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| RESEARCH ARTICLE

PEGylation of Mesoporous Silica Nanoparticles for Drug Delivery Applications

Mahadi Hasan[1] ✉ Md. Faisal Kabir[2] and Md. Khalil Miah Pathan[3]
[1]Department of Chemistry, University of South Dakota, Vermillion, USA
[23]Department of Applied Chemistry and Chemical Engineering, University of Dhaka, Bangladesh
Corresponding Author: Mahadi Hasan, **E-mail**: mahadi.hasan01@coyotes.usd.edu

| ABSTRACT
Mesoporous silica nanoparticles (MSNs) and PEGylated mesoporous silica nanoparticles (PEG-MSNs) were synthesized and characterized for potential targeted drug delivery applications. In this study, MSNs were synthesized via a sol-gel process to investigate in vitro drug release efficacy and subsequently PEGylated to impart colloidal stability and biocompatibility for future mouse model experiment. Comprehensive characterization techniques, including Scanning Electron Microscopy (SEM), Fourier Transform Infrared Spectroscopy (FTIR), Brunauer-Emmett-Teller (BET) analysis, and zeta potential measurements were employed. SEM analysis revealed uniformly distributed spherical nanoparticles with smooth surfaces, while FTIR confirmed the successful PEGylation in the surface of MSNs. BET analysis also indicated a reduction in surface area, pore volume, and pore size upon PEGylation, suggesting that PEG chains influence the nanoparticle structure. Zeta potential measurements showed a shift from negative to positive surface charge post-PEGylation, indicating improved colloidal stability. Drug loading and release studies utilizing doxorubicin hydrochloride (DOX) demonstrated a controlled release profile, with MSNs exhibiting a higher cumulative release compared to PEG-MSNs over 24 h. These findings underscore the potential of PEG-MSNs for controlled drug delivery, offering advantages such as reduced systemic toxicity and enhanced therapeutic efficacy for PEG-MSNs nanocarrier in the animal studies due to their increased colloidal stability.

| KEYWORDS

Mesoporous Silica Nanoparticles; Drug Delivery Applications

| ARTICLE INFORMATION

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1. Introduction

Mesoporous silica nanoparticles have gained significant attention in the field of drug delivery systems as nanocarriers due to their unique structural properties, including high surface area, tunable pore size, ease of surface functionalization and biocompatibility. These properties make MSNs ideal candidates for drug delivery applications, allowing for high drug loading capacities and controlled release profiles. The versatility of MSNs is further enhanced by surface functionalization, which can improve their dispersibility, biocompatibility, and target-specific delivery.

One of the notable modifications to MSNs is PEGylation, the process of grafting polyethylene glycol (PEG) chains onto the nanoparticle surface. PEGylation is known to reduce protein adsorption and minimize recognition by the mononuclear phagocyte system, thereby prolonging circulation time in the bloodstream. Additionally, PEGylation can modulate the surface charge of nanoparticles, influencing their stability and interaction with biological membranes.

Previous studies have demonstrated the potential of PEGylated MSNs in drug delivery systems. For instance, Popat et al. (2011) explored the use of PEG-MSNs for the delivery of hydrophobic drugs, showing enhanced solubility and sustained release profiles. Similarly, He et al. (2015) reported that PEG-MSNs could effectively deliver chemotherapeutic agents to tumor cells, reducing systemic toxicity and improving therapeutic outcomes.

The present study aims to synthesize and characterize MSNs and PEG-MSNs, evaluating their structural and functional properties for drug delivery applications. This research focuses on the synthesis of MSNs using a sol-gel process and their subsequent PEGylation. The structural characteristics of the nanoparticles were analyzed using SEM, FTIR, and BET analysis. Additionally, the surface charge was assessed through surface zeta potential measurements, and the drug loading efficiency and in vitro release profiles were studied using doxorubicin hydrochloride as a model drug.

The comprehensive characterization of these nanoparticles provides valuable insights into their potential as drug delivery vehicles. The study also explores the impact of PEGylation on the drug release kinetics, stability, and overall performance of the nanoparticles in delivering therapeutic agents. This investigation contributes to the growing body of literature on the use of functionalized MSNs in nanomedicine, particularly in enhancing drug delivery efficacy and safety.

