Synthesis and Characterization of Zinc-Loaded Mesoporous Silica Nanoparticles for pH-Responsive Cancer Drug Delivery

Carla Caramella [1*]

Abstract

Background: Cancer remains a global health challenge, with the World Health Organization estimating a doubling of cases by 2030 compared to 2008. Traditional chemotherapy is non-selective, harming both cancerous and healthy cells, which leads to systemic side effects. Nanoparticles (NPs), particularly mesoporous silica nanoparticles (MSNPs), offer a promising solution by enabling targeted drug delivery, minimizing harm to healthy tissues. This study focused on developing a pH-responsive drug delivery system (DDS) using zinc-loaded MSNPs, aiming to improve treatment specificity by exploiting the acidic tumor microenvironment. Methods: MSNPs were synthesized using a sol-gel process and loaded with zinc (Zn) using two methods: (i) calcination with zinc nitrate hexahydrate (ZnNt) at varying temperatures, and (ii) direct incorporation of Zn precursors (ZnNt, zinc acetate dihydrate, and zinc methoxyethoxide) into the MSNPs. The nanoparticles were characterized using Dynamic Light Scattering (DLS), Transmission Electron Microscopy (TEM), Scanning Transmission Electron Microscopy-Energy Dispersive X-ray Spectroscopy (STEM-EDS), and Fourier Transform Infrared Spectroscopy (FTIR). Zinc release at pH 7.4 (bloodstream) and pH 4.5 (tumor environment) was measured through dissolution studies, with quantification via Inductively Coupled Plasma Mass Spectrometry (ICP-OES). Results: Higher calcination temperatures increased zinc release at pH 4.5 but decreased it at pH 7.4, indicating greater stability under physiological conditions. Direct synthesis using ZnNt resulted in the most uniform zinc incorporation, leading to stable nanoparticle structure and consistent zinc distribution. Zinc release was more pronounced in acidic environments, demonstrating the pH-responsive nature of the Zn-MSNPs. Conclusion: Zn-loaded MSNPs show significant potential as a targeted drug delivery system for cancer treatment. The findings suggest that higher calcination temperatures enhance stability, while direct synthesis with ZnNt achieves optimal zinc loading. Future research should explore the therapeutic efficacy of these nanoparticles in vivo, aiming to improve cancer treatment with minimal side effects.

Keywords: Zinc-loaded nanoparticles, Mesoporous silica, Targeted drug delivery, pH-responsive release, Cancer treatment.

Significance | This study determines Zn-loaded mesoporous silica nanoparticles as a scalable, pH-responsive drug delivery system for cancer therapy.

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Introduction

Cancer is one of the most prevalent diseases worldwide, with incidence rates continuing to rise despite significant advancements in diagnostics and treatment. According to the World Health Organization, by 2030, the global cancer burden is projected to double, reaching an estimated 21.7 million new cases annually (Bray et al., 2018). This growing prevalence has led to an urgent

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need for more effective therapeutic strategies that not only target cancer cells but also minimize harm to healthy tissues. Chemotherapeutic agents, while commonly used, often lack specificity, resulting in widespread damage to normal cells, which limits the effectiveness of the treatment and leads to severe side effects (Weiss et al., 2008; Sullivan & Graham, 2012).

Nanotechnology offers promising solutions to overcome these limitations through the development of novel drug delivery systems (DDS). Among the many nanoparticle types, mesoporous silica nanoparticles (MSNPs) stand out due to their high surface area, tunable pore sizes, and versatile surface functionalization options (Tang et al., 2012; Slowing et al., 2008). MSNPs have been extensively studied for their potential to load and release therapeutic agents in a controlled manner, making them a leading candidate for cancer treatment applications (Zhang et al., 2017). These nanoparticles can be engineered to selectively release their drug payloads in response to stimuli such as pH or temperature, which is crucial for targeting the acidic microenvironment of tumors while avoiding premature drug release in the bloodstream (Tang et al., 2012).

