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УСОВЕРШЕНСТВОВАНИЕ СИНТЕЗА И ИНЖИНИРИНГ ПОВЕРХНОСТНЫХ СВОЙСТВ НАНОЧАСТИЦ ОКСИДА МАРГАНЦА (II) ДЛЯ БИОМЕДИЦИНСКОГО ПРИМЕНЕНИЯ В МРТ, ГИПЕРТЕРМИИ И ТЕРАНОСТИКЕ

Аннотация. В данном обзоре представлены способы синтеза наночастиц оксида марганца (Mn_xO_γ NPs) и физико-химические свойства, важные для биомедицинского применения. В статье рассмотрен выбор методов синтеза (например, гидротермический и термическое разложение) и показано, каким образом это предопределяет размер наночастиц, их кристаллическую структуру и химические особенности поверхностных свойств. В статье подчеркивается первоочередное использование наночастиц оксида марганца в качестве контрастных веществ Т1-взвешенного изображения для магнитно-резонансной томографии (МРТ), в роли носителей, обладающих уникальными магнитными свойствами для магнитной гипертермии. Также обсуждается критически важная роль для функционализации поверхностных свойств, которая заключается в увеличении биосовместимости, в создании многофункциональных тераностических платформ. В заключении обзорно рассматриваются актуальные трудности и перспективы для клинического применения.

Abstract. This review summarizes the synthesis of manganese oxide nanoparticles (MnO NPs) and its impact on their physicochemical properties for biomedical applications. It examines how synthetic methods like hydrothermal and thermal decomposition tailor nanoparticle size, crystallinity, and surface chemistry. The paper highlights their primary uses as T1-weighted contrast agents in magnetic resonance imaging (MRI) and as mediators for magnetic hyperthermia, driven by their unique magnetic profiles. The critical role of surface functionalization in enhancing biocompatibility and creating multifunctional theranostic platforms is also discussed, concluding with an overview of current challenges and future prospects for clinical translation.

Ключевые слова: наночастицы оксида марганца (MnO NPs); синтез наночастиц; гидротермический синтез; температурное разложение; магнитно-резонансная томография (МРТ); Т1-контрастные вещества; магнитная гипертермия; тераностика; функциональзация поверхностных свойств; покрытие слоем диоксида кремния; магнетофорез; биосовместимость; доставка лекарственных веществ;

Keywords: Manganese Oxide Nanoparticles (MnO NPs); Nanoparticle Synthesis; Hydrothermal Synthesis; Thermal Decomposition; Magnetic Resonance Imaging (MRI); T1 Contrast Agent; Magnetic Hyperthermia; Theranostics; Surface Functionalization; Silica Coating; Magnetophoresis; Biocompatibility; Drug Delivery

Introduction

Manganese oxide nanoparticles (MnO NPs) are attracting significant attention in biomedicine due to their unique magnetic and chemical properties, which make them highly suitable for applications such as magnetic resonance imaging (MRI), hyperthermia cancer therapy, and drug delivery. The performance of these nanoparticles is critically dependent on their synthesis, which governs their final physicochemical characteristics. This review examines key synthesis methods, connecting them to structural and functional outcomes. We further explore the importance of surface functionalization, the application of magnetophoresis for sustainable processing, and the overarching challenges related to the scalable production of MnO NPs for clinical and industrial use.

Physicochemical Basis of Manganese Oxide Nanoparticles

Magnetic Properties and Biomedical Relevance

Manganese oxide nanoparticles exhibit a range of magnetic behaviors, from weak paramagnetism to antiferromagnetism and superparamagnetism, depending on their size, composition, and crystalline structure. The magnetic susceptibility of MnO NPs is orders of magnitude smaller than that of superparamagnetic iron oxide nanoparticles (SPIONs), yet sufficient for manipulation under high-gradient magnetic fields, as demonstrated in magnetophoresis [23,54]. Their moderate magnetic responsiveness enables efficient MRI contrast enhancement—especially as T1-weighted agents—while minimizing artifacts compared to SPIONs [12,13,15]. Additionally, the ability to modulate the Curie temperature and saturation magnetization through compositional tuning is advantageous for hyperthermia therapies and self-regulating heating systems [14].

