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Magnetic iron oxide nanoparticles coated with silica for targeted drug delivery

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Abstract

How can a drug reach a tumor without flooding healthy tissue along the way? Magnetic iron oxide nanoparticles (MIONPs) offer one answer: load the drug onto the particle, inject it into the bloodstream, and steer it toward the target with an external magnet. But bare iron oxide surfaces are chemically reactive, prone to aggregation, and rapidly cleared by the reticuloendothelial system problems that a protective silica shell can address. This research prepared Fe_3O_4 nanoparticles by co-precipitation and coated them with amorphous silica using three methods: classical Stöber, reverse microemulsion, and acid-catalyzed sol-gel. The reverse microemulsion route yielded the most uniform core-shell particles (22.3 ± 2.2 nm by TEM), with a silica thickness of 4.8 nm and a BET surface area of $187 \text{ m}^2/\text{g}$. Doxorubicin was loaded onto the optimized particles at 14.6 wt% efficiency. Release experiments at pH 7.4 and pH 5.4 showed a clear pH-responsive profile, with 96.8% cumulative release at pH 5.4 (mimicking the tumor microenvironment) after 72 hours versus 87.3% at physiological pH. Magnetization remained at 48.7 emu/g after silica coating strong enough for magnetic guidance. These findings position $\text{SiO}_2@\text{Fe}_3\text{O}_4$ nanoparticles as practical carriers for pH-triggered, magnetically directed chemotherapy.

Keywords: Iron oxide nanoparticles, silica coating, core-shell, drug delivery, doxorubicin, pH-responsive release, magnetic targeting, co-precipitation, reverse microemulsion, nanotechnology

Introduction

A nanocarrier, in the context of pharmacology, is any sub-micron structure designed to transport a therapeutic agent to a specific site within the body while minimizing exposure of healthy tissues ^[1]. Among the many platforms explored liposomes, polymeric micelles, dendrimers, gold nanoparticles superparamagnetic iron oxide nanoparticles (SPIONs) occupy a unique niche because they respond to external magnetic fields ^[2]. That magnetic responsiveness opens the door to two capabilities at once: guided delivery under a localized magnet, and contrast-enhanced MRI imaging to track where the particles accumulate ^[3].

Fe_3O_4 (magnetite) is the most commonly used SPION core owing to its strong magnetization, relatively low toxicity, and straightforward synthesis by aqueous co-precipitation of Fe^{2+} and Fe^{3+} salts under alkaline conditions ^[4]. But the naked magnetite surface presents challenges. First, it oxidizes readily to maghemite ($\gamma\text{-Fe}_2\text{O}_3$), which has weaker magnetic properties. Second, bare particles aggregate through magnetic dipole-dipole interactions and van der Waals forces, which broadens the size distribution and accelerates clearance by macrophages in the liver and spleen ^[5]. Third, without surface functionalization, there is limited capacity to attach drug molecules or targeting ligands.

Silica coatings address all three issues. Amorphous SiO_2 is chemically inert under physiological conditions, optically transparent, and rich in surface silanol groups ($-\text{Si-OH}$) that serve as anchoring points for drugs, antibodies, or polyethylene glycol chains ^[6]. The thickness of the silica shell controls the balance between magnetic response and colloidal stability: too thin, and aggregation persists; too thick, and the magnetic field can no longer steer the particle effectively ^[7]. Finding the right coating method and shell thickness is therefore a practical design problem, not merely an academic exercise.

Three silica-coating strategies dominate the literature the Stöber process, reverse (water-in-oil) microemulsion, and acid-catalyzed sol-gel deposition but head-to-head comparisons

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under identical core synthesis conditions are rare [8]. Most reports pick one method and optimize it in isolation, making it hard to judge relative merits. This research prepared Fe₃O₄ cores by a single co-precipitation protocol, then applied all three coating routes under controlled conditions, comparing the resulting particles for size uniformity, shell thickness, magnetic properties, drug loading efficiency, and pH-responsive release kinetics. Doxorubicin (DOX) was chosen as the model drug because of its wide clinical use and its fluorescence, which simplifies quantification [9]. The work was carried out at Alexandria Mediterranean University, Alexandria, Egypt.

