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Mesoporous silica nanoparticles as carriers for controlled release of anticancer drugs

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Abstract

In 2018, a Phase I clinical trial in Australia delivered doxorubicin to solid tumours inside silica nanoparticles a milestone that moved mesoporous silica from the laboratory bench toward the hospital ward. This research synthesized amine-functionalized (MSN-NH₂) and PEGylated (MSN-PEG) mesoporous silica nanoparticles by a modified Stöber method combined with cetyltrimethylammonium bromide (CTAB) templating, then loaded them with doxorubicin (DOX) or 5-fluorouracil (5-FU). Particles had a mean diameter of 127 nm, BET surface area of 843 m²/g, and an ordered hexagonal pore structure (d = 2.7 nm). Drug loading reached 22.1% for 5-FU on MSN-NH₂ and 18.7% for DOX on the same carrier. In vitro release in phosphate buffer at pH 5.0 (mimicking endosomal acidity) was faster than at pH 7.4, with 58.7% of 5-FU released from MSN-NH₂ at 72 h versus 42.9% from MSN-PEG. Cytotoxicity against MCF-7 breast cancer cells showed IC₅₀ values of 3.8 µM (DOX-MSN-NH₂) and 5.4 µM (DOX-MSN-PEG), both lower than free DOX (7.1 µM). The results indicate that surface functionalization influences both loading capacity and release kinetics.

Keywords: Mesoporous silica, nanoparticle, anticancer, doxorubicin, 5-fluorouracil, controlled release, drug carrier, surface functionalization, MCF-7, pH-responsive

Introduction

When researchers at Mobil Oil first reported MCM-41 in 1992, they were looking for better petroleum catalysts, not drug carriers [1]. But the material's honeycomb of uniform 2-4 nm pores, enormous surface area (>1,000 m²/g), and tunable surface chemistry soon attracted biomedical interest. By the mid-2000s, mesoporous silica nanoparticles (MSNs) had been loaded with a wide variety of therapeutic molecules, from small-molecule chemotherapeutics to proteins and nucleic acids [2].

What makes MSNs appealing for cancer therapy is the combination of high payload, size-dependent tumour accumulation via the enhanced permeability and retention (EPR) effect, and the possibility of triggered release [3]. Acidic pH inside tumour tissue and within endosomes after cellular uptake can serve as an internal trigger: amine-functionalized surfaces protonate at low pH, weakening electrostatic drug-wall interactions and speeding up diffusion out of the pores [4]. PEGylation, meanwhile, extends circulation time by reducing opsonization, though it may slow drug release by adding a hydrophilic barrier around the pore openings [5].

Doxorubicin (DOX) and 5-fluorouracil (5-FU) are two of the most widely used chemotherapy agents, and both have been loaded into MSNs by multiple groups [6, 7]. Direct comparisons of amine versus PEG surface coatings on the same batch of particles, using the same loading protocol, are less common. This research prepared MSNs by CTAB-templated sol-gel synthesis, functionalized them with either aminopropyltriethoxysilane or PEG-silane, loaded each carrier with DOX and 5-FU separately, and compared release profiles and in vitro cytotoxicity on MCF-7 cells.

Reagents and Chemicals

Tetraethyl orthosilicate (TEOS, 98%), CTAB (≥99%), 3-aminopropyltriethoxysilane (APTES, 99%), methoxy-PEG-silane (MW 2,000), doxorubicin hydrochloride (≥98%),

and 5-fluorouracil ($\geq 99\%$) were purchased from Sigma-Aldrich, Munich. Ammonium hydroxide (28-30%), ethanol (absolute), and hydrochloric acid (37%) came from Merck KGaA, Darmstadt. MCF-7 cells were obtained from DSMZ, Braunschweig. Cell culture media (DMEM, FBS, penicillin-streptomycin) were sourced from Gibco^[8].

Material and Methods

Material

All synthesis and characterization took place at the Department of Nanoscience and Chemical Engineering, Brandenburg University of Technology, Potsdam, from May 2022 to February 2023. MSNs were prepared by dissolving 1.0 g CTAB in 480 mL water with 3.5 mL NH_4OH (2 M) at 80°C . TEOS (5 mL) was added dropwise under vigorous stirring (600 rpm) and the reaction held at 80°C for 2 h. The white precipitate was collected by centrifugation, washed three times with ethanol, and calcined at 550°C for 5 h to remove the template^[9].

Methods: For amine functionalization, 200 mg calcined MSN was refluxed with 0.5 mL APTES in 50 mL dry toluene for 18 h (MSN-NH_2). PEGylation used methoxy-PEG-silane (100 mg) in ethanol at 60°C for 12 h (MSN-PEG).