Structural and Surface Chemistry Considerations

The crystal structure of manganese oxides (e.g., MnO, Mn_3O_4, Mn_2O_3, MnO_2) affects their magnetic, catalytic, and redox properties. At the nanoscale, surface effects become dominant, influencing colloidal stability, aggregation, and biocompatibility [14,23]. Surface functionalization, such as silica or polymer coatings, is often employed to improve dispersion in physiological environments, enhance biocompatibility, and provide sites for conjugation with targeting ligands or therapeutic agents [25,54]. The choice of synthesis method directly impacts particle size, morphology, crystallinity, and surface chemistry.

Methodology

Synthesis Strategies for Manganese Oxide Nanoparticles

Overview of Synthetic Approaches

The synthesis of MnO NPs can be broadly categorized into physical, chemical, and biological methods. Table 1 summarizes the main synthetic strategies, their typical features, and the resulting nanoparticle characteristics.

Table 1. Common Synthesis Methods for Manganese Oxide Nanoparticles

Method	Key Features	Particle Size/Shape	Surface Chemistry	References
Thermal Decomposition	High crystallinity, size control	5–100 nm, spherical/anisotropic	Hydrophobic/native	27,54
Hydrothermal/Solvothermal	Facile, tunable morphology	10–100 nm, spheres/rods	Hydrophilic, OH-groups	10,15,54
Sol-Gel	Low temperature, uniform distribution	10–50 nm, spherical	Silanol-rich	20,26
Microemulsion	Narrow size distribution	5–30 nm, spherical	Surfactant-coated	25,27
Ball Milling (Physical)	Large-scale, polydisperse	50–200 nm, irregular	Native, requires coating	14
Biological (Green)	Eco-friendly, biocompatible	10–50 nm, variable	Biomolecule-capped	10

Thermal Decomposition

The thermal decomposition of manganese precursors (e.g., manganese oleate, acetylacetonate) in high-boiling organic solvents yields monodisperse, highly crystalline MnO NPs. The reaction temperature, time, and surfactant concentration allow precise control over particle size and morphology [27]. For example, Douglas et al. synthesized octapod-shaped MnO NPs with enhanced magnetic properties through kinetically controlled decomposition of polynuclear manganese complexes [27].

Hydrothermal and Solvothermal Methods

Hydrothermal synthesis, involving the reaction of manganese salts in aqueous media under high pressure and temperature, is widely used due to its simplicity and scalability. This method enables the formation of various manganese oxide phases (MnO, Mn_3O_4, MnO_2) with controlled sizes and morphologies by adjusting parameters such as temperature, pH, and precursor concentration [10,15,54]. Addisu et al. reported a bioinspired, manganese-chelated alginate–polydopamine nanomaterial synthesized hydrothermally for efficient T1-weighted MRI [10]. Li et al. demonstrated a one-pot hydrothermal synthesis of hydrophilic MnO NPs for molecular MRI of renal carcinoma [15].

Sol-Gel Synthesis

The sol-gel process involves the hydrolysis and condensation of manganese alkoxides or salts, often in the presence of silica precursors (e.g., tetraethoxysilane, TEOS) to produce core-shell or embedded nanostructures [20,26]. This approach allows the fabrication of mesoporous or silica-coated MnO NPs with enhanced colloidal stability and tunable magnetic relaxivity [19,20,26].

Microemulsion and Surfactant-Assisted Methods

Microemulsion techniques employ water-in-oil or oil-in-water systems stabilized by surfactants to confine nanoparticle growth within nanodroplets, resulting in uniform particle sizes [25,27]. The choice of surfactant and the water-to-oil ratio dictate the final size and dispersity.

Ball Milling and Top-Down Methods

Mechanical milling of bulk manganese oxide produces NPs with broad size distributions and irregular shapes. Subsequent size selection and surface modification, such as silica coating via the Stöber method, are necessary to obtain stable, biocompatible dispersions [14].

Green and Biomimetic Synthesis

Biological or green synthesis leverages plant extracts, biomolecules, or polymers as reducing and stabilizing agents, minimizing the use of toxic chemicals. Such methods yield biocompatible MnO NPs with functionalized surfaces suitable for drug delivery or imaging [10].

Case Study: Silica-Coated MnO Nanoparticles for Hyperthermia

Villanueva et al. synthesized manganese oxide perovskite nanoparticles (La0.56(SrCa)0.22MnO3) by ceramic methods followed by ball milling and size selection. The particles were subsequently coated with silica using the Stöber process, which involved hydrolysis of TEOS in the presence of ammonia and 2-propanol at 20°C [14]. The silica shell (5–10 nm) enhanced aqueous stability and biocompatibility, while also shifting the isoelectric point and reducing magnetization (Fig. 1).

