Inorganic Drug Release from Mesoporous Silica Nanoparticles for Cancer Treatment

Carla Caramella [1*]

Abstract

Mesoporous Silica Nanoparticles (MSNs) were synthesized via a modified sol-gel Stöber process. The effect of various parameters - sodium hydroxide concentration, co-solvent, stirring rate, aging time and stirring time – on the size, morphology and monodispersity of the particles was investigated. The reproducible MSNs developed were spherical, 80.24 ± 11.80 nm in size, monodispersed, had a large surface area (690.34 m2/g) and pore volume (0.89 cm3/g). These properties deemed our MSNs ideal carriers for the delivery of therapeutic ions to cancer cells. Zinc and iron were incorporated, together and separately, into the silica network via a post-synthetic incorporation technique followed by calcination. Zinc ions have a preferential toxicity towards cancer cells, which leads to a pH-triggered release. The addition of ions to the particles did not affect their size or morphology. The washing step was proven crucial to preserve the monodispersity of the particles. Results suggest that zinc is probably acting as a network modifier (decreases network connectivity) and iron as a network former (increases network connectivity). The behaviour of iron(III) chloride and iron(III) nitrate as precursors was compared. Iron(III) chloride produced predominantly large localized hematite crystals (25.75 ± 3.19 nm). Iron(III) nitrate gave rise to mainly small homogeneously-spread magnetite crystals (2.70 ± 0.50 nm), which is desired. The incorporation of iron into to the MSN-Zn network slowed down the release of zinc, making the release less toxic. Iron tightens the silica network and it does not get released.

Keywords: Mesoporous Silica Nanoparticles (MSNs), Drug Delivery Systems, Cancer Therapy, Zinc and Iron Ions, Controlled Release Mechanism

Significance | The study demonstrates that controlled synthesis of mesoporous silica nanoparticles enables efficient, targeted cancer treatment with reduced toxicity.

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Editor Md Shamsuddin Sultan Khan, Ph.D., And accepted by the Editorial Board Sep 09, 2023 (received for review Jul 17, 2023)

Introduction

Mesoporous silica nanoparticles (MSNs) have garnered significant attention in recent years for their potential as drug delivery vehicles, particularly in cancer therapy. These nanoparticles are highly valued due to their large surface area, tunable pore sizes, chemical stability, biocompatibility, and capacity for functionalization, which collectively make them superior to other organic and inorganic nanoparticles (Tang et al., 2012; Mamaeva et al., 2013). Among various applications, MSNs have been explored for the delivery of therapeutic agents such as genes, proteins, drugs, and metal ions to combat diseases like diabetes, hard-tissue regeneration, and cancer (Slowing et al., 2008; Tang et al., 2012; Mamaeva et al., 2013).

The pioneering sol-gel process for the synthesis of spherical and monodispersed silica particles was first reported by Stöber et al. (1968). This method involves the hydrolysis of a silica precursor, typically tetraethyl orthosilicate (TEOS), in the presence of a basic catalyst to produce monodispersed silica nanoparticles. The Stöber process has since been modified to produce MSNs, which exhibit a highly ordered porous structure formed through the self-assembly of surfactant micelles around the silica network (Zhao et al., 1998).

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Please cite this article:
Carla Caramella (2024). Inorganic Drug Release from Mesoporous Silica Nanoparticles for Cancer Treatment, Biosensors and Nanothernaostics, 2(1), 1-6, 9842

These MSNs have demonstrated significant potential as carriers for therapeutic ions, which are released as the silica network degrades in biological environments (Slowing et al., 2008).

Zinc oxide nanoparticles (ZnO NPs) have been extensively studied for their anticancer properties. ZnO NPs exhibit preferential toxicity towards various cancer cell types, including T-cells, glioma, leukemia, and breast cancer cells (Rasmussen et al., 2010; Brayner et al., 2006; Zhang et al., 2014). The rapid dissolution of ZnO NPs in acidic environments, typical of tumor sites, leads to a controlled release of Zn^{2+} ions, which induces reactive oxygen species (ROS) and oxidative stress, ultimately resulting in cancer cell death (Jiang et al., 2008). However, ZnO NPs often suffer from uncontrolled burst release, limiting their direct application in vivo (Slowing et al., 2008).

