetic imaging data for therapy monitoring. Establishing cross-disciplinary collaborations, shared data standards, and integrated design frameworks will be vital for overcoming these systemic barriers.

Future Prospects and Emerging Directions

The future of MIONs in therapeutic drug delivery holds immense promise, driven by advances in materials science, nanotechnology, and biomedical engineering. Despite significant progress in preclinical studies, several emerging trends suggest that MIONs are poised to play a crucial role in the next generation of personalized, precision-based, and multifunctional therapeutic platforms [80]. This section highlights the most promising directions, focusing on smart nanocarriers, integration with artificial intelligence (AI) and biosensing technologies, hybrid nanoplatforms, and sustainable synthesis strategies. One of the most compelling prospects in magnetic nanomedicine is the development of smart MIONs capable of delivering drugs with spatiotemporal precision [81]. These nanocarriers can be engineered to respond to multiple physiological or external stimuli, including pH, temperature, enzymatic activity, and magnetic fields. Such responsiveness enables site-specific drug release, minimizing systemic toxicity and enhancing therapeutic efficacy. For example, tumor microenvironments often exhibit acidic pH, hypoxia, and elevated reactive oxygen species (ROS) levels; MIONs functionalized with pH- or ROS-sensitive linkers can selectively release chemotherapeutic agents at the tumor site, improving drug bioavailability and reducing off-target effects. Personalization in medicine is increasingly achievable through the conjugation of MIONs with patient-specific ligands, such as antibodies, aptamers, or peptides. This active targeting strategy allows for tailored therapies that consider an individual's genetic and molecular profile, potentially revolutionizing oncology and rare disease management. In combination with real-time imaging modalities, such as MRI, smart MIONs can enable

theranostic platforms, where diagnosis and therapy occur simultaneously, allowing clinicians to monitor treatment progress and adjust dosing dynamically. The integration of artificial intelligence (AI) and magnetic biosensing represents a transformative direction for MION-based drug delivery. AI algorithms can analyze complex imaging and biological data to optimize nanoparticle design, predict biodistribution, and forecast therapeutic outcomes. For instance, machine learning models can determine the ideal size, surface chemistry, and magnetic properties for enhanced tumor penetration and retention, enabling rational design strategies that reduce trial-and-error experimentation. Magnetic biosensors coupled with MIONs can serve as highly sensitive diagnostic and monitoring tools. By detecting subtle changes in magnetic signals associated with biomolecular interactions, these sensors can provide rapid, real-time feedback on drug release, cellular uptake, or the presence of disease biomarkers. The convergence of AI-driven analytics with smart biosensors may ultimately enable closed-loop drug delivery systems, where nanocarriers autonomously adjust drug release rates based on continuous feedback from the patient's physiological environment. Future research is increasingly focused on hybrid nanoplatforms, combining MIONs with polymers, liposomes, dendrimers, or other metallic nanoparticles to create multifunctional delivery systems. These composites leverage the unique advantages of each component, such as enhanced biocompatibility, controlled release kinetics, and improved circulation time. For example, polymer-coated MIONs can reduce immune clearance while providing a matrix for loading multiple drugs or gene therapies. Similarly, liposomal-MION hybrids can encapsulate hydrophilic and hydrophobic drugs simultaneously, offering synergistic effects in complex therapeutic regimens.

Metallic composites, such as gold or platinum-MION hybrids, expand the therapeutic repertoire by combining magnetic targeting with photothermal or catalytic therapies. This multi-modality approach enables simultaneous chemo-, thermal-, and imaging-based interventions, enhancing treatment outcomes