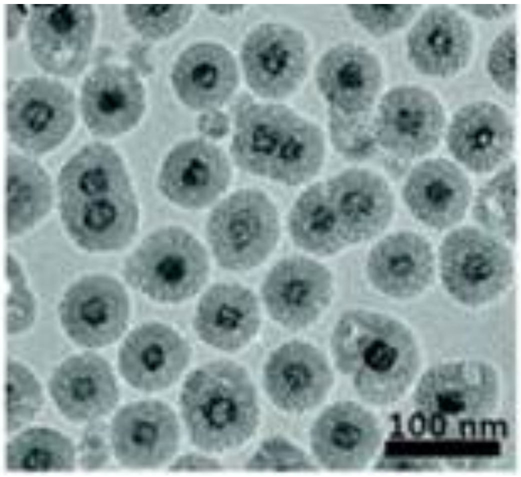

Figure 1. TEM Images of Silica-Coated MnO Nanoparticles

TEM images of silica-coated MnO nanoparticles showing a uniform shell and well-dispersed particles. Adapted from [14].

Results and discussion

Comparative Analysis of Synthesis Protocols

The selection of synthetic strategy depends on the target application. For biomedical use, hydrothermal and sol-gel methods are favored due to their ability to produce hydrophilic and biocompatible NPs. Thermal decomposition is preferred when high crystallinity and monodispersity are required. Ball milling, although scalable, necessitates additional processing steps to achieve narrow size distributions and adequate surface chemistry for biological applications.

Table 2. Synthesis Methods and Resulting MnO NP Properties

Synthesis Method	Particle Size (nm)	Crystallinity	Surface Coating	Magnetic Behavior	Application Example	Reference
Hydrothermal	8–30	High	Alginate–PDA, PEG	Paramagnetic	MRI Contrast, Drug Delivery	10,15,54
Thermal Decomposition	5–20	Very High	Oleic acid, Silica	Superparamagnetic	Dual-mode MRI, Hyperthermia	27,54
Ball Milling + Stöber	100–200	Moderate	Silica	Ferromagnetic	Hyperthermia, Cell Therapy	14
Sol-Gel	10–50	High	Silica, Polymers	Paramagnetic	Multimodal Imaging	20,26

Magnetophoresis and Magnetic Separation of MnO Nanoparticles

Theoretical Foundations

Magnetophoresis refers to the motion of magnetic particles within a fluid under a nonuniform magnetic field. The net magnetic energy (F_m) on a spherical MnO NP is given by:

$$\mathbf{F}_m = \frac{4\pi}{3} R_p^3 \frac{\Delta\chi_V}{\mu_0} (\mathbf{B} \cdot \nabla) \mathbf{B},$$

where R_p is the radius of the magnetizable volume of the particle, $\Delta\chi_V$ is the difference in magnetic susceptibility between the particle and the surrounding medium, and B is the magnetic flux density [23].

Experimental Insights

Rassolov et al. systematically investigated the magnetophoresis of weakly paramagnetic MnO NPs (50 nm radius) in aqueous suspensions under varying magnetic field gradients (0–110 T^2/m) [23]. Their experiments, supported by multiphysics simulations, revealed that the particle depletion rate was independent of the initial concentration but strongly dependent on the magnetic field gradient. High gradients accelerated particle capture at regions of maximal field strength. Notably, field-induced aggregation was observed for particles with radii of 130 nm or larger, indicating the potential for magnetic separation and scalable metal recovery from electronic waste.