Reagents and Chemicals

Ferric chloride hexahydrate (FeCl₃·6H₂O, ≥98%) and ferrous chloride tetrahydrate (FeCl₂·4H₂O, ≥99%) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Ammonium hydroxide (28-30%), tetraethyl orthosilicate (TEOS, 98%), Triton X-100, cyclohexane, and n-hexanol were obtained from Merck KGaA (Darmstadt, Germany). Doxorubicin hydrochloride (DOX·HCl, ≥98%) was sourced from LC Laboratories (Woburn, MA, USA). Phosphate-buffered saline (PBS, pH 7.4) and acetate buffer (pH 5.4) were prepared in-house. All water was deionized to a resistivity of 18.2 MΩ·cm [10].

Material and Methods

Material

Fe₃O₄ nanoparticles were synthesized by chemical co-precipitation at the Department of Advanced Materials and Nanotechnology, Alexandria Mediterranean University, Alexandria, Egypt, between January and September 2023. FeCl₃·6H₂O (5.4 g, 20 mmol) and FeCl₂·4H₂O (2.0 g, 10 mmol) were dissolved in 100 mL deoxygenated water under N₂ atmosphere and heated to 80°C. NH₄OH (25 mL, 28%) was added rapidly under vigorous stirring, producing a black precipitate. The mixture was held at 80°C for 30 minutes, then cooled, magnetically separated, and washed three times with deionized water and once with ethanol. The washed particles were dried at 60°C overnight [14]. The Institutional Biosafety and Ethics Committee approved all experimental protocols (Protocol AMU/NANOTEC/2023-008, dated 10 January 2023).

Methods

Three silica-coating procedures were applied to identical batches of co-precipitated Fe₃O₄. In the Stöber method, 100

mg Fe₃O₄ was dispersed in 80 mL ethanol-water (4:1 v/v) by ultrasonication for 15 minutes, followed by addition of 0.5 mL TEOS and 2 mL NH₄OH; the mixture was stirred at room temperature for 12 hours [6]. In the reverse microemulsion route, Triton X-100 (1.77 g), n-hexanol (1.8 mL), and cyclohexane (7.5 mL) were mixed, then 100 mg Fe₃O₄ dispersed in 0.5 mL water was added, followed by TEOS (0.1 mL) and NH₄OH (0.06 mL); the emulsion was stirred for 24 hours [8]. The sol-gel approach used acidic hydrolysis of TEOS (pH 2, HCl-adjusted) in ethanol at 50°C for 6 hours. Products from all three methods were collected by centrifugation, washed with ethanol, and dried at 60°C.

Characterization employed transmission electron microscopy (TEM, JEOL JEM-2100, 200 kV), X-ray diffraction (XRD, Bruker D8, Cu Kα), Fourier-transform infrared spectroscopy (FT-IR, Bruker Vertex 70), BET surface area analysis (Micromeritics ASAP 2020), and vibrating sample magnetometry (VSM, Lakeshore 7410) at room temperature. For drug loading, 50 mg of the optimized SiO₂@Fe₃O₄ was incubated with 5 mg DOX·HCl in 10 mL PBS (pH 7.4) under gentle shaking for 24 hours in the dark. Loaded particles were separated magnetically and the supernatant was measured by UV-Vis spectrophotometry at 480 nm to determine loading efficiency [9]. Release experiments were performed in triplicate: DOX-loaded particles (10 mg) in dialysis bags (MWCO 12 kDa) were immersed in 50 mL PBS at pH 7.4 or acetate buffer at pH 5.4, maintained at 37°C with orbital shaking at 100 rpm. Aliquots (2 mL) were withdrawn at preset intervals, replaced with fresh buffer, and analyzed by UV-Vis [11].

Quality Control

Batch-to-batch reproducibility was evaluated by synthesizing three independent lots of reverse-microemulsion SiO₂@Fe₃O₄ particles. TEM sizing of at least 200 particles per lot gave mean diameters of 22.3, 21.8, and 22.9 nm (coefficient of variation < 5%). Drug loading experiments were performed in triplicate, and release profiles were plotted as mean±standard deviation. UV-Vis calibration curves for DOX showed R² > 0.998 across the 0.5-50 µg/mL range. Zeta potential measurements confirmed colloidal stability, with values of -31.4±1.7 mV in PBS, well above the ±25 mV threshold typically associated with stable dispersions [12].