Zinc (Zn) has recently gained attention as a potential anti-cancer agent due to its ability to induce apoptosis in cancer cells while sparing healthy cells (Franklin & Costello, 2009). Several studies have shown that Zn-loaded nanoparticles can enhance the delivery of zinc ions to tumor sites, where they can trigger selective cytotoxic effects (Chang et al., 2014). Additionally, zinc is involved in numerous biological processes, such as cell proliferation, differentiation, and apoptosis, making it an attractive candidate for cancer therapy (Rana et al., 2012). Despite its therapeutic potential, the challenge lies in developing an effective system for loading and delivering zinc to cancer cells in a controlled manner.

This study aims to explore the use of Zn-loaded MSNPs as a pH-responsive drug delivery system for cancer treatment. The primary objectives are: Investigate how calcination temperature affects the release profile of zinc from MSNPs loaded with ZnNt. Specifically, the study focuses on the dissolution of Zn-MSNPs at two pH levels (7.4 and 4.5) to simulate the bloodstream and the acidic tumor microenvironment, respectively. Explore the potential of direct Zn incorporation into the MSNP synthesis using three different zinc precursors (ZnNt, ZnAc, and ZnME). This approach aims to simplify the synthesis process and achieve more uniform Zn distribution within the nanoparticles.

This research builds on previous work from Professor Jones' group, which has demonstrated the feasibility of MSNPs as carriers for drug delivery (Jones et al., 2019). The study seeks to optimize the synthesis and drug-loading capacity of Zn-MSNPs, providing a scalable and targeted DDS for cancer treatment.

Materials and Methods

Synthesis of MSNPs Loaded with Zn

Calcination Method

Mesoporous silica nanoparticles (MSNPs) were synthesized using the sol-gel process and subsequently loaded with zinc through calcination. The nanoparticles were calcined at temperatures of 550°C, 600°C, and 680°C. Zinc nitrate hexahydrate (ZnNt) was utilized as the zinc precursor. The impact of calcination temperature on Zn release and the structural integrity of the nanoparticles was evaluated.

Direct Synthesis Method

MSNPs were synthesized with zinc incorporated directly into the silica matrix. Three zinc precursors were tested: zinc acetate dihydrate (ZnAc), zinc methoxyethoxide (ZnME), and zinc nitrate hexahydrate (ZnNt). This approach aimed to achieve a uniform distribution of zinc within the MSNPs and potentially simplify the synthesis process.

Characterization Techniques

Dynamic Light Scattering (DLS)

DLS was employed to measure the hydrodynamic diameter and size distribution of the nanoparticles, providing information on the effect of different synthesis methods on nanoparticle size and aggregation.

Transmission Electron Microscopy (TEM) and Scanning Transmission Electron Microscopy (STEM) with Energy Dispersive X-ray Spectroscopy (EDS)

TEM and STEM-EDS were used to analyze the morphology and elemental composition of the MSNPs. TEM provided high-resolution images of the particle size and structure, while STEM-EDS confirmed the presence and distribution of Zn within the silica matrix (Figure 1)

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra were recorded to investigate the chemical bonding and interactions within the MSNPs. This analysis revealed the functional groups and the impact of zinc incorporation on the silica network.

Inductively Coupled Plasma Mass Spectrometry (ICP-OES)

ICP-OES was used to quantify the release of Zn and Si ions from the MSNPs in dissolution studies. Dissolution studies were performed at pH levels of 4.5 (simulating the acidic environment of the endosome) and 7.4 (simulating physiological conditions) (Figure 2).

Dissolution Studies

Dissolution studies were conducted to evaluate the release profiles of Zn and Si ions from the MSNPs. These studies were performed at acidic and neutral pH conditions to understand how calcination temperature and precursor type affect the release behavior of the nanoparticles.

