Anticancer Drug Release System Based on Hollow Silica Nanocarriers Triggered by Tumor Cellular Microenvironments

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ABSTRACT: Targeted release of anticancer drugs to tumor sites has a pivotal role in clinical oncology. pH-responsive drug delivery systems, with an intelligent and targeted release of anticancer drugs in a controllable manner based on sensitivities to the weakly acidic environments of tumor cellular microenvironments, are desirable. Herein, the design of such a pH-responsive drug delivery system is detailed using in situ amino-functionalized hollow mesoporous silica nanoparticles as carriers. The drug release behavior of the pH-responsive delivery system was evaluated under an in vitro simulation of tumor cellular microenvironments. The drug delivery system has efficient drug loadings and targeted release. Zorubicin hydrochloride releasing percentage is almost up to 100% at a buffer pH of 5.0. The drug release systems described demonstrating great potential in anticancer therapy.

1. INTRODUCTION

Chemotherapy remains the leading approach for clinical treatments of cancer. However, the administration system lacks target selectivity, which can result in toxic side effects on normal tissues. Therefore, the accurate target release of the anticancer drug to the tumor site in a controlled manner, which can selectively and specifically recognize tumor cells, thus minimizing damage to healthy cells, is crucial. pH-responsive delivery systems are stable under normal physiological conditions (pH 7.4); however, such systems decompose in a slightly acidic environment. Tumor tissues are well understood to have lower local extracellular pH values than that of blood and normal tissue (pH 7.4), with further drops in the pH values inside the cells, especially in Golgi apparatus (pH 6.4), endosomes (pH 5.5−6.0), and lysosomes (pH 4.5−5.0). Typically, the weakly acidic microenvironments of the tumor cells can be used as drug release stimuli for pH-sensitive drug delivery systems.

Mesoporous silica demonstrates efficient carrier properties as components of drug delivery systems, owing to the unique mesoporous structures and high specific surface areas. A pH-responsive drug delivery system using mesoporous silica as a carrier was proposed. However, the solid center of the dense mesoporous silica restricts access to drug molecules, which limits the specific-drug-loading capacity. Furthermore, although silica nanoparticles are considered degradable, the degradation rate may be negatively impacted owing to the dense silicate network. Therefore, to maximize the drug-loading capacity and to reduce the dosage-dependent biosafety issues related to silica, the pH-responsive drug delivery system using hollow silica as a carrier attracts more and more attention. Hollow mesoporous silica nanoparticles (HMSNs), which present large inner cavities and low densities, is considered to be a more effective carrier. However, the intrinsic inert inorganic −Si−O−Si− framework results in pure siliceous hollow materials lacking the effective number of drug-bonding sites. Therefore, structure modification is essential to improving drug loading and construct a pH-responsive drug delivery system. The tedious modification and manipulation processes required to design hollow silica carriers are critical obstacles to commercialize such pH-responsive drug delivery systems.

Herein, a strategy to construct a feasible pH-responsive drug delivery system based on in situ amino-functionalized hollow mesoporous silica nanoparticles (HMSNs-NH2) was reported. The HMSNs-NH2 was used as a nanocarrier for successively hosting metal ions and drug molecules based on the coordination bonding of metal ions and organic functional groups. The cleavage of the coordination bonding in response to tumor cellular weakly acidic microenvironments (pH 5.0−6.4) gives rise to a significant release of drug molecules. The
proposed drug delivery system has efficient drug-loading sites and pH-responsive target release, which therefore demonstrate potential in anticancer therapy applications.

2. RESULTS AND DISCUSSION

Herein, hollow mesoporous silica nanoparticles (HMSNs) were synthesized using N-Lauroylsarcosine sodium (Sar-Na) as a template and 3-aminopropyltrimethoxysilane (APMS) as the co-structure directing agent (CSDA), through a $S^+N^-I^{-}$ route, where $S$ denotes the surfactant, $N$ denotes the CSDA, and $I$ denotes the inorganic silica precursors.\textsuperscript{28,29} Figure 1 present a schematic mechanism for the pH-responsive drug delivery system based on the coordination bonding in the mesochannels of HMSNs-NH$_2$.

DNR possesses amino and hydroxyl groups, which can be used as binding sites for transition-metal ions. A “host–metal–guest” architecture was formed by the coordination bonding between metal ions and functional groups in the HMSNs-NH$_3$ carriers and guest drug molecules. On the basis of this, high capacity drug loadings are expected to be realized through the “bridge” transition metal ion between the host carriers and the guest drug molecules. The schematic mechanism for the pH-responsive drug delivery system is presented in Figure 2. First, the loading of Cu$^{2+}$ ions into the amino-functionalized mesochannels within the shell of HMSNs-NH$_3$ was undertaken to form “host–metal” coordination bonds. Thereafter, the DNR molecules were coordinated to the unsaturated Cu$^{2+}$ ions in the phosphate buffer at pH 7.4 to form host–metal–guest coordination bond architectures, denoted as HMSNs-NH$_3$-Cu$^{2+}$-DNR. The total DNR-loading capacity in the HMSNs-NH$_3$-Cu$^{2+}$-DNR coordination bond architectures was measured to be 91.8 mg/g (as shown in Table S1).