2. Experimental Section

2.1 Synthesis of MSNs and PEG-MSNs

To synthesize MSNs, 1.0 g of CTAB was added in 500 mL of deionized water at standard temperature. Then 7 mL of NH_4OH (25-28%) was added to the solution and stirred for 10 min to ensure complete dissolution. 5 mL of TEOS was then added dropwise to the mixture while stirring vigorously for 2 h. After that the mixture was centrifuged at 8,000 rpm for 12 min washed several times with absolute ethanol and milliQ water to get the MSNs. Then the particles were dried in the oven at 70°C overnight. The CTAB template was removed by refluxing the MSNs in an acidic ethanol medium for 24 h.

The PEGylation of MSN was achieved by grafting PEG chains onto the surface of the nanoparticles. A PEG-silane coupling agent was used, which reacted with the surface silanol groups on the MSN to form covalent bonds, thus attaching PEG to the nanoparticles. The PEGylation process was designed to enhance the colloidal stability and biocompatibility of the nanoparticles.

2.2 Scanning Electron Microscopy Analysis

SEM analysis was conducted to characterize the morphology of the MSNs. The samples were prepared by dispersing the nanoparticles in ethanol, followed by deposition on a conductive substrate. After drying, the samples were coated with a thin layer of gold to improve conductivity. The SEM images were obtained using an electron microscope, with magnifications sufficient to observe the surface morphology and size distribution of the nanoparticles.

2.3 Fourier Transform Infrared Spectroscopy Analysis

FTIR analysis was performed to determine the PEGylation of MSNs on the surface. The samples were prepared by mixing 2 mg of the dried particles with 200 mg of dry potassium bromide (KBr). After grinding the mixture to a fine, homogeneous powder, a transparent pellet using a hydraulic press was made to place it in the FTIR spectrometer sample holder. Then the spectra were recorded over a range of 4000-400 cm^{-1}, ensuring the resolution is set to 4 cm^{-1}.

2.4 Zeta Potential Measurement

Zeta potential measurements were carried out to evaluate the surface charge of MSNs and PEG-MSNs in aqueous suspension. The nanoparticles were dispersed in deionized water, and the zeta potential was measured using a zeta potential analyzer. The measurements were conducted at room temperature, and the results were averaged over multiple runs to ensure accuracy.

2.5 Brunauer-Emmett-Teller Analysis

BET analysis was performed to determine the specific surface area, pore volume, and pore size distribution of MSNs and PEG-MSNs. The samples were degassed under vacuum at 125°C to remove adsorbed gases and moisture. Nitrogen adsorption-desorption isotherms were obtained at liquid nitrogen temperature, and the data were analyzed using the BET method to calculate the surface area and pore properties.

2.6 Drug Loading and Release Study

1 mL of 0.1 mg/mL Doxorubicin hydrochloride (DOX) was loaded onto 5 mg MSNs and PEG-MSNs separately by incubating the nanoparticles in the DOX solution under gentle stirring. The drug loading was performed at room temperature, and the DOX-loaded nanoparticles were collected by centrifugation, followed by washing to remove excess DOX.

The release of DOX from the nanoparticles was studied in phosphate-buffered saline (PBS) at 7.4 pH condition. The DOX-loaded MSNs and PEG-MSNs were dispersed in PBS and incubated at 37°C under gentle agitation. At predetermined time intervals, samples were withdrawn, centrifuged, and the supernatant was analyzed for DOX content using UV-Vis spectroscopy. The cumulative release percentage was calculated based on the initial drug loading and the amount of DOX released into the solution.

This comprehensive methodology outlines the synthesis, characterization, and drug release studies of MSNs and PEG-MSNs, providing a detailed understanding of their structural and functional properties.

3. Results and Discussion

3.1 SEM Analysis

The scanning electron microscopy images **in figure 1** depict mesoporous silica nanoparticles with a well-defined spherical morphology. The nanoparticles exhibit a range of sizes, generally clustering together, which is indicative of a uniform particle distribution. The surface of the particles appears smooth, suggesting a high-quality synthesis process with minimal aggregation. The scale bar at the bottom left of the image represents 200 nm, providing a reference for the particle dimensions, which predominantly fall within the nanoscale range. The image highlights the uniformity and consistency in size and shape, essential characteristics for applications in drug delivery systems.