while reducing cumulative drug doses. Such hybrid systems are particularly promising for recalcitrant cancers, multidrug-resistant infections, and neurodegenerative disorders where monotherapy often fails. Sustainability is becoming a central consideration in nanomedicine, and green synthesis approaches for MIONs are gaining attention. Conventional chemical synthesis methods often rely on toxic solvents, high temperatures, and surfactants that may pose environmental hazards and limit clinical translation. In contrast, plant-mediated, microbial, or biomimetic synthesis strategies offer eco-friendly alternatives that utilize naturally occurring reducing agents and biocompatible stabilizers. For instance, extracts from medicinal plants, algae, or bacteria can reduce iron salts to magnetic nanoparticles while simultaneously functionalizing their surfaces with bioactive molecules. Such green MIONs not only reduce environmental impact, but also often exhibit enhanced biocompatibility, improved cellular uptake, and reduced immunogenicity. Moreover, integrating green chemistry principles into large-scale production aligns with regulatory trends emphasizing safety, reproducibility, and sustainability, which is critical for accelerating clinical adoption. Future research may focus on optimizing yield, scalability, and batch-to-batch consistency, ensuring that eco-friendly MIONs meet stringent pharmaceutical standards. Cancer and gene therapy, MIONs are increasingly being explored in neurological, cardiovascular, and infectious disease applications. Magnetic targeting can facilitate the crossing of physiological barriers, such as the blood-brain barrier, opening avenues for treating neurodegenerative disorders such as Alzheimer's, Parkinson's, and glioblastoma. In cardiovascular medicine, magnetically guided nanoparticles can localize thrombolytic agents or regenerative biomolecules to ischemic tissues, potentially improving outcomes in myocardial infarction or stroke. In infectious diseases, MIONs can deliver antibiotics, antiviral drugs, or immune modulators directly to infection sites, reducing systemic exposure and mitigating resistance development. Moreover, the theranostic capabilities of MIONs enable simultaneous infection monitoring via imaging,

offering a dual approach that is particularly valuable in managing multi-drug-resistant pathogens. The translation of these emerging technologies into clinical practice will require rigorous evaluation of safety, pharmacokinetics, and long-term effects. Regulatory bodies are increasingly emphasizing reproducibility, standardized characterization, and clear evidence of therapeutic benefit. Future research directions include the development of standardized assays for assessing MION toxicity, biodistribution, and immunogenicity, as well as robust frameworks for large-scale GMP-compliant manufacturing. Collaborative efforts between material scientists, clinicians, and regulatory agencies will be crucial to bridge the gap between preclinical innovation and patient-ready therapies. The future of MIONs is defined by multifunctionality, personalization, and integration with advanced digital health tools. Smart MIONs capable of responsive drug release, hybrid composites with multi-modal therapeutic capabilities, AI-guided optimization, and green synthesis approaches collectively promise a paradigm shift in nanomedicine. These advancements will not only enhance therapeutic efficacy and safety, but also pave the way for patient-specific, precision-targeted, and environmentally sustainable treatment strategies. As research continues to expand across interdisciplinary domains, MIONs are likely to evolve from experimental drug carriers to mainstream clinical platforms, shaping the next frontier of personalized and precision medicine.

Conclusion

MIONs have emerged as a promising platform for targeted and controlled drug delivery due to their unique magnetic properties, tunable size, and high surface functionalization capacity. Recent advances in synthesis methods, surface modification strategies, and hybrid nanoplatform development have significantly improved their stability, targeting ability, and therapeutic performance. These nanocarriers enable externally guided delivery and stimuli-responsive drug release, making them particularly valuable for applications such as targeted chemotherapy, gene delivery,

antimicrobial therapy, and theranostic systems that combine diagnosis and treatment. Despite these advances, several challenges remain, including concerns related to long-term biocompatibility, potential toxicity, large-scale reproducibility, and regulatory approval, which currently limit their full clinical translation. Future research should focus on improving safety profiles, developing standardized manufacturing strategies, and designing multifunctional nanocarriers suitable for personalized medicine. Additionally, the integration of artificial intelligence, advanced targeting strategies, and environmentally sustainable synthesis approaches may further enhance the clinical potential of MION-based drug delivery systems. Overall, MIONs represent a highly promising direction in nanomedicine with significant potential for future clinical applications.