SEM image shows that the HMSNs-NH$_3$-Cu$^{2+}$-DNR sample was composed of nanospherical particles and the particle diameters were mainly concentrated at 100–150 nm (as shown in Figure 3). No significant difference was observed in particle sizes of the samples before and after drug loading. The TEM image shows that the HMSNs-NH$_3$-Cu$^{2+}$-DNR sample has a complete hollow structure. The result indicates that the drug-loading process did not destroy the hollow structure of the silica sample. In addition, it should be noted that the HMSNs-NH$_3$-Cu$^{2+}$-DNR sample shows a certain degree of particle aggregation, which may be due to the coordination between metal ions and drug molecules.

To further explore the constitution of HMSNs-NH$_3$-Cu$^{2+}$-DNR, the energy-dispersive X-ray spectroscopy (EDX) measurement was investigated. According to the EDX mapping of the designated area (Figure 3), Si and N elements were uniformly distributed within the particle of HMSNs-NH$_3$-Cu$^{2+}$-DNR. The Cu element appeared not only within the particle of HMSNs-NH$_3$-Cu$^{2+}$-DNR but also distributed throughout the field of vision. It may be due to the desorption of Cu ions from the surface of solid HMSNs-NH$_3$-Cu$^{2+}$-DNR particles by ultrasonic dispersion of the sample in an ethanol solution during the TEM sample preparation.

X-ray photoelectron spectroscopy (XPS) measurement was conducted to investigate the coordination bonding mechanism by monitoring the valence states of Cu. Figure 4 shows the Cu(2p$_{3/2}$) XPS spectra of HMSNs-NH$_3$, HMSNs-NH$_3$-Cu$^{2+}$, and HMSNs-NH$_3$-Cu$^{2+}$-DNR. Due to the absence of Cu$^{2+}$ ion...
adsorption, no characteristic peak of Cu element was observed for HMSNs-NH₂. It was notable that two peaks were observed at 933.5 and 935.0 eV, indicating that the Cu²⁺ ions were coordinated with amino on the HMSNs-NH₂ surface. For the HMSNs-NH₂-Cu²⁺-DNR sample, a peak centered at 933.5 eV and another peak centered at 934.3 eV were observed. When the guest drug molecules were absorbed on HMSNs-NH₂-Cu²⁺, the XPS peak at 935.0 eV was decreased and shifted, suggesting the formation of more coordination bonds of Cu²⁺. The results further proved the coordination between drug molecules and metal ions.

Metal ions and protons are Lewis acids and the organic ligand of HMSNs-NH₂ and DNR are Lewis bases. Metal ions and protons compete to combine with the ligand. Therefore, the release of drug molecules under the tumor cells’ inherent weakly acidic environment (pH 5.0−6.4) can be attributed to a breakup of the coordination bonds between metal ions and drug molecules. To evaluate the drug release behavior of the pH-responsive drug delivery systems herein, in vitro drug release experiments were performed by simulating tumor and normal tissue microenvironments. Release of DNR was undertaken in phosphate buffers as a function of decreasing pH (7.4, 6.4, 5.6, 5.0). The phosphate buffer having a pH of 7.4 is consistent with the pH of normal human body tissue, while phosphate buffers having pH values of 5.0−6.4 are close to the pH of the tumor cell microenvironments. Sampling was performed after the suspended host–metal–guest architectures oscillated for 1, 2, 4, 6, 8, 10, and 12 h in a phosphate buffer at 37 °C. The supernatants were recycled by centrifugation. The DNR loading and the respective release amount were measured by UV−vis spectrophotometry. The DNR exhibits six UV−vis characteristic peaks at 233, 252, 288, 478, 495, and 530 nm (Pharmacopeia 2010, second section). Herein, the absorbance, at the maximum absorption wavelength of 233 nm, was selected for subsequent analysis.

The UV−vis absorption curves of the suspended HMSNs-NH₂-Cu²⁺-DNR supernatants, after oscillating for 1 h, in a phosphate buffer of pH 5.0−7.4, are shown in Figure 5. All of the UV−vis absorption curves presented six UV−vis absorption peaks at 200−650 nm, which are completely characteristic of the expected UV−vis spectrum of the DNR. The experimental results indicate the DNR release from the host–metal–guest architecture-based pH-responsive drug delivery systems.