To address these limitations, MSNs have been proposed as carriers for ZnO NPs, offering controlled release and enhanced biocompatibility (Mamaeva et al., 2013). Furthermore, the addition of network-forming ions, such as iron (Fe^{3+}), to the MSN framework has been suggested to slow the release of Zn^{2+} ions, thereby reducing toxicity and improving therapeutic outcomes (Kim et al., 2008). Iron also offers the added benefit of serving as a contrast agent for magnetic resonance imaging (MRI) or as a component in hyperthermia treatment for cancer (Lee et al., 2011). In this study, we synthesized MSNs using a modified Stöber process and investigated the effects of various synthesis parameters—sodium hydroxide concentration, co-solvent, stirring rate, aging time, and stirring time—on the size, morphology, and monodispersity of the nanoparticles. We then incorporated zinc and iron ions, both separately and together, into the MSN framework to evaluate their potential as therapeutic ion carriers. The effects of different iron precursors, iron(III) chloride, and iron(III) nitrate, on the formation of iron oxide within the MSN structure were also compared.

2. Methods and Materials

2.1 Preparation of Mesoporous Silica Nanoparticles (MSNs)

MSNs were synthesized using a modified Stöber process. Tetraethyl orthosilicate (TEOS) was used as the silica precursor. A mixture of ethanol, deionized water, and ammonium hydroxide was prepared as the reaction medium. The silica precursor was added dropwise to the reaction medium under continuous stirring. The effects of various parameters—including sodium hydroxide concentration, stirring rate, co-solvent (e.g., ethanol), solution volume, aging time, and stirring time—on the size, morphology, and monodispersity of the MSNs were systematically studied. The resulting MSNs were collected by centrifugation, washed several times with ethanol and deionized water, and dried under vacuum.

2.2 Incorporation of Zinc and Iron Ions in MSNs

The incorporation of zinc and iron ions into the MSNs was performed using a post-synthetic method. For zinc incorporation, a solution of zinc nitrate was prepared and added to the MSN dispersion. The mixture was stirred for 24 hours, followed by drying and calcination at 550°C to remove any organic residues and to stabilize the metal ions within the silica framework.

For iron incorporation, two different iron precursors were used: iron(III) chloride and iron(III) nitrate. The precursors were dissolved in deionized water and added separately to the MSN dispersion. The mixtures were stirred for 24 hours, dried, and calcinated. The effects of these two precursors on the formation of iron oxide within the MSNs were compared.

2.3 Characterization Techniques

The synthesized MSNs were characterized using various techniques. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) were used to analyze the morphology and size distribution of the nanoparticles. X-ray diffraction (XRD) was employed to determine the crystalline phases of the incorporated ions. Fourier-transform infrared spectroscopy (FTIR) was used to confirm the removal of organic templates and the incorporation of metal ions into the silica network. Surface area and pore volume were measured using the Brunauer-Emmett-Teller (BET) method, and pore size distribution was determined using the Barrett-Joyner-Halenda (BJH) method.

2.4 Dissolution Studies

The dissolution behavior of the zinc and iron ions from the MSNs was investigated by dispersing the MSNs in simulated body fluid (SBF) at 37°C. The concentration of released ions was measured over time using inductively coupled plasma optical emission spectrometry (ICP-OES). The release profiles were compared to evaluate the effect of iron incorporation on the release kinetics of zinc ions.

3. Results

3.1 Effect of Synthesis Parameters on MSN Properties

The size, morphology, and monodispersity of the MSNs were significantly influenced by the synthesis parameters. Figure 1 illustrates the general sol-gel synthesis process of MSNs, while Figure 2 (a-c)depicts the specific effects of varying sodium hydroxide concentration and stirring rate on the particle size and morphology. As shown in Figure 2(a), an increase in sodium hydroxide concentration led to a reduction in particle size, resulting in more uniform and spherical particles(Fig 2b). Additionally, a higher stirring rate promoted better distribution, leading to a narrower size distribution of the MSNs(Fig2 c).

3.2 Incorporation of Zinc and Iron Ions

Zinc ions were successfully incorporated into the MSNs without altering their size or morphology, as confirmed by the TEM images

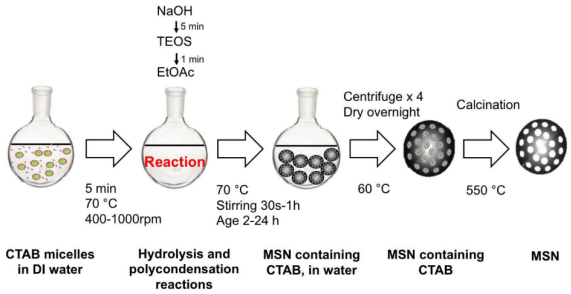

Figure 1: Schematic representation of the sol-gel synthesis process of MSNs from TEOS.