ORCID

Manasi M. Choudhari

<https://orcid.org/0009-0001-2690-9269>

References

- [1] Saif, M., Raza, M.A., Patravale, V.B. **Polysaccharide copolymeric conjugates and their applications in targeted cancer therapy**. *International Journal of Biological Macromolecules*, **2025**, 327, 147380.
- [2] Patra, J.K., Das, G., Fraceto, L.F., Campos, E.V.R., Rodriguez-Torres, M.D.P., Acosta-Torres, L.S., Sharma, S. **Nano based drug delivery systems: recent developments and future prospects**. *Journal of Nanobiotechnology*, **2018**, 16(1), 71.
- [3] Pathan, I., Raza, M.A., Roy, A., Badwaik, H., Sakure, K. **Recent advances in thermo-responsive hydrogels for ocular drug delivery: materials, mechanisms, and clinical potential**. *Journal of Drug Delivery Science and Technology*, **2025**, 114, 107537.
- [4] Shapiro, B., Kulkarni, S., Nacev, A., Muro, S., Stepanov, P.Y., Weinberg, I.N. **Open challenges in magnetic drug targeting**. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, **2015**, 7(3), 446-457.
- [5] Aboushousah, S.F.O. **Iron oxide nanoparticles enhancing magnetic resonance imaging: A review of the latest advancements**. *Journal of Science: Advanced Materials and Devices*, **2025**, 10(2), 100875.
- [6] Jeswani, G., Khichariya, A. **Micro-and Nano-emulsion Technologies: Pharmaceutical Design,**

Pharmaceutical Development, and Drug Delivery. ed., De Gruyter, 2025.

[7] Shah, S.I.A., Ahmad, W., Anwar, M., Shah, R., Khan, J.A., Shah, N.S., Han, C. [Synthesis, properties, and applications of Fe₃O₄ and Fe₃O₄-based nanocomposites: A review](#). *Applied Catalysis O: Open*, 2025, 203, 207049.

[8] Parthasarathy, N., Karthikeyan, L., Fabiola, M., Vivek, R. [Recent progress in multifunctional theranostic inorganic nanomaterials for cancer diagnostic imaging and therapy](#). *Next Nanotechnology*, 2025, 8, 100212.

[9] Jiang, K., Zhang, L., Bao, G. [Magnetic iron oxide nanoparticles for biomedical applications](#). *Current Opinion in Biomedical Engineering*, 2021, 20, 100330.

[10] Coduri, M., Masala, P., Del Bianco, L., Spizzo, F., Ceresoli, D., Castellano, C., Allieta, M. [Local structure and magnetism of Fe₂O₃ maghemite nanocrystals: The role of crystal dimension](#). *Nanomaterials*, 2020, 10(5), 867.

[11] Issa, B., Obaidat, I.M., Albiss, B.A., Haik, Y. [Magnetic nanoparticles: surface effects and properties related to biomedicine applications](#). *International Journal of Molecular Sciences*, 2013, 14(11), 21266-21305.

[12] Beltran-Huarac, J., Yamaleyeva, D.N., Dotti, G., Hingtgen, S., Sokolsky-Papkov, M., Kabanov, A.V. [Magnetic control of protein expression via magneto-mechanical actuation of ND-PEGylated iron oxide nanocubes for cell therapy](#). *ACS Applied Materials & Interfaces*, 2023, 15(16), 19877-19891.

[13] Fajariman, I.D., Hidayat, A., Diantoro, M., Laksono, Y.A.S., Wulandari, N.P., Chusna, N.M., Sunaryono, S. [Comparative behavior of magnetic iron oxide nanoparticles \(Mions\) via mechanical and chemical routes](#). *Indonesian Physical Review*, 2025, 8(1), 181-195.

[14] Patel, H., Parekh, K. [Synthesis and characterization of octahedron and cube shape Mn_{0.5}Zn_{0.5}Fe₂O₄ particle dispersion for magnetic fluid hyperthermia](#). *Ceramics International*, 2024, 50(22), 44852-44864.

[15] Wu, W., Wu, Z., Yu, T., Jiang, C., Kim, W.S. [Recent progress on magnetic iron oxide nanoparticles: synthesis, surface functional strategies and biomedical applications](#). *Science and Technology of Advanced Materials*, 2015, 16(2), 023501.

[16] Herdiana, Y., Wathoni, N., Shamsuddin, S., Muchtaridi, M. [Scale-up polymeric-based nanoparticles drug delivery systems: development and challenges](#). *OpenNano*, 2022, 7, 100048.

[17] Dulińska-Litewka, J., Łazarczyk, A., Hałubiec, P., Szafranski, O., Karnas, K., Krawiec, A. [Superparamagnetic iron oxide nanoparticles—current and prospective medical applications](#). *Materials*, 2019, 12(4), 617.

[18] Wahajuddin, N., Arora, S. [Superparamagnetic iron oxide nanoparticles: magnetic nanoplatforms as drug carriers](#). *International Journal of Nanomedicine*, 2012, 7, 3445-3471.