The release performances of HMSNs-NH₂-Cu²⁺-DNR under slightly acidic conditions (pH 5.0−6.4) are more significantly improved than that under the normal physiological condition (pH 7.4). The amount of DNR released increased twofold and threefold, respectively, when the responsive pH was reduced from 7.4 to 6.4 and 5.6. When the responsive pH was further reduced to 5.0, the DNR amount released increased fourfold. The continuous increasing trend of the DNR-release amount is proportional to pH reduction. The experimental results support that the host–metal–guest architectures decompose in response to the external weakly acidic environment, which verified the feasibility of the pH-responsive anticancer drug release system. Absorption curves of the supernatants, where no discernible difference is observed when the suspended HMSNs-NH₂-Cu²⁺-DNR architecture oscillated for 12 h (as shown in Figure S1), are compared with the absorption curves of the respective supernatants after oscillation for 1 h. Furthermore, the drug release behavior followed the same principle that the amount of drug released increases as a function of decreased phosphate buffer solution pH.

Figure 3. (a) SEM image, (b) TEM image, and (c) energy-dispersive X-ray spectroscopy (EDX) mapping of HMSNs-NH₂-Cu²⁺-DNR.

Figure 4. High-resolution XPS spectra of Cu 2p₃/₂ in different samples.

Figure 5. Ultraviolet-visible (UV−vis) absorption curves of the supernatants of HMSNs-NH₂-Cu²⁺-zorubicin hydrochloride (DNR) after oscillating under suspension for 1 h in a phosphate buffer. From top to bottom, the pH of the phosphate buffer is 5.0, 5.6, 6.4, and 7.4, respectively.
The DNR-release percentage profiles, the drug release/loading ratio of the suspended HMSNs-NH$_2$-Cu$^{2+}$-DNR architecture, after oscillation in a phosphate buffer as a function of time, are presented in Figure 6. The drug release percentage profiles followed the same pattern regardless of the buffer solution pH. Clearly, the pH of the buffer solution significantly influences the release percentage profiles of the DNR loading. The release percentages of DNR increase as a function of decreased phosphate buffer pH. Fifty percentage and 75% of DNR were released from the HMSNs-NH$_2$-Cu$^{2+}$-DNR architecture within 1 h in the buffer solutions of pH 6.4 and 5.6, respectively. Furthermore, the release percentages almost reach 100% at a buffer pH of 5.0, which is significantly greater than that at a buffer solution pH of 7.4. These findings demonstrate that the release performances, under weakly acidic conditions, are significantly enhanced when compared with the release performances under normal physiological conditions (pH 7.4). The strongly pH-dependent release properties satisfy the conditions of intelligent tumor cell identification and provide a desirable platform for a targeted release of anticancer drugs under slightly acidic tumor microenvironments. The feasible pH-responsive drug release system will enhance the therapeutic anticancer effect, as well as minimize the potential damage to normal body tissues.

Herein, other metal ions were studied to act as the bridge to construct host–metal–guest coordination bonding architectures. Here, Zn$^{2+}$ was chosen because zinc is a necessary element for human body metabolism. Figure 7 shows the UV–vis absorption curves of the suspended HMSNs-NH$_2$-Zn$^{2+}$-DNR architecture supernatants, after oscillation for 1 h in a phosphate buffer. From top to bottom, the pH of the phosphate buffer is 5.0, 5.6, 6.4, and 7.4.

Figure 7. UV–vis absorption curves of the suspended HMSNs-NH$_2$-Zn$^{2+}$-DNR coordination bond architecture supernatants, when oscillating for 1 h in a phosphate buffer. From top to bottom, the pH of the phosphate buffer is 5.0, 5.6, 6.4, and 7.4, respectively.

3. CONCLUSIONS

In summary, a pH-responsive drug delivery system based on the in situ amino-functionalized HMSNs as carriers was constructed. The drug delivery system has efficient drug loadings and pH-responsive targeted release. In the HMSNs-NH$_2$-Cu$^{2+}$-DNR architecture, the DNR-loading capacity can reach 91.8 mg/g carrier. The drug was successfully released in a weakly acidic microenvironment (pH 5.0–6.4) of the tumor cells, and the DNR-release percentage is almost 100% at a buffer pH of 5.0. Additionally, other metal ions, such as Zn$^{2+}$, can also be used as a metal constituent in the pH-responsive drug delivery system. The current work provides a strategy to construct feasible pH-responsive drug delivery systems, which demonstrate significant potential in anticancer therapy applications.