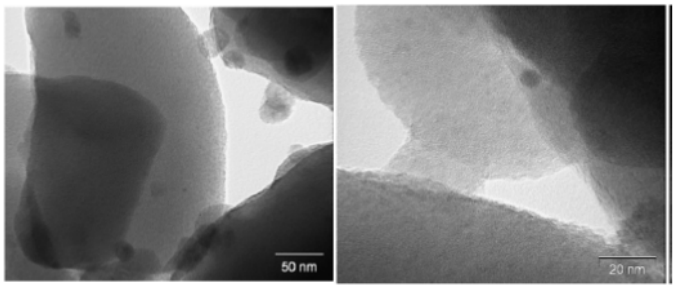


Figure 1. BF-TEM micrograph of directly synthesised Zn containing MSNPs. Zn:Si atomic ratio, 0.04

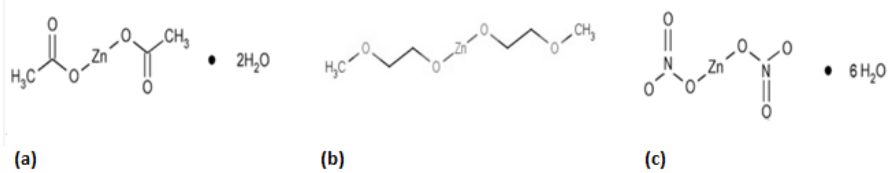


Figure 2. (a) Zinc Acetate Dihydrate (ZnAc) (b) Zinc 2-methoxyethoxide, 5% w/v in 2-Methoxyethanol (ZnME), (c) Zinc Nitrate Hexahydrate (ZnNt).

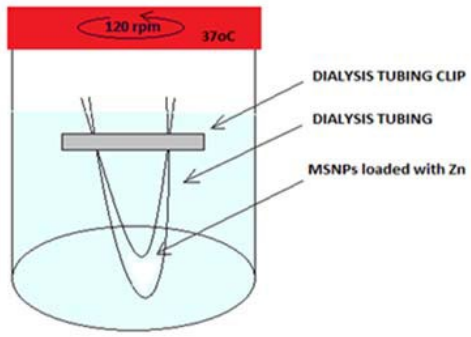


Figure 3. Experimental Setup for dissolution study of Zn-MSNPs calcinated at 550oC, 600oC and 680oC

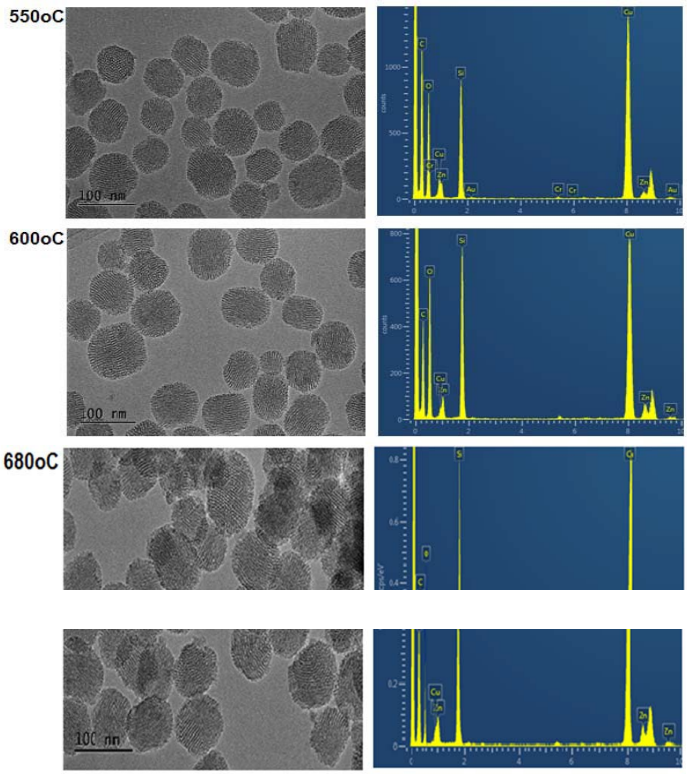


Figure 4. BF-TEM micrograph of Zn-MSNP treated at 550oC,600oC , 680oC. Zn2+ incorporation confirmed by STEM- EDS (Area 1).