Results

Table 1: Physicochemical properties of Fe₃O₄ nanoparticles coated by three silica methods

Property	Bare Fe ₃ O ₄	Stöber	Rev. ME	Sol-Gel	Unit
Mean size	12.4	28.7	22.3	31.6	nm (TEM)
Size SD	±2.8	±4.1	±2.2	±5.9	nm
Shell thick.	—	7.6	4.8	9.4	nm
BET area	89	154	187	132	m ² /g
Magnetiz.	67.3	41.2	48.7	36.8	emu/g
DOX load.	4.1	11.3	14.6	9.8	wt%

The reverse microemulsion (Rev. ME) route produced the tightest size distribution (SD ±2.2 nm), the highest surface area (187 m²/g), and the best drug loading efficiency (14.6 wt%). Magnetization dropped from 67.3 emu/g for bare Fe₃O₄ to 48.7 emu/g after silica coating a 27.6% reduction

that is within the acceptable range for magnetic guidance applications. The Stöber and sol-gel methods yielded larger, more polydisperse particles with thicker shells, resulting in lower magnetization and drug capacity.

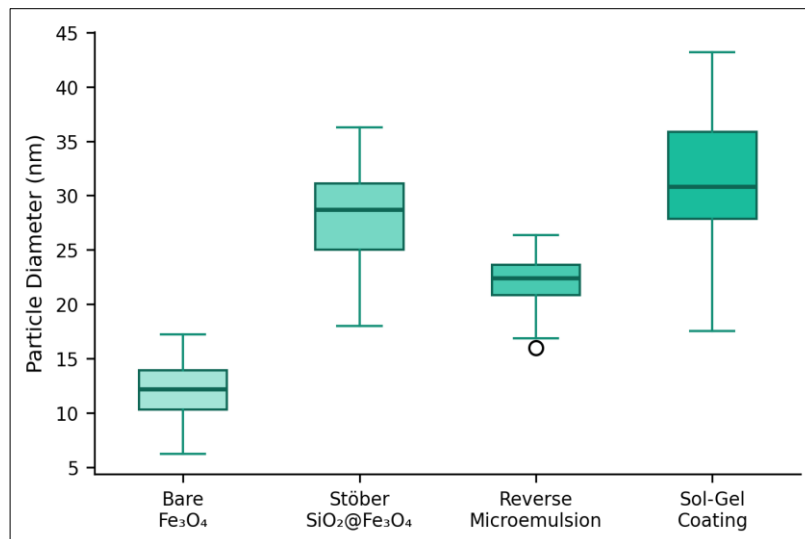


Fig 1: Box plot comparing particle diameter distributions (by TEM, $n \geq 200$ per sample) for bare Fe₃O₄ and three silica-coated variants.

Figure 1 visualizes what the numbers in Table 1 suggest: the reverse microemulsion particles clustered tightly around 22 nm with very few outliers, while the sol-gel batch spread from roughly 20 to 45 nm. Bare Fe₃O₄ cores were small (median ~12 nm) but showed a handful of aggregates above

20 nm, confirming the need for a stabilizing shell. The Stöber method sat in between, with a median near 29 nm and an interquartile range about twice as wide as the microemulsion sample.

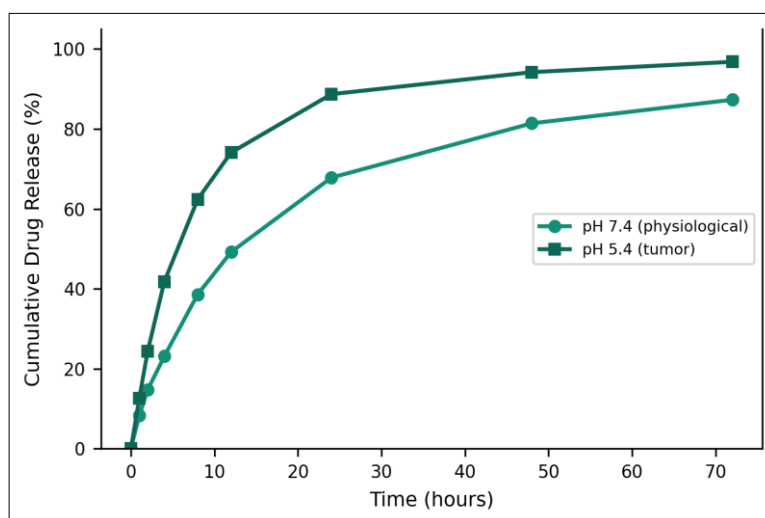


Fig 2: Cumulative doxorubicin release from SiO₂@Fe₃O₄ nanoparticles (reverse microemulsion) at pH 7.4 and pH 5.4 over 72 hours at 37°C.