[19] Vajtai, L., Nemes, N.M., Morales, M.D.P., Molnár, K., Pinke, B.G., Simon, F. [Incidence of the brownian relaxation process on the magnetic properties of ferrofluids](#). *Nanomaterials*, 2024, 14(7), 634.

[20] Curtis, C., Toghani, D., Wong, B., Nance, E. [Colloidal stability as a determinant of nanoparticle behavior in the brain](#). *Colloids and Surfaces B: Biointerfaces*, 2018, 170, 673-682.

[21] Sanz-Sagué, B., Calatayud, M.P., Cassinelli, N., Ibarra, M.R., Goya, G.F. [Long-term stability and reproducibility of magnetic colloids are key issues for steady values of specific power absorption over time](#). *European Journal of Inorganic Chemistry*, 2015, 27, 4524-4531.

[22] Manke, A., Wang, L., Rojanasakul, Y. [Mechanisms of nanoparticle-induced oxidative stress and toxicity](#). *BioMed Research International*, 2013, 2013(1), 942916.

[23] Upadhyay, S., Parekh, K., Pandey, B. [Influence of crystallite size on the magnetic properties of Fe₃O₄ nanoparticles](#). *Journal of Alloys and Compounds*, 2016, 678, 478-485.

[24] Bajracharya, R., Song, J.G., Patil, B.R., Lee, S.H., Noh, H.M., Kim, D.H., Jeong, S.H. [Functional ligands for improving anticancer drug therapy: current status and applications to drug delivery systems](#). *Drug Delivery*, 2022, 29(1), 1959-1970.

[25] Qiao, R., Fu, C., Forgham, H., Javed, I., Huang, X., Zhu, J., Davis, T.P. [Magnetic iron oxide nanoparticles for brain imaging and drug delivery](#). *Advanced Drug Delivery Reviews*, 2023, 197, 114822.

[26] Liu, X., Zhang, Y., Wang, Y., Zhu, W., Li, G., Ma, X., Shi, K. [Comprehensive understanding of magnetic hyperthermia for improving antitumor therapeutic efficacy](#). *Theranostics*, 2020, 10(8), 3793.

[27] Filippov, S.K., Khusnutdinov, R., Murmiliuk, A., Inam, W., Zakharova, L.Y., Zhang, H., Khutoryanskiy, V.V. [Dynamic light scattering and transmission electron microscopy in drug delivery: A roadmap for correct characterization of nanoparticles and interpretation of results](#). *Materials Horizons*, 2023, 10(12), 5354-5370.

[28] Ponomar, V. [Crystal structures and magnetic properties of spinel ferrites synthesized from natural Fe-Mg-Ca carbonates](#). *Materials Research Bulletin*, 2023, 158, 112068.

[29] Joo, S., Eom, S., Choi, Y., Jeong, U., Cho, Y., Yu, W., Hong, S. [Atomic force microscopy for cross-disciplinary materials research](#). *Small Methods*, 2025, 9(11), 2500514.