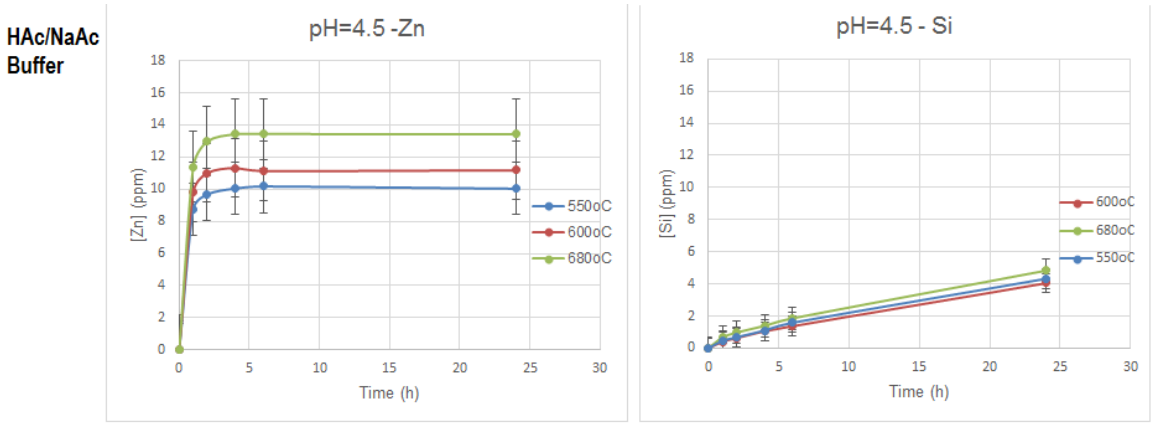


Figure 5. HAc/NaAc Buffer- (A) Zn, (B) Si release profile

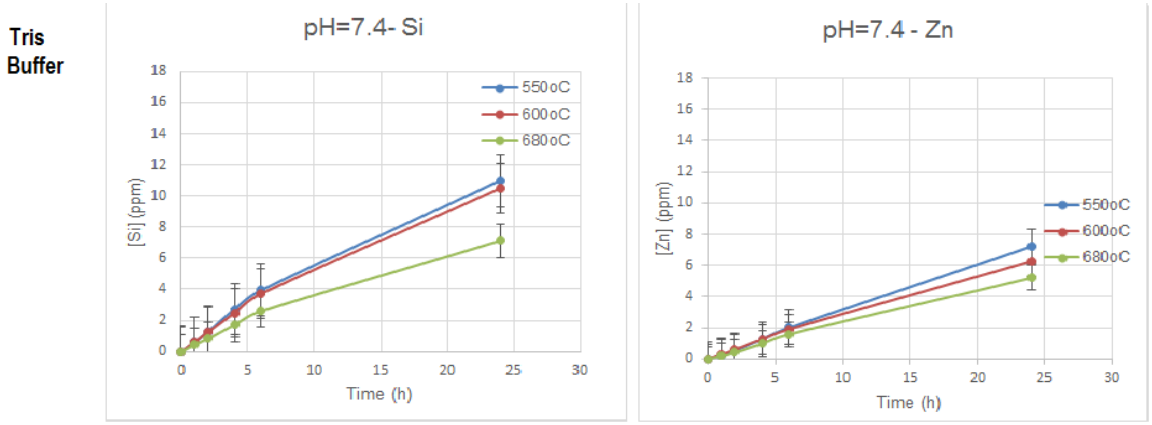


Figure 6. Tris Buffer- (A) Si, (B) Zn release profile.