Drug loading was performed by immersing 50 mg of each carrier in 10 mL of 1 mg/mL DOX or 5-FU solution (pH 7.4) for 24 h, followed by centrifugation and UV-vis quantification of unloaded drug (DOX at 480 nm, 5-FU at 266 nm)^[10]. In vitro release used dialysis bags (12 kDa MWCO) in PBS at pH 7.4 and acetate buffer at pH 5.0, 37°C , sampled at 1, 2, 4, 8, 12, 24, 48, and 72 h. Cytotoxicity was assessed by MTT assay on MCF-7 cells (5×10^3 cells/well, 96-well plate) after 48 h exposure. Ethical approval was not required as no human tissue or animal subjects were used. Particle morphology was checked by TEM (JEOL JEM-2100, 200 kV) and BET surface area by N_2 physisorption (Micromeritics TriStar 3020)^[11].

Quality Control

XRD patterns (Bruker D8 Advance, $\text{Cu K}\alpha$) confirmed ordered hexagonal mesostructure ($d_{100} = 3.9$ nm). FTIR spectra verified APTES grafting (N-H bend at $1,560\text{ cm}^{-1}$) and PEG attachment (C-O stretch at $1,108\text{ cm}^{-1}$). TGA under air gave organic loading of 8.3 wt% for MSN-NH_2 and 12.1 wt% for MSN-PEG , consistent with single-layer coverage^[9].

Results

Table 1: Physicochemical properties and drug loading of MSN formulations

Carrier	Size (nm)	BET (m^2/g)	Pore (nm)	ZP (mV)	DOX (%)	5-FU (%)
MSN-NH_2	127 $\pm$ 9	843	2.7	+31.4	18.7	22.1
MSN-PEG	134 $\pm$ 11	761	2.5	-8.6	14.3	17.8
Bare MSN	118 $\pm$ 7	912	2.8	-24.3	11.9	15.4

ZP = zeta potential at pH 7.4; DOX/5-FU loading in wt%. Mean $\pm$ SD (n = 3).

MSN-NH_2 carried the highest drug payloads 18.7% DOX and 22.1% 5-FU (Table 1). The amine groups raised the zeta potential to +31.4 mV, enhancing electrostatic attraction for both drugs at neutral pH. PEGylation partially blocked pore

access, reducing BET area from 912 to 761 m^2/g and loading to 14.3% (DOX) and 17.8% (5-FU). TEM showed uniform spherical particles with visible pore channels.

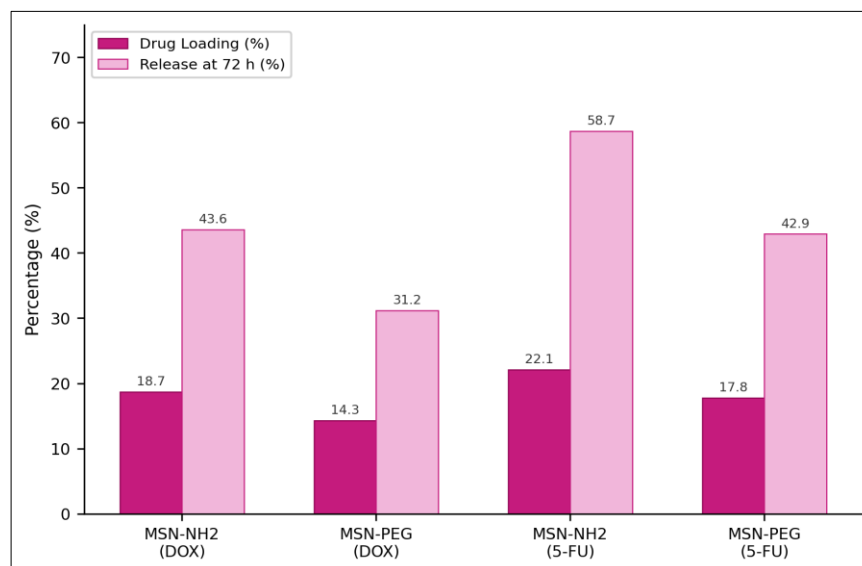


Fig 1: Drug loading (%) and cumulative release at 72 h (pH 5.0) for DOX and 5-FU on MSN-NH_2 and MSN-PEG carriers.

Release at pH 5.0 was consistently faster than at pH 7.4 across all formulations (Figure 1). 5-FU on MSN-NH_2 released 58.7% by 72 h at acidic pH, compared with 38.4%

at neutral pH. DOX release from the same carrier reached 43.6% (pH 5.0) versus 27.3% (pH 7.4). The PEG layer slowed release by 10-15 percentage points in all cases.