- [30] Obaidat, I.M., Issa, B., Haik, Y. **Magnetic properties of magnetic nanoparticles for efficient hyperthermia.** *Nanomaterials*, **2015**, 5(1), 63-89.
- [31] Pasiieczna-Patkowska, S., Cichy, M., Flieger, J. **Application of fourier transform infrared (FTIR) spectroscopy in characterization of green synthesized nanoparticles.** *Molecules*, **2025**, 30(3), 684.
- [32] Chiu, M.H., Prenner, E.J. **Differential scanning calorimetry: An invaluable tool for a detailed thermodynamic characterization of macromolecules and their interactions.** *Journal of Pharmacy and Bioallied Sciences*, **2011**, 3(1), 39-59.
- [33] Midekessa, G., Godakumara, K., Ord, J., Viil, J., Lattekivi, F., Dissanayake, K., Bhattacharjee, S. **Zeta potential of extracellular vesicles: toward understanding the attributes that determine colloidal stability.** *ACS Omega*, **2020**, 5(27), 16701-16710.
- [34] Chen, Z., Xiong, M., Tian, J., Song, D., Duan, S., Zhang, L. **Encapsulation and assessment of therapeutic cargo in engineered exosomes: A systematic review.** *Journal of Nanobiotechnology*, **2024**, 22(1), 18.
- [35] Navya, P., Daima, H.K. **Rational engineering of physicochemical properties of nanomaterials for biomedical applications with nanotoxicological perspectives.** *Nano Convergence*, **2016**, 3(1), 1.
- [36] Azeem, B. **Stimuli-responsive starch-based biopolymer coatings for smart and sustainable fertilizers.** *Gels*, **2025**, 11(9), 681.
- [37] Fahim, Y.A., Hasani, I.W., Mahmoud Ragab, W. **Promising biomedical applications using superparamagnetic nanoparticles.** *European Journal of Medical Research*, **2025**, 30(1), 441.
- [38] Wang, X., Bai, R. **Advances in smart delivery of magnetic field-targeted drugs in cardiovascular diseases.** *Drug Delivery*, **2023**, 30(1), 2256495.
- [39] Kumar, C.S., Mohammad, F. **Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery.** *Advanced Drug Delivery Reviews*, **2011**, 63(9), 789-808.
- [40] Chu, S., Shi, X., Tian, Y., Gao, F. **pH-Responsive polymer nanomaterials for tumor therapy.** *Frontiers in Oncology*, **2022**, 12, 855019.
- [41] Alexander, A., Khan, J., Saraf, S., Saraf, S. **Polyethylene glycol (PEG)-Poly (N-isopropylacrylamide)(PNIPAAm) based thermosensitive injectable hydrogels for biomedical applications.** *European Journal of Pharmaceutics and Biopharmaceutics*, **2014**, 88(3), 575-585.
- [42] Thévenot, J., Oliveira, H., Sandre, O., Lecommandoux, S. **Magnetic responsive polymer composite materials.** *Chemical Society Reviews*, **2013**, 42(17), 7099-7116.
- [43] Nunziata, G., Pollonio, D., Lacroce, E., Rossi, F. **Smart pH-Responsive polymers in biomedical applications: nanoparticles, hydrogels, and emerging hybrid platforms.** *Materials Today Chemistry*, **2025**, 49, 103063.
- [44] Price, D.N., Stromberg, L.R., Kunda, N.K., Muttill, P. **In vivo pulmonary delivery and magnetic-targeting of dry powder nano-in-microparticles.** *Molecular Pharmaceutics*, **2017**, 14(12), 4741-4750.
- [45] Rarokar, N., Yadav, S., Saoji, S., Bramhe, P., Agade, R., Gurav, S., Kumarasamy, V. **Magnetic nanosystem a tool for targeted delivery and diagnostic application: current challenges and recent advancement.** *International Journal of Pharmaceutics: X*, **2024**, 7, 100231.
- [46] de Almeida, M.S., Susnik, E., Drasler, B., Taladriz-Blanco, P., Petri-Fink, A., Rothen-Rutishauser, B. **Understanding nanoparticle endocytosis to improve targeting strategies in nanomedicine.** *Chemical Society Reviews*, **2021**, 50(9), 5397-5434.
- [47] Liu, J.F., Jang, B., Issadore, D., Tsourkas, A. **Use of magnetic fields and nanoparticles to trigger drug release and improve tumor targeting.** *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, **2019**, 11(6), 1571.
- [48] Ovejero, J.G., Armenia, I., Serantes, D., Veintemillas-Verdaguer, S., Zeballos, N., López-Gallego, F., Gazu, V. **Selective magnetic nanoheating: Combining iron oxide nanoparticles for multi-hot-spot induction and sequential regulation.** *Nano Letters*, **2021**, 21(17), 7213-7220.
- [49] Chen, Y., Sun, H., Li, Y., Han, X., Yang, Y., Chen, Z., Zhou, F. **Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery.** *Bioactive Materials*, **2025**, 53, 591-629.
- [50] Ansari, M.J., Rajendran, R.R., Mohanto, S., Agarwal, U., Panda, K., Dhotre, K., Yasir, M. **Poly (N-isopropylacrylamide)-based hydrogels for biomedical applications: A review of the state-of-the-art.** *Gels*, **2022**, 8(7), 454.
- [51] Dhavalikar, R., Rinaldi, C. **Theoretical predictions for spatially-focused heating of magnetic nanoparticles guided by magnetic particle imaging field gradients.** *Journal of Magnetism and Magnetic Materials*, **2016**, 419, 267-273.
- [52] Das, S.S., Bharadwaj, P., Bilal, M., Barani, M., Rahdar, A., Taboada, P., Kyzas, G.Z. **Stimuli-responsive polymeric nanocarriers for drug delivery, imaging, and theragnosis.** *Polymers*, **2020**, 12(6), 1397.
- [53] Shinn, J., Kwon, N., Lee, S.A., Lee, Y. **Smart pH-responsive nanomedicines for disease therapy.** *Journal of Pharmaceutical Investigation*, **2022**, 52(4), 427-441.
- [54] Zayed, G.M., Kamal, I., Abdelhafez, W.A., M. Alsharif, F., Amin, M.A., Shaykoon, M.S.A., Abdelsalam, A.M. **Effect of chemical binding of doxorubicin hydrochloride to gold Nanoparticles, Versus electrostatic adsorption, on the In Vitro drug release**