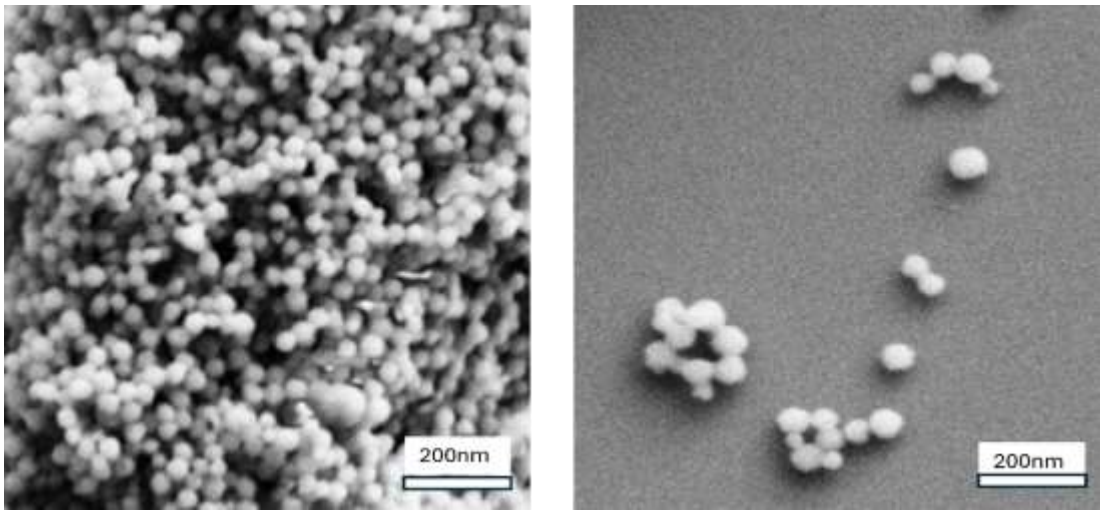

Figure 1: Scanning electron microscopy images of mesoporous silica nanoparticles

3.2 FTIR Analysis

Figure 2 illustrates the FTIR spectra showing the characteristic absorption bands for mesoporous silica nanoparticles and PEGylated mesoporous silica nanoparticles. In both spectra, prominent peaks are observed around 1080, 800, and 460 cm^{-1} correspond to the asymmetric stretching, symmetric stretching, and bending vibrations of Si-O-Si bonds, respectively, which are typical for silica-based materials. In the PEGylated MSNs spectrum, additional peaks are observed around 2870 cm^{-1} and 1340 cm^{-1}, which correspond to the C-H stretching and C-H bending vibrations of the PEG moiety, indicating successful PEGylation. The broad absorption band around 3400 cm^{-1} is associated with the O-H stretching vibration, likely from surface hydroxyl groups or adsorbed water which is less in PEG-MSNs due to PEGylation. However, the PEGylation process does not significantly alter the silica network structure, as evidenced by the persistence of the Si-O-Si bands, but introduces new peaks attributable to the PEG chains, confirming the successful functionalization of the MSNs.