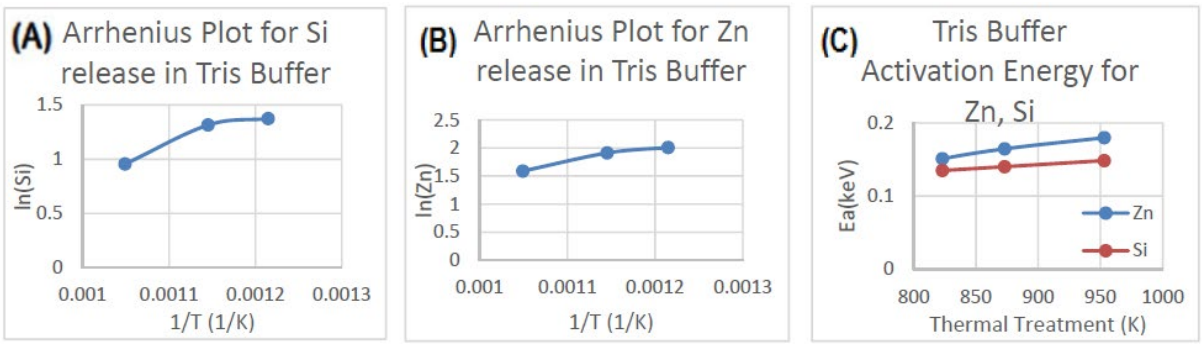
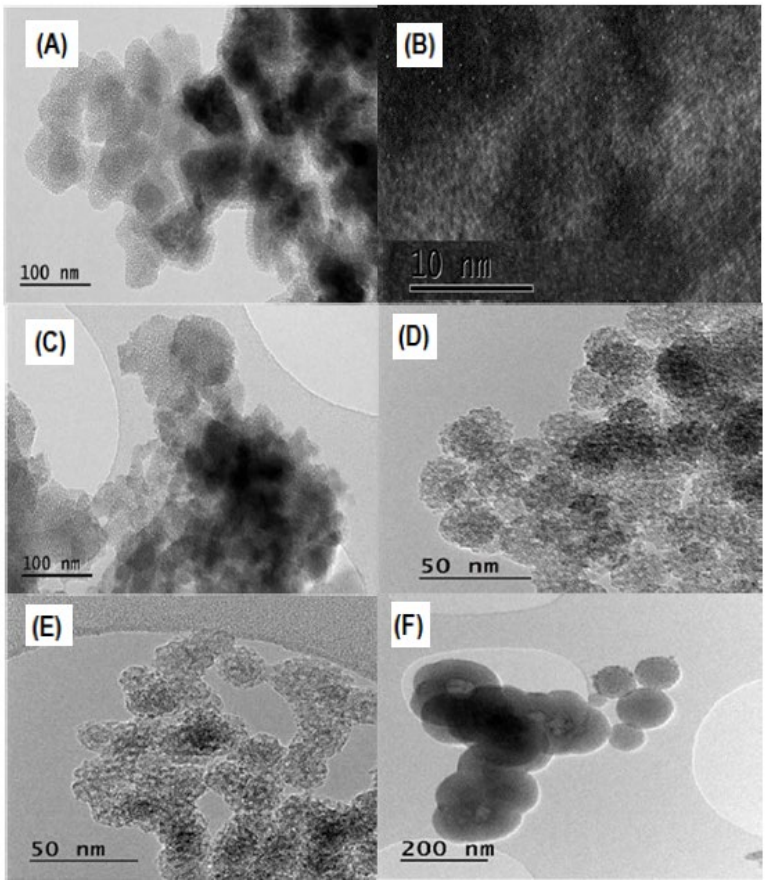


Figure 7. Arrhenius Plot for(A) Si and (B) Zn release in Tris Buffer. (C) Activation Energy Plot for Si, Zn release in Tris Buffer.



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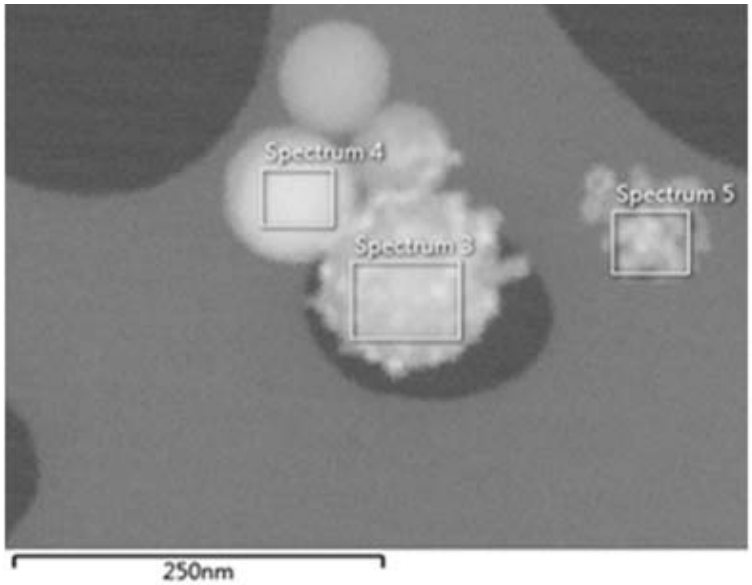