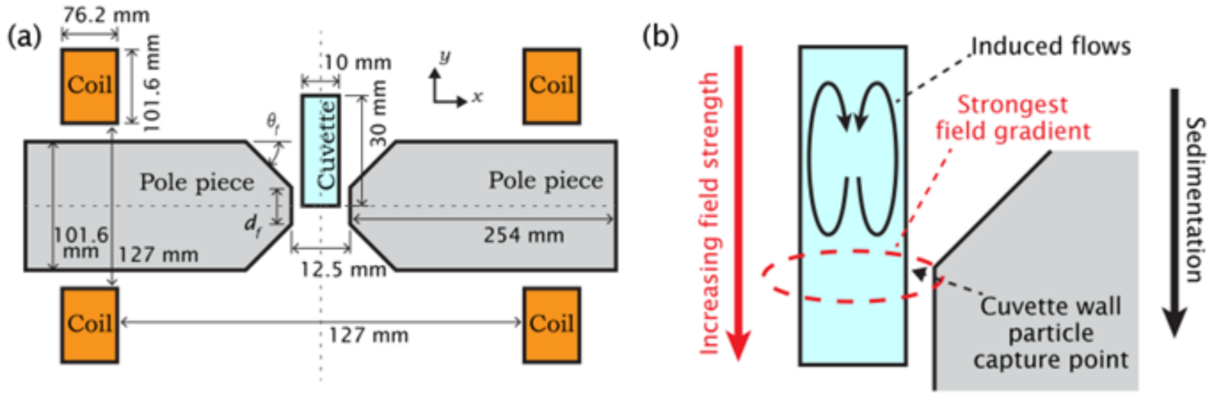

Figure 2. Schematic of Magnetophoresis Experimental Setup

Schematic of cuvette and coil apparatus for magnetophoresis experiments. Adapted from [23].

Dimensionless Numbers and Transport Phenomena

The interplay between magnetophoresis, diffusion, and sedimentation is characterized by dimensionless numbers such as the magnetic Peclet number ((Pe_m)), gravitational Peclet number ((Pe_g)), and magnetic Grashof number ((Gr_m)), which compare the relative strengths of these processes. When ($Pe_m > 1$), magnetophoresis dominates over diffusion, leading to efficient particle separation [23]. Bulk fluid flows induced by concentration gradients further enhance capture rates.

Applications in Metal Recovery and Sustainable Processing

The findings underscore the potential of magnetophoresis for sustainable and environmentally friendly recovery of critical materials, such as manganese, from spent electronics and lithium-ion batteries. Magnetic separation offers high selectivity, scalability, and energy efficiency compared to chemical or electrochemical methods [23].

Surface Functionalization and Biocompatibility

Polymeric and Inorganic Coatings

Surface modification is pivotal for ensuring the colloidal stability, biocompatibility, and functional versatility of MnO NPs. Common strategies include:

- **Silica Coating:** Provides steric and electrostatic stabilization, biocompatibility, and modifiable surfaces for further conjugation [14,20,26].
- **Polyethylene Glycol (PEG):** Improves hydrophilicity, reduces protein adsorption, and extends circulation time in vivo [54].
- **Polysaccharides (e.g., Dextran, Alginate):** Enhance dispersibility and offer sites for ligand attachment [10,24].
- **Polydopamine and Cyclodextrin:** Enable facile conjugation with drugs or targeting moieties [10,54].

Impact on Magnetic and Biological Properties

Coatings can alter magnetic properties by introducing diamagnetic materials or affecting the effective magnetic core size. For example, silica coating reduced the Curie temperature and saturation magnetization of perovskite MnO NPs, which may affect their hyperthermia performance but enhance safety by limiting excessive heating [14]. PEGylation and alginate–polydopamine shells improved biocompatibility and enabled efficient cellular uptake without toxicity [10,54].

In Vitro and In Vivo Biocompatibility

Cell viability assays (e.g., MTT, Alamar Blue) showed negligible cytotoxicity for silica- and PEG-coated MnO NPs at relevant concentrations, both in cancer cell lines

(HeLa, MCF-7) and normal cells [10,14,54]. The internalization and subcellular localization were confirmed via optical and fluorescence microscopy, demonstrating cytoplasmic uptake and potential for targeted delivery [14].

Biomedical Applications: MRI, Hyperthermia, and Theranostics

MRI Contrast Enhancement

MnO NPs are established as T1-weighted MRI contrast agents due to their moderate magnetic moment and relatively fast water exchange rates. Surface engineering can further optimize relaxivity and target specificity [12,13,15]. For instance, Cai et al. reported that MnO NPs provided strong T1 contrast in tumor multimodal imaging, while Chevallier et al. demonstrated efficient clearance of PEGylated ultra-small MnO NPs [12,13]. Table 3 summarizes representative studies of MnO NP-based MRI agents.