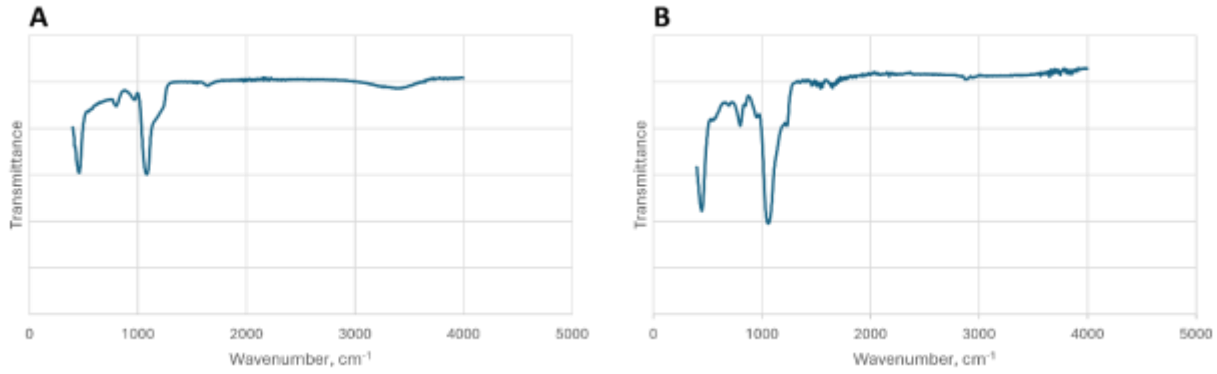

Figure 2: FTIR spectra of A) mesoporous silica nanoparticles and B) PEGylated mesoporous silica nanoparticles

3.3 Zeta Potential Measurements

Figure 3 displays the zeta potential measurements for mesoporous silica nanoparticles and PEGylated mesoporous silica nanoparticles. The zeta potential is a measure of the surface charge of nanoparticles in a colloidal system and is represented in millivolts (mV) on the vertical axis. The graph shows that MSNs has a negative zeta potential of approximately -20 mV, indicating a negatively charged surface, which is typical for silica nanoparticles due to the presence of silanol groups. In contrast, PEG-MSN exhibits a positive zeta potential of around +10 mV, suggesting that PEGylation alters the surface characteristics, potentially by shielding the negative charges or introducing positive charges. This shift from negative to positive zeta potential due to PEGylation will introduce more colloidal stability and reduced agglomeration in biological environments, which can be advantageous for drug delivery applications.

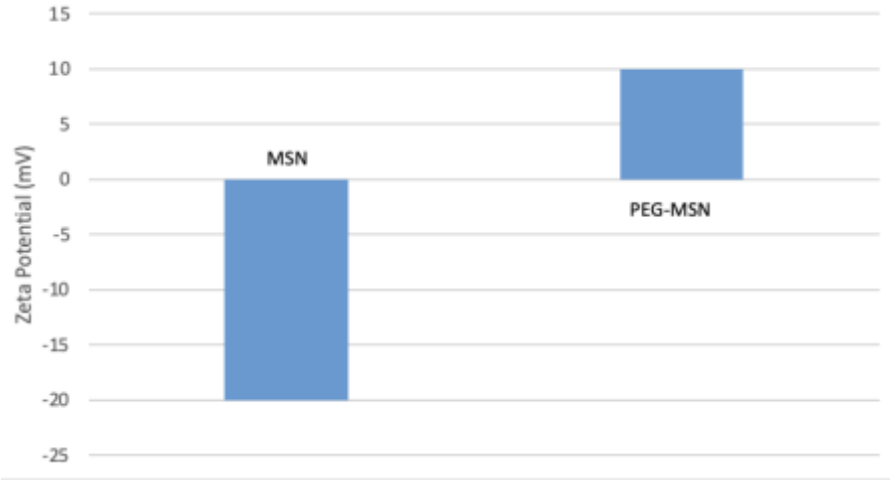

Fig 3: Zeta potential measurements for MSNs and PEG-MSNs

3.4 BET Analysis

Parameter	MSN	PEG-MSN
BET Surface Area (m^2/g)	782±6.5	651±5.2
Pore Volume (cc/g)	0.80±0.005	0.75±0.003
Pore Size (nm)	3.5±0.02	2.5±0.01

Table 1: BET data table for MSNs and PEG-MSNs

The BET data table for mesoporous silica nanoparticles and PEGylated mesoporous silica nanoparticles highlights key surface and porosity characteristics. The BET surface area, a measure of the total surface area per unit mass, is higher for MSNs at 782 m^2/g compared to 651 m^2/g for PEG-MSNs, indicating that MSNs has a more extensive surface area available for interactions. The pore volume, which represents the total volume of pores per unit mass, is slightly higher in MSNs (0.80 cc/g) than in PEG-MSNs (0.75 cc/g). This slight reduction in pore volume after PEGylation suggests a partial filling or blockage of pores by the PEG chains. Furthermore, the pore size is reduced from 3.5 nm in MSNs to 2.5 nm in PEG-MSNs, indicating that PEGylation affects the internal pore structure, potentially through the coating of the internal surfaces or the narrowing of pore entrances. These changes are consistent with the expected modifications introduced by PEGylation, which can influence the material's surface chemistry, interaction with molecules, and overall porosity.