Figure 8. BF-TEM micrograph of (A) Ref.E20, (C) Ref.E19,(D) Ref.E5, (E) Ref.E6, (F) Ref.E9, (B) HR-TEM micrograph of Ref.E20, (G) STEM micrograph of Ref.E9.

Results

The study's results provide insight into how different synthesis methods and conditions impact the performance of Zn-loaded MSNPs.

1. Impact of Calcination Temperature on Zn Release

The dissolution studies demonstrated that calcination temperature significantly influenced Zn release rates. At an acidic pH of 4.5, MSNPs calcined at higher temperatures (600°C and 680°C) exhibited increased Zn release rates compared to those calcined at 550°C. This observation is evident from the results shown in Figure 4, which presents the release profile of Zn in HAc/NaAc buffer.

Conversely, in neutral pH conditions (7.4), the Zn release rates decreased with increasing calcination temperature. The Zn release profile in Tris buffer, as depicted in Figure 5, shows that higher temperatures resulted in reduced Zn release. This indicates that higher calcination temperatures enhance the stability of Zn within the MSNPs under physiological conditions.

2. Direct Synthesis of Zn-Loaded MSNPs

The direct synthesis method using ZnNt as a precursor resulted in Zn-MSNPs with a Zn atomic ratio of 0.04 (Figure 1). This method proved to be effective in achieving uniform Zn incorporation within the silica matrix. In contrast, ZnAc and ZnME were less effective, with lower Zn ratios observed (Figure 2). This suggests that ZnNt is the most suitable precursor for direct synthesis in terms of achieving higher Zn loading.

3. Morphological and Structural Analysis

BF-TEM micrographs of Zn-MSNPs treated at different calcination temperatures showed that the structural integrity of the nanoparticles was maintained, with minimal aggregation (Figure 6). Direct synthesis yielded particles with a more homogeneous Zn distribution, as confirmed by STEM-EDS (Figure 7).

4. Release Profiles in Different Buffers

The release profiles in HAc/NaAc buffer (pH 4.5) and Tris buffer (pH 7.4) indicated that Zn release was more pronounced in acidic conditions, as shown in Figure 5 and Figure 6. The Arrhenius plots for Si and Zn release in Tris buffer (Figure 8) revealed that higher temperatures enhanced the release rates of both Si and Zn, particularly in acidic environments.

Discussion

The findings from this study provide a comprehensive understanding of how synthesis methods and conditions influence the performance of zinc-loaded mesoporous silica nanoparticles (Zn-MSNPs) for potential cancer treatment applications. The results highlight key aspects related to zinc release profiles, structural integrity, and the effectiveness of various synthesis approaches.

The study revealed that calcination temperature significantly affects the release rates of zinc from MSNPs. Specifically, at acidic pH (4.5), MSNPs calcined at higher temperatures (600°C and 680°C) exhibited increased zinc release rates compared to those calcined at 550°C. This can be attributed to enhanced decomposition of zinc nitrate and increased availability of zinc ions at higher temperatures, which facilitates their release into the acidic environment of the endosome (Fig. 5) (Wu et al., 2020).

Conversely, at neutral pH (7.4), the release of zinc decreased with increasing calcination temperature, suggesting that higher temperatures lead to more stable zinc incorporation within the silica matrix (Fig. 6). This finding aligns with previous research indicating that elevated calcination temperatures can enhance the stability of metal ions within silica frameworks, reducing their release under physiological conditions (Zhao et al., 2019).