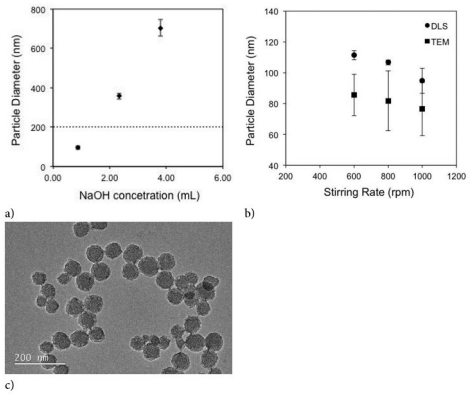

Figure 2. a) DLS results for MSNs synthesized with different NaOH concentration (S-0.88mL; S-2.73mL; S-3.79mL). Error bars show the standard deviation (n=6). b) DLS and TEM results for MSNs synthesized at different stirring rates (S-600rpm; S-800rpm; S-1000rpm). c) TEM image of S-600rpm. Error bars show the standard deviation (n=6 DLS; n=50 TEM).

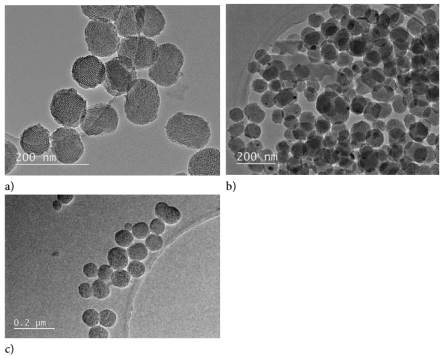

Figure 3. a) TEM image of MSN:Zn before post-calcination washing. b) TEM image of MSN:FeCl3, with no washing. c) TEM image of MSN with zinc and iron incorporated using iron(III) nitrate as a precursor.

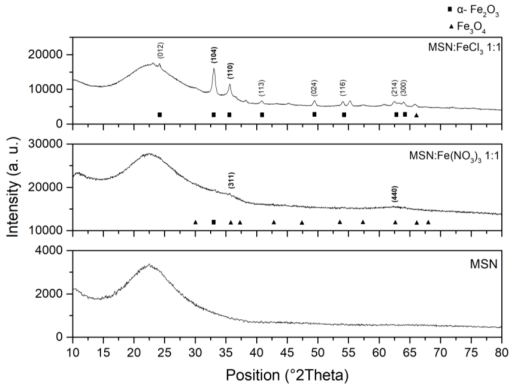

Figure 4. Comparison of parent's MSN XRD pattern (bottom) and that obtained when incorporating iron using iron(III) chloride (top) and iron(III) nitrate (middle) as precursors. The squares represent the diffraction pattern for hematite and the triangles for magnetite. The most representative miller indices are in bold.

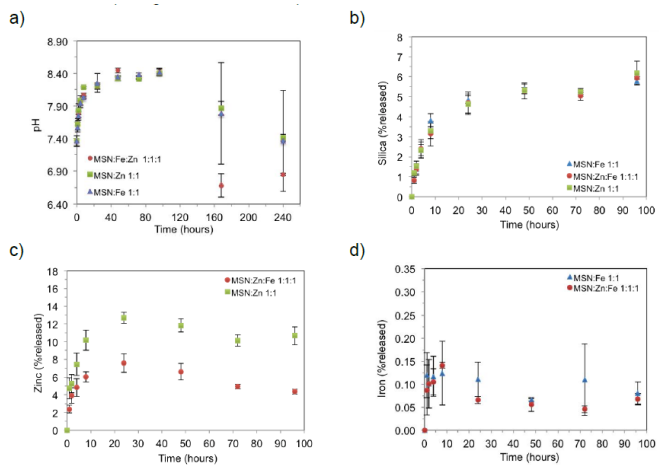

Figure 5. Dissolution study results in α-MEM from MSN:Zn 1:1, MSN:Fe 1:1 and MSN:Zn:Fe 1:1:1 (iron nitrate precursor) a) pH b) Si c) Zn d) Fe release. Error bars calculated