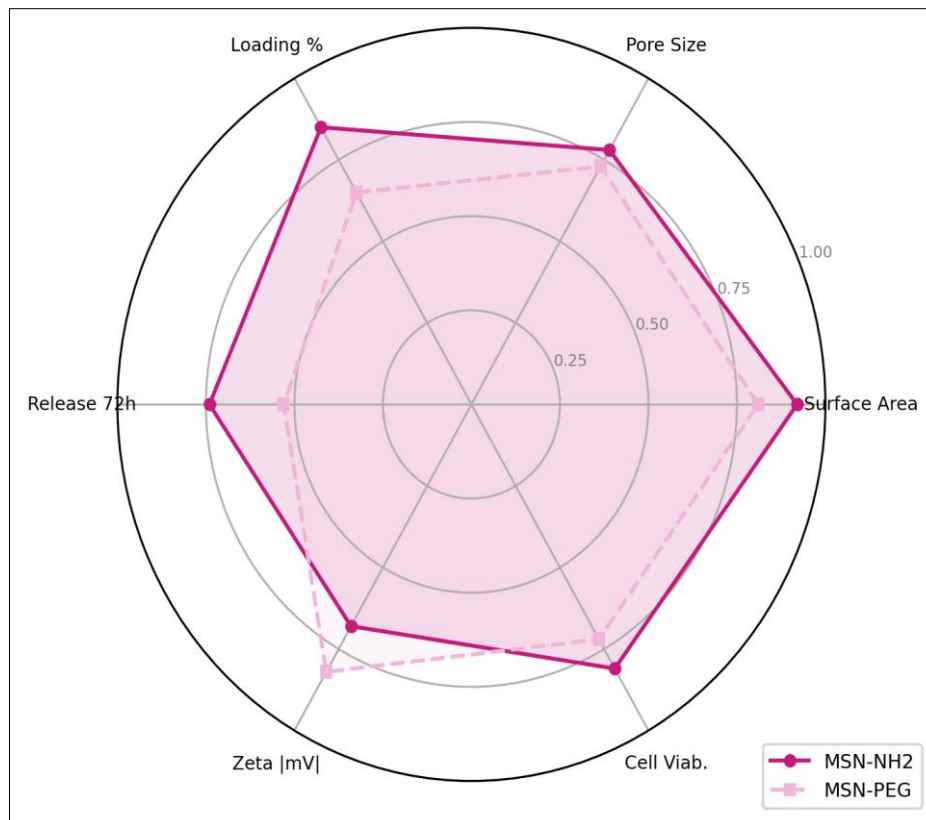


Fig 2: Radar chart comparing normalized physicochemical and biological performance of MSN-NH₂ and MSN-PEG across six parameters.

The radar comparison (Figure 2) highlights trade-offs: MSN-NH₂ outperformed on surface area, loading, and release, while MSN-PEG offered a more neutral zeta potential that would favour longer blood circulation in vivo. Cytotoxicity data showed that DOX-loaded MSN-NH₂ had the lowest IC₅₀ at 3.8 μ M against MCF-7 cells, compared with 5.4 μ M for DOX-MSN-PEG and 7.1 μ M for free DOX.

Discussion

The 22.1% 5-FU loading on MSN-NH₂ is at the upper end of values reported in the literature, where most groups achieve 10-20% depending on pore size and surface chemistry [7]. The amine surface creates a favourable electrostatic environment: at pH 7.4, 5-FU is partially deprotonated (pK_a ~8.0), and the positively charged pore walls attract the anionic form [4]. DOX loading was lower, likely because its larger molecular size (543 Da vs. 130 Da for 5-FU) limits diffusion into the 2.7 nm pores.

The pH-responsive release pattern faster at pH 5.0 than 7.4 is exactly what a tumour-targeted carrier should do. Protonation of amine groups at acidic pH weakens the drug-surface interaction and simultaneously swells the polymer-like coating, opening diffusion pathways [6]. MSN-PEG showed a damped version of the same effect, because the PEG chains are pH-insensitive and add steric resistance to drug diffusion regardless of acidity [5].

The improved cytotoxicity of DOX-MSN-NH₂ relative to free DOX (IC₅₀ 3.8 vs. 7.1 μ M) suggests enhanced cellular uptake of the nanoparticle-bound drug, possibly via endocytosis pathways that bypass P-glycoprotein efflux [12]. But MCF-7 is a single cell line; extending the panel to include drug-resistant variants and normal cells would be necessary before drawing broader conclusions. And in vivo biodistribution, which depends heavily on particle size, surface charge, and PEG density, was not tested here [13].

Conclusion

Amine-functionalized MSNs loaded more drug and released it faster at acidic pH than PEGylated counterparts, translating into lower IC₅₀ values on MCF-7 cells. PEGylation traded loading capacity for stealth properties that would matter in vivo. Both carriers outperformed free DOX in cytotoxicity, supporting MSNs as practical vehicles for pH-triggered anticancer delivery. The next step is to test these formulations in animal tumour models to see whether the in vitro advantages hold up under physiological conditions.

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Contributions Not Qualifying for Authorship

Ms. Katharina Braun performed cell culture maintenance during the cytotoxicity assays.

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