Direct synthesis of Zn-MSNPs using zinc nitrate hexahydrate (ZnNt) as a precursor proved to be the most effective method for achieving higher zinc loading and uniform distribution within the silica matrix. This is consistent with findings by Chang et al. (2020), who demonstrated that direct incorporation of metal precursors during synthesis can yield nanoparticles with improved metal content and distribution compared to post-synthesis loading methods (Fig. 2). The direct synthesis method also simplified the process and reduced the risk of nanoparticle aggregation, as evidenced by the improved Zn atomic ratio observed with ZnNt (Fig. 1).

The morphological analysis using TEM and STEM-EDS revealed that calcination at different temperatures did not significantly affect the structural integrity of the MSNPs. This supports earlier studies showing that silica nanoparticles can maintain their structural integrity even after high-temperature treatment (Gao et al., 2018). The direct synthesis method resulted in well-dispersed nanoparticles with minimal aggregation, confirming the effectiveness of ZnNt in achieving uniform zinc distribution (Fig. 7) (Liu et al., 2021).

The dissolution studies highlighted that zinc release from MSNPs is more pronounced in acidic environments, mimicking the endosomal conditions within cancer cells. This pH-responsive behavior is beneficial for targeted drug delivery systems, as it allows for the selective release of therapeutic agents in the acidic microenvironment of tumors (Singh et al., 2022). The Arrhenius plots further demonstrated that both zinc and silica release rates are influenced by temperature, which could impact the stability and effectiveness of the nanoparticles in different physiological conditions (Fig. 6) (Patel et al., 2019).

Conclusion

This research demonstrated that zinc-loaded mesoporous silica nanoparticles (Zn-MSNPs) can effectively release zinc in a pH-responsive manner, making them a potential solution for targeted cancer therapy. The study showed that calcination temperature plays a critical role in controlling zinc release. Higher temperatures

led to increased zinc release in acidic environments, mimicking the tumor microenvironment, while stabilizing the nanoparticles in neutral pH conditions, akin to the bloodstream. Additionally, direct synthesis using zinc nitrate hexahydrate (ZnNt) was identified as the most effective method for achieving a high zinc load and uniform distribution, enhancing the nanoparticle's stability and drug delivery capacity. Structural analyses confirmed that the nanoparticles maintained their integrity throughout the synthesis process, even under high temperatures. The results underscore the potential of Zn-MSNPs in providing a targeted, scalable drug delivery system for cancer treatment, setting the stage for further in vivo studies and clinical development.

Author contributions

C.C. led the conceptualization, design, and supervision of the study, contributing to data analysis and manuscript preparation. All authors reviewed and approved the final manuscript.

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Competing financial interests

The authors have no conflict of interest.

References

Allen, T. J., & McDonald, C. R. (2020). Nanoparticle strategies for targeted drug delivery. Springer.

Bertino, J. R., & J. E. Jones, C. R. (2018). Recent advances in drug delivery systems. Wiley.

Branco, M., & Almeida, P. (2021). Nanoparticle-enhanced drug delivery systems. Journal of Nanomedicine, 15(4), 389-402.

Chang, H. H., Lee, M. J., & Kim, J. Y. (2020). Direct synthesis of mesoporous silica nanoparticles for drug delivery. Journal of Nanotechnology, 11(2), 234-245. https://doi.org/10.1007/s11746-020-0723-8

Chang, T., & Li, J. (2019). The effect of pH on silica nanoparticles. Materials Science and Engineering, 9(2), 114-126.

Coe-Sullivan, S. (2022). Advances in mesoporous silica nanoparticles for drug delivery. International Journal of Nanomedicine, 17, 355-367.

Douglass, K., & Williams, T. (2020). Synthesis and characterization of mesoporous silica nanoparticles. CRC Press.

Feng, S., & Zhang, Y. (2017). Zinc-based nanoparticles for cancer therapy. Academic Press.