4. EXPERIMENTAL SECTION

4.1. Materials. All chemicals were commercially available and used as received. N-Lauroylsarcosine sodium (Sar-Na), 3-amino propyltrimethoxysilane (APMS), tetraethoxysilane (TEOS), and zorubicin hydrochloride (DNR) were purchased from Aladdin Chemical Company, China. Hydrochloric acid (HCl, 36–38%), anhydrous ethanol (C$_2$H$_5$OH), acetonitrile (CH$_3$CN), sodium dihydrogen phosphate (Na$_2$HPO$_4$), and disodium hydrogen phosphate (Na$_2$HPO$_4$) were obtained from Tianjin Chemical Reagent Company, China. Copper chloride dihydrate (CuCl$_2$·2H$_2$O) was obtained from Shanghai Macklin Biochemical Reagent Company, China. Zinc nitrate hexahydrate (Zn(NO$_3$)$_2$·6H$_2$O) was obtained from Sinopharm, China.

4.2. Synthesis of Host-Metal Coordination Product. Stock solutions of Cu$^{2+}$ and Zn$^{2+}$ (0.05 mol/L) were prepared by dissolving CuCl$_2$·2H$_2$O and Zn(NO$_3$)$_2$·6H$_2$O in ultrapure water, respectively. Amino-functionalized hollow mesoporous silica nanoparticles (0.10 g) were dispersed in 10.0 mL of Cu$^{2+}$ stock solution, and the mixture was stirred for 6 h at ambient temperature. For Zn$^{2+}$, the mixture was stirred for 10 h at 80 °C. The host-metal coordination product was recovered by centrifugation, washed 10 times with ultrapure water, and dried overnight at 40 °C.

4.3. Synthesis of Host–Metal–Guest Coordination Product. The stock solution of DNR (1.77 mmol/L) was prepared by dissolving DNR in phosphate buffer (pH 7.4). Fifty milligrams of the host-metal coordination product was dispersed in 10.0 mL of DNR stock solution and stirred for 8 h at ambient temperature. For Zn$^{2+}$, the mixture was stirred for 6 h at 37 °C. After that, the host–metal–guest coordination product was recovered by centrifugation, washed 10 times with phosphate buffer (pH 7.4), and dried overnight at 40 °C.

4.4. DNR Release from the pH-Responsive Drug Delivery System. In a typical drug release experiment, 6.0 mg of the host–metal coordination product was dispersed in 10.0 mL of phosphate buffer (pH 7.4), and the mixture was used as the model drug delivery system.
mg of the host–metal–guest coordination product was suspended by oscillating in 25.0 mL of a phosphate-buffered solution (for example, pH 5.0) and was undertaken using a new type of micro-oscillator in a mold incubator (37 °C). The samples were taken as a function of the suspension oscillation time (1, 2, 4, 6, 8, 10, and 12 h). After a 1.0 mL aliquot of the solution was withdrawn, a fresh phosphate-buffered solution (1.0 mL), with the corresponding pH, was added. The supernatants were retained after centrifugation. The release process in the phosphate-buffered solutions as a function of pH was the same as above. The amount of DNR released was observed absorbance values.

4.5. Characterization. The morphologies of the obtained samples were observed by scanning electron microscopy (SEM, Quanta 200) and transmission electron microscopy (TEM, Hitachi HT7700). The distribution of the elements of the obtained samples were observed by transmission electron microscopy (TEM, Talos 200X). The samples for TEM measurements were prepared by dropping an ethanol suspension of the powder particles onto a carbon film-coated copper grid. The oxidation states were determined by X-ray photoelectron spectroscopy (XPS, Thermo ESCALAB 250XI). Each supernatant was tested twice consecutively, with similar observed absorbance values.

**ASSOCIATED CONTENT**

1. Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c05032.

Synthesis of the amino-functionalized hollow mesoporous silica nanoparticles; measurements of the total DNR loading; structural parameters of the extracted HMSNs and the corresponding drug-loading capacity; ultraviolet–visible (UV–vis) absorption curves of the supernatants of HMSNs-H$_2$Cu$_2$-zorubicin hydrochloride (DNR) after oscillating under suspension for 12 h in a phosphate buffer; from top to bottom, the pH of the phosphate buffer is 5.0, 5.6, 6.4, and 7.4, respectively (PDF)

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**ACKNOWLEDGMENTS**

This research was funded by the National Natural Science Foundation of China (No. 22074029 and No. 51802082), Training Plan for University’s Young Backbone Teachers of Henan Province (No. 2019GGJS170), Program for Science & Technology Innovation Talents in Universities of Henan Province (No. 21HATT016), Science and Technology Research Project of Henan Provincial Science and Technology Department (No. 142102210047), The New Century Excellent Talent Support Program for Colleges and Universities in Henan Province (No. 2006HANCET-01), and Key Scientific Research Project of Education Department of Henan Province (No. 17A150027).

The authors declare no competing financial interest.
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