Table 3. Representative MnO NP-Based MRI Contrast Agents

Particle Type	Coating/ Functionalization	MRI Modality	Target/ Application	Key Findings	Reference
MnO@Alginate–PDA	Alginate-Polydopamine	T1	In vivo MRI	High relaxivity, biocompatible	10
MnO@Silica	Silica	T1	Renal carcinoma imaging	One-pot synthesis, high contrast	15
PEG-MnO NPs	PEG	T1/T2	Dual mode imaging	Stable, non-toxic, dual contrast	54
MnO@Dextran	Dextran	T1	Liver imaging	High colloidal stability	24

Magnetic Hyperthermia

The application of alternating magnetic fields to MnO NPs induces localized heating via hysteresis and relaxation losses, enabling selective cancer cell ablation (magnetic hyperthermia). Villanueva et al. showed that silica-coated MnO perovskite NPs internalized by HeLa cells produced significant apoptotic cell death upon exposure to an alternating magnetic field, even with minimal bulk temperature increase (<0.5°C), suggesting efficient intracellular heating mechanisms [14]. The ability to tune Curie temperature via composition and coating thickness enables self-regulating hyperthermia treatments.

Theranostics and Multimodal Platforms

Advancements in surface engineering have led to the development of multifunctional MnO NP platforms capable of simultaneous imaging, drug/gene delivery, and therapy (theranostics). For example, PEG-coated Zn-Mn ferrite NPs exhibited dual T1/T2 MRI contrast and efficient cell uptake, while hybrid nanocomposites with gold or carbon shells extended functionality to photothermal and photoacoustic imaging [54,11,32,37]. The integration with polymers, mesoporous silica, and targeting ligands further enhances tumor specificity and therapeutic efficacy [10,20,54].

Challenges and Future Directions

Scalability and Environmental Sustainability

While laboratory-scale syntheses of MnO NPs are well established, scalable, cost-effective, and green production methods are needed for industrial and clinical translation. Magnetophoresis-driven separation offers a promising route for the recycling and recovery of MnO NPs from electronic waste streams, reducing reliance on mining and mitigating environmental impact [23].

Control of Size, Shape, and Aggregation

Precise control over particle size, morphology, and aggregation state remains a challenge, especially when scaling up. Field-induced aggregation during magnetophoresis can affect separation efficiency and downstream applications.

Advanced synthetic protocols, real-time monitoring, and post-synthesis processing must be optimized to minimize batch-to-batch variability [23,54].

Surface Functionalization and Targeting

The development of robust, reproducible, and tunable surface modification strategies is essential for the safe and effective use of MnO NPs in vivo. Multifunctional coatings must balance stability, biocompatibility, targeting, and retention of magnetic properties. Emerging approaches, such as biomimetic and stimuli-responsive coatings, hold promise for next-generation theranostic agents [10,54].

Regulatory and Safety Considerations

Comprehensive toxicological studies, including long-term biodistribution, clearance, and immunogenicity assessments, are necessary to ensure the clinical safety of MnO NPs. Regulatory frameworks must keep pace with advances in nanoparticle synthesis and application to facilitate translation from bench to bedside [50,54].

Conclusion

The synthesis of manganese oxide nanoparticles underpins their success in diverse applications, particularly in biomedicine. Advances in synthetic methodologies—ranging from hydrothermal and sol-gel to green and top-down approaches—enable fine-tuning of particle size, morphology, and surface chemistry, directly impacting magnetic, catalytic, and biological properties. Insights from experimental and modeling studies of magnetophoresis reveal new opportunities for scalable, sustainable processing and metal recovery. Surface functionalization strategies, especially with silica and polymeric materials, enhance colloidal stability, biocompatibility, and functional integration, paving the way for safe and effective MRI contrast agents, hyperthermia therapeutics, and multifunctional theranostic platforms. Future research must focus on scalable, green synthesis, precise control over nanoparticle features, and systematic safety evaluation to unlock the full potential of MnO NPs in clinical and industrial settings.

Manganese oxide nanoparticles represent a highly versatile class of nanomaterials with significant potential in biomedical imaging and therapy. Through advances in synthesis, surface functionalization, and theoretical understanding, MnOx NPs can be engineered for optimized magnetic, pharmacokinetic, and biocompatibility profiles. Their role as MRI contrast agents and in multimodal theranostics is increasingly substantiated by experimental and simulation studies. However, challenges remain in ensuring long-term safety, clinical translatability, and scalable production. Continued interdisciplinary research—bridging chemistry, materials science, biology, and medicine—is essential to realize the full potential of MnOx NPs in next-generation diagnostics and therapeutics.

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