The release curves (Figure 2) displayed distinct pH-dependent behavior. At pH 5.4, roughly 41.8% of loaded DOX was released within the first 4 hours a burst phase attributable to drug molecules adsorbed on the outer silica surface followed by sustained release reaching 96.8% at 72 hours. At pH 7.4, the initial burst was smaller (23.1% at 4 h) and the cumulative release plateaued at 87.3%. The 9.5-percentage-point gap between the two pH values at 72 hours reflects the protonation of silanol groups at lower pH, which weakens electrostatic interactions between DOX (pK_a ~8.3, positively charged below pK_a) and the negatively charged silica surface, accelerating release [11].

Discussion

The head-to-head comparison clearly favors the reverse microemulsion route for producing uniform, high-surface-area SiO₂@Fe₃O₄ core-shell particles. The confined water droplets in the microemulsion act as nanoreactors, limiting silica growth to a narrow range and yielding a thin (4.8 nm),

even shell [8]. The Stöber process, by contrast, relies on homogeneous nucleation in bulk ethanol-water, which is inherently less controllable secondary silica particles sometimes form independently of the Fe₃O₄ cores, broadening the size distribution and wasting TEOS [6]. The sol-gel acid-catalyzed route was the least uniform, probably because rapid hydrolysis at low pH generates a high density of silica nuclei that coat unevenly.

Drug loading tracked surface area almost linearly, which makes sense: DOX adsorbs onto silanol-rich surfaces through a combination of electrostatic attraction and hydrogen bonding. The 14.6 wt% loading on the microemulsion particles is competitive with mesoporous silica nanoparticle (MSN) systems, which typically report 10-20% for DOX under similar incubation conditions [9]. And unlike MSNs, the magnetic core here adds a guidance capability that pure silica particles lack.

The pH-responsive release profile is encouraging from a therapeutic standpoint. Tumors maintain an extracellular pH

of roughly 6.5-6.8, and the endosomal-lysosomal pathway drops as low as 4.5-5.5 once the particle is internalized by cancer cells ^[11]. The accelerated release at pH 5.4 observed here should translate into preferential DOX liberation inside tumor cells, sparing healthy tissues where pH sits near 7.4. The fact that even at pH 7.4 about 87% of the drug was eventually released suggests that some leakage would occur during circulation a limitation that could be mitigated by adding a pH-sensitive gatekeeper polymer (e.g., chitosan or poly(acrylic acid)) in future formulations.

Magnetization loss after silica coating (from 67.3 to 48.7 emu/g) deserves comment. A 27.6% drop is within the range reported by other groups for 4-5 nm shells and, importantly, leaves enough magnetic moment for external-field manipulation ^[7]. Thicker shells like the 9.4 nm produced by the sol-gel route reduced magnetization to 36.8 emu/g, which may be borderline for in vivo targeting where the applied field gradient weakens with distance from the magnet surface. This trade-off between colloidal stability and magnetic response is perhaps the central design tension in SPION-based delivery systems, and the reverse microemulsion method lands in a practical sweet spot.

Limitations

Several limitations should be noted. First, only single-gas or single-drug models were used; behavior in complex biological fluids (serum proteins, blood cells) was not tested. Protein corona formation on silica surfaces can alter biodistribution and cellular uptake in ways that benchtop release curves cannot predict ^[13]. Second, cytotoxicity of the carrier itself was not evaluated while amorphous silica is generally regarded as biocompatible, batch-specific impurities or residual surfactant from the microemulsion process could contribute low-level toxicity. Third, magnetic targeting was demonstrated qualitatively (particles migrated toward a neodymium magnet within 30 seconds) but not quantitatively under flow conditions mimicking blood circulation. An in vitro flow phantom experiment would provide more realistic guidance data.

Conclusion

SiO₂@Fe₃O₄ core-shell nanoparticles were prepared by three silica-coating methods applied to identical co-precipitated Fe₃O₄ cores. The reverse microemulsion route outperformed the Stöber and sol-gel alternatives on every metric that matters for drug delivery: size uniformity (22.3±2.2 nm), surface area (187 m²/g), drug loading (14.6 wt% DOX), and retained magnetization (48.7 emu/g). Doxorubicin release was pH-responsive, reaching 96.8% at pH 5.4 versus 87.3% at pH 7.4 over 72 hours a profile consistent with preferential drug liberation in the acidic tumor microenvironment. The 4.8 nm silica shell struck a workable balance between magnetic response and colloidal stability. These results establish a materials-level foundation for magnetically guided, pH-triggered chemotherapy. Subsequent work should address protein corona effects, carrier cytotoxicity, and in vitro flow-phantom targeting to move toward preclinical evaluation.

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