in Figure 3(a-c). The XRD patterns in Figure 4 show the crystalline phases of the MSNs with incorporated zinc and iron ions. When using iron(III) nitrate as the precursor, smaller and more uniformly distributed magnetite crystals were formed compared to the larger, localized hematite crystals produced using iron(III) chloride. The FTIR spectra, also in Figure 4, indicate the successful removal of the surfactant template and confirm the incorporation of metal ions into the silica network. The combination of zinc and iron ions slowed down the release of zinc, suggesting that iron serves as a network former, which tightens the silica matrix.

3.3 Dissolution Studies

The dissolution profiles presented in Figure 5 reveal the pH-dependent release of zinc ions from the MSNs. The release was more rapid under acidic conditions, which is advantageous for targeting the acidic microenvironment of cancer cells. The incorporation of iron into the MSN matrix significantly slowed the release rate of zinc ions, providing a more controlled release mechanism (Figure 5). This controlled release is particularly important for reducing potential toxicity and enhancing the therapeutic efficacy of the nanoparticles.

4. Discussion

The synthesis of mesoporous silica nanoparticles (MSNs) with controlled size, morphology, and monodispersity is crucial for their application in drug delivery, especially for cancer treatment. The results of this study demonstrate that careful control of the synthesis parameters, such as sodium hydroxide concentration, stirring rate, and the use of co-solvents, can significantly influence the physical properties of MSNs (Tang et al., 2012; Zhao et al., 1998). Achieving the optimal particle size (70-200 nm) and ensuring monodispersity are vital for the efficient uptake of nanoparticles by cancer cells and for minimizing toxicity (Mamaeva et al., 2013).

The successful incorporation of zinc and iron ions into the MSN framework without altering the nanoparticles' morphology is a promising advancement. Zinc ions have been widely studied for their anticancer properties, particularly for their ability to induce apoptosis in cancer cells via oxidative stress and the generation of reactive oxygen species (ROS) (Jiang et al., 2008; Rasmussen et al., 2010). However, the uncontrolled burst release of zinc from nanoparticles poses a significant challenge for their use in clinical settings (Slowing et al., 2008). The incorporation of iron ions into the silica matrix, as demonstrated in this study, offers a viable solution by slowing the release of zinc and thereby reducing its potential toxicity (Kim et al., 2008).

The comparison between the two iron precursors, iron(III) chloride, and iron(III) nitrate, revealed significant differences in the formation of iron oxide within the MSNs. Iron(III) nitrate was found to produce smaller, more uniformly distributed magnetite crystals, which are more desirable for biomedical applications, including magnetic resonance imaging (MRI) and hyperthermia treatment (Lee et al., 2011). The formation of larger hematite crystals using iron(III) chloride could potentially limit the effectiveness of the nanoparticles as drug delivery vehicles.

The dissolution studies further confirmed the potential of these MSNs as effective carriers for zinc and iron ions in cancer treatment. The pH-dependent release of zinc is particularly advantageous for targeting the acidic microenvironment of tumors, ensuring that the therapeutic ions are released primarily at the site of action (Jiang et al., 2008). The slower release of zinc in the presence of iron, as shown in the dissolution profiles, underscores the role of iron as a network former that stabilizes the silica matrix and provides a more controlled release mechanism (Kim et al., 2008; Slowing et al., 2008).

5. Conclusion

This study successfully synthesized mesoporous silica nanoparticles (MSNs) with controlled size, morphology, and monodispersity by optimizing various synthesis parameters. The incorporation of zinc and iron ions into the MSN framework was achieved without compromising the physical properties of the nanoparticles. The use of iron as a network former significantly slowed the release of zinc ions, offering a controlled release mechanism that could reduce potential toxicity and improve therapeutic outcomes in cancer treatment. The findings highlight the potential of these MSNs as versatile carriers for therapeutic ions, with applications in both drug delivery and diagnostic imaging. Future work should focus on in vivo studies to further evaluate the efficacy and safety of these nanoparticles in clinical settings.

Author contributions

C.C. conceptualized and led the study, contributed to the analysis, and reviewed the manuscript.

Acknowledgment

Author was grateful to their department.

Competing financial interests

The authors have no conflict of interest.

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