3.5 In Vitro Drug Release Profile

Figure 4 illustrates the drug release profile of doxorubicin from mesoporous silica nanoparticles and PEGylated mesoporous silica nanoparticles over a 24 h. The cumulative release percentage of DOX is plotted against time (hours). The graph shows that MSNs has a higher drug release rate, reaching approximately 60% cumulative release by the end of the 24 h period, while PEG-MSN achieves around 50% release. Both release profiles exhibit an initial burst release within the first few hours, followed by a slower, sustained release phase. The lower release rate from PEG-MSN can be attributed to PEGylation, which may hinder drug diffusion by creating a steric barrier or altering the hydrophilicity of the nanoparticle surface. This controlled release profile is crucial for ensuring a steady delivery of the drug over time, potentially enhancing therapeutic efficacy and reducing side effects.

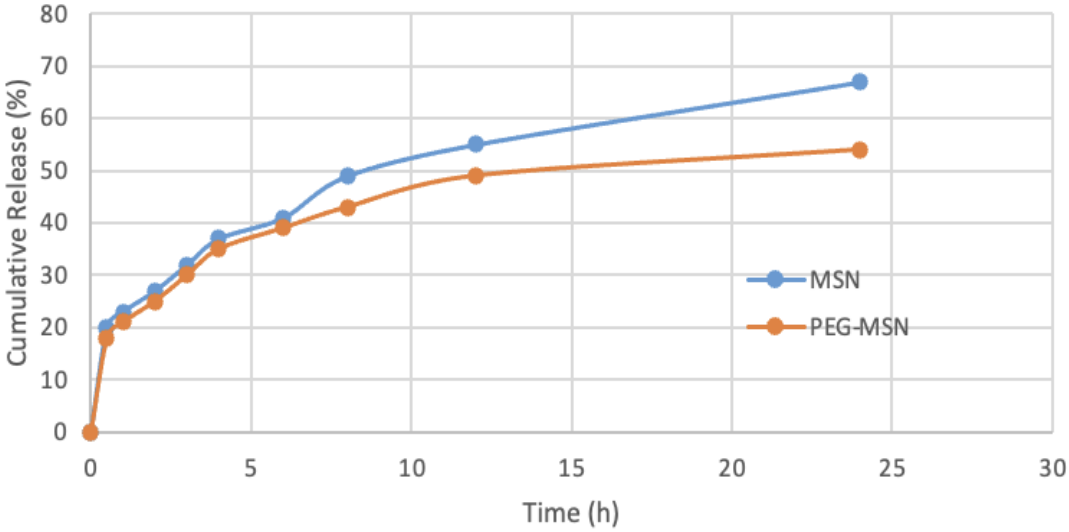

Figure 4: Drug release profile for MSNs and PEG-MSNs for 24h with DOX

4. Conclusion

This study successfully synthesized and characterized mesoporous silica nanoparticles and PEGylated mesoporous silica nanoparticles to evaluate their potential as drug delivery systems. Comprehensive analyses including SEM, FTIR, BET, and zeta potential measurements demonstrated the structural integrity, amorphous nature, and surface characteristics of the nanoparticles. The PEGylation process effectively modified the surface charge and porosity of the MSNs which will result in improved colloidal stability and biocompatibility for future animal studies. In vitro drug loading and release studies using doxorubicin hydrochloride revealed that MSNs exhibited a higher cumulative release compared to PEG-MSNs, with both showing an initial burst release followed by sustained release. The reduced release rate from PEG-MSNs indicates the influence of PEGylation in controlling drug diffusion, potentially enhancing therapeutic efficacy and reducing systemic toxicity. The findings from this study highlight the promise of PEG-MSNs in nanomedicine, particularly for applications requiring controlled and sustained drug delivery. Future work should explore in vivo evaluations and the potential for targeting specific tissues or cells to maximize therapeutic benefits.

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