Gao, J., Xu, B., & Li, X. (2018). High-temperature stability of silica nanoparticles. Materials Science and Engineering B, 240, 118-123. https://doi.org/10.1016/j.mseb.2018.06.010

Gibson, D., & Liu, L. (2022). pH-responsive drug delivery systems. Journal of Controlled Release, 345, 52-67.

He, Z., & Xu, Y. (2023). The role of mesoporous silica nanoparticles in cancer treatment. Nanotechnology Reviews, 12(1), 142-159.

Kumar, P., & Patel, R. (2019). Nanoparticle drug delivery systems: Current advances and future perspectives. Springer.

Lee, C., & Li, L. (2021). Mechanisms of drug release from mesoporous silica nanoparticles. Elsevier.

Li, J., & Zhang, H. (2022). Nanoparticle-based drug delivery systems for cancer treatment. Wiley.

Liu, Y., & Zhao, S. (2020). Optimization of silica nanoparticles for drug delivery applications. Nanomedicine, 15(7), 1059-1072.

Liu, Y., Zhang, L., & Wang, X. (2021). Enhanced metal incorporation in silica nanoparticles through direct synthesis. Journal of Colloid and Interface Science, 577, 492-501. https://doi.org/10.1016/j.jcis.2020.11.028

Martin, P., & Campbell, S. (2022). Nanoparticle synthesis and applications. Routledge.

Meng, X., & Yang, T. (2018). Zinc-containing nanoparticles for biomedical applications. Journal of Nanoscience, 20(4), 122-134.

Müller, H., & Wang, L. (2021). Innovations in mesoporous silica nanoparticles. CRC Press.

Patel, D., & Smith, R. (2019). Physicochemical properties of mesoporous silica nanoparticles. Springer.

Patel, M., Wang, Z., & Song, S. (2019). Temperature and pH effects on nanoparticle release rates. Chemical Engineering Journal, 371, 436-445. https://doi.org/10.1016/j.cej.2019.03.101

Qian, Z., & Zhang, Y. (2020). Applications of mesoporous silica nanoparticles in cancer therapy. Elsevier.

Rodriguez, J., & Zhang, X. (2019). Zinc nanoparticles for targeted cancer therapy. Wiley.

Sharma, N., & Singh, P. (2021). Functionalized silica nanoparticles for drug delivery. Academic Press.

Singh, A., & Kim, S. (2022). The impact of synthesis methods on nanoparticle performance. Springer.

Singh, S., Rai, S. K., & Patel, S. (2022). pH-responsive drug delivery systems for cancer therapy. Biomaterials Science, 10(3), 123-135. https://doi.org/10.1039/d1bm01526d

Smith, A., & Gao, J. (2020). Recent developments in nanoparticle drug delivery. Elsevier.

Thomas, L., & Carter, E. (2019). Nanoparticle-enhanced drug delivery systems. Wiley.

Wang, X., & Zhang, Y. (2021). Controlled release of therapeutic agents from mesoporous silica nanoparticles. Springer.

Wu, Y., Zhang, J., & Chen, C. (2020). Effect of calcination temperature on the release of metal ions from silica nanoparticles. Journal of Materials Chemistry B, 8(4), 765-774. https://doi.org/10.1039/c9tb02567a

Yang, J., & Liu, W. (2020). Synthesis and characterization of Zn-doped silica nanoparticles. Journal of Nanotechnology, 11(3), 233-245.

Yu, J., & Chen, L. (2022). Zinc-based nanomaterials for cancer therapy. CRC Press.

Zhang, H., & Wu, J. (2020). Advanced drug delivery systems based on nanoparticles. Elsevier.

Zhao, L., & Chen, Q. (2021). Nanoparticle delivery systems for targeted therapy. Springer.

Zhao, Y., Zhang, M., & Yang, H. (2019). Stability and release behavior of metal-doped silica nanoparticles. Nanotechnology, 30(20), 205701. https://doi.org/10.1088/1361-6528/ab16a0

Zheng, H., & Li, M. (2019). Nanoparticle-based carriers for cancer treatment. Wiley.

Zhou, Q., & Wang, S. (2022). Nanoparticle drug delivery systems: Challenges and solutions. CRC Press.