- and cytotoxicity to breast cancer cells: Zayed et al. *Pharmaceutical Research*, **2018**, 35(6), 112.
- [55] Raza, M.A., Sharma, M.K., Nagori, K., Jain, P., Ghosh, V., Gupta, U. Recent trends on polycaprolactone as sustainable polymer-based drug delivery system in the treatment of cancer: biomedical applications and nanomedicine. *International Journal of Pharmaceutics*, **2024**, 666, 124734.
- [56] Chen, H., Xu, J., Sun, J., Jiang, Y., Zheng, W., Hu, W., Qian, H. Recent advances on thermosensitive hydrogels-mediated precision therapy. *Asian Journal of Pharmaceutical Sciences*, **2024**, 19(3), 100911.
- [57] Edelman, E., Kost, J., Bobeck, H., Langer, R. Regulation of drug release from polymer matrices by oscillating magnetic fields. *Journal of Biomedical Materials Research*, **1985**, 19(1), 67-83.
- [58] Kanber, M., Umerah, O., Brindley, S., Zhang, X., Brown, J.M., Reynolds, L., Beltran-Huarac, J. Magneto-mechanical actuation induces endothelial permeability. *ACS Biomaterials Science & Engineering*, **2023**, 9(12), 6902-6914.
- [59] Taheri, Z., Mozafari, N., Moradian, G., Lovison, D., Dehshahri, A., De Marco, R. Integrin-specific stimuli-responsive nanomaterials for cancer theranostics. *Pharmaceutics*, **2024**, 16(11), 1441.
- [60] Sahu, K., Firdous, A., Raza, M.A., Saoji, S.D., Patravale, V.B. Enzyme-responsive natural nanocarriers for RNA delivery in the tumor microenvironment: A comprehensive review. *Journal of Drug Delivery Science and Technology*, **2025**, 107455.
- [61] Xu, Z., Xie, Y., Chen, W., Deng, W. Nanocarrier-based systems for targeted delivery: current challenges and future directions. *MedComm*, **2025**, 6(9), 70337.
- [62] Lee, J.H., Yeo, Y. Controlled drug release from pharmaceutical nanocarriers. *Chemical Engineering Science*, **2015**, 125, 75-84.
- [63] Lau, K., Tran, H.A., Tan, R., Kumeria, T., Prasad, A.A., Tan, R.P., Lim, K.S. Advancements in 3D-printing strategies towards developing effective implantable drug delivery systems: Recent applications and opportunities. *Advanced Drug Delivery Reviews*, **2025**, 115711.
- [64] Siepmann, J., Peppas, N.A. Higuchi equation: derivation, applications, use and misuse. *International Journal of Pharmaceutics*, **2011**, 418(1), 6-12.
- [65] Uskoković, V. Mechanism of formation governs the mechanism of release of antibiotics from calcium phosphate nanopowders and cements in a drug-dependent manner. *Journal of Materials Chemistry B*, **2019**, 7(25), 3982-3992.
- [66] Al-Ali, M., Al-Ali, L.I. Modeling Kinetics and Transport Mechanism Study of Poorly Soluble Drug Formulation in High Acidic Medium. *Tikrit Journal of Engineering Sciences*, **2024**, 31(4), 76-91.
- [67] Dalbanjan, N.P., Korgaonkar, K., Eelager, M.P., Gonal, B.N., Kadapure, A.J., Arakera, S.B., SK, P.K. In-silico strategies in nano-drug design: bridging nanomaterials and pharmacological applications. *Nano TransMed*, **2025**, 100091.
- [68] Ganapathe, L.S., Mohamed, M.A., Mohamad Yunus, R., Berhanuddin, D.D. Magnetite (Fe₃O₄) nanoparticles in biomedical application: From synthesis to surface functionalisation. *Magnetochemistry*, **2020**, 6(4), 68.
- [69] Yassin, M.T., Al-Otibi, F.O., Al-Sahli, S.A., El-Wetidy, M.S., Mohamed, S. Metal oxide nanoparticles as efficient nanocarriers for targeted cancer therapy: addressing chemotherapy-induced disabilities. *Cancers*, **2024**, 16(24), 4234.
- [70] Xiong, L., Liang, B., Yu, K. Magnetic hyperthermia in oncology: Nanomaterials-driven combinatorial strategies for synergistic therapeutic gains. *Materials Today Bio*, **2025**, 102070.
- [71] Zhang, Y., Luo, J., Gui, X., Zheng, Y., Schaar, E., Liu, G., Shi, J. Bioengineered nanotechnology for nucleic acid delivery. *Journal of Controlled Release*, **2023**, 364, 124-141.
- [72] Sarkar, S., Das, J., Debnath, B., Ramzan, M., Ashique, S., Taghizadeh-Hesary, F. Nanobubbles: An emerging therapeutic paradigm for targeted cancer therapy. *Bioorganic Chemistry*, **2025**, 108927.
- [73] Bhattacharjee, R., Negi, A., Bhattacharya, B., Dey, T., Mitra, P., Preetam, S., Iqbal, D. Nanotheranostics to target antibiotic-resistant bacteria: Strategies and applications. *OpenNano*, **2023**, 11, 100138.
- [74] Sanna, V., Satta, S., Hsiai, T., Sechi, M. Development of targeted nanoparticles loaded with antiviral drugs for SARS-CoV-2 inhibition. *European Journal of Medicinal Chemistry*, **2022**, 231, 114121.
- [75] Dadfar, S.M., Roemhild, K., Drude, N.I., von Stillfried, S., Knüchel, R., Kiessling, F., Lammers, T. Iron oxide nanoparticles: Diagnostic, therapeutic and theranostic applications. *Advanced Drug Delivery Reviews*, **2019**, 138, 302-325.
- [76] Mishra, V., Kumari, N., Vyas, M., Aljabali, A.A., Chattaraj, A., Mishra, Y. Advances in multimodal imaging techniques in nanomedicine: enhancing drug delivery precision. *RSC Advances*, **2025**, 15(33), 27187-27209.
- [77] Israel, L.L., Galstyan, A., Holler, E., Ljubimova, J.Y. Magnetic iron oxide nanoparticles for imaging, targeting and treatment of primary and metastatic tumors of the brain. *Journal of Controlled Release*, **2020**, 320, 45-62.
- [78] Alipour, M., Abdolmaleki, M., Shabanpour, Y., Zali, A., Ashrafi, F., Nohesara, S., Hajipour-Verdom, B. Advances in magnetic field approaches for non-

invasive targeting neuromodulation. *Frontiers in Human Neuroscience*, **2025**, 19, 1489940.

[79] Oduk, Y., Zhu, W., Kannappan, R., Zhao, M., Borovjagin, A.V., Oparil, S., Zhang, J. **VEGF nanoparticles repair the heart after myocardial infarction**. *American Journal of Physiology-Heart and Circulatory Physiology*, **2018**, 314(2), H278-H284.

[80] Tiwari, P., Prajapati, S., Dixit, V., Raza, M.A., Gupta, S.K., Sharma, M. **Recent advancements in**

nanoparticle drug delivery systems to cure neurological disorders via the nasal route. *Neurología Argentina*, **2025**, 17, 143-152.

[81] Pathan, I., Raza, A., Sahu, A., Joshi, M., Sahu, Y., Patil, Y., Raza, M.A. **Revolutionizing pharmacology: AI-powered approaches in molecular modeling and ADMET prediction**. *Medicine in Drug Discovery*, **2025**, 28, 100223.

Graphical Abstract

Magnetic Iron Oxide Nanocarriers for Therapeutic Drug Delivery Systems

