Facile synthesis of redox-responsive paclitaxel drug release platform using metal-organic frameworks (ZIF-8) for gastric cancer treatment

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Abstract

This paper investigated the dual-role of cystamine as a surface modification linker and stimuli-responsive material, and simplify redox-responsive drug delivery system synthesis. ZIF-8 is used as the drug delivery vehicle (due to its exceptional biocompatibility), cystamine is used as the linker and redox-sensitive material, and paclitaxel (PTX) is selected as the anti-tumor drug. Redox-responsive paclitaxel drug delivery platform based on metal-organic frameworks (MOFs) was synthesized by using ZIF-8 as the drug delivery vehicle, and cystamine as the linker and redox-sensitive material. The morphology of ZIF-8 was determined by the Transmitting Electron Microscope (TEM), and the crystal structure was determined by x-ray diffraction (XRD). The surface modification of ZIF-8 was studied by the Fourier-transform infrared (FT-IR) spectroscopy. The Brunauer–Emmett–Teller (BET) study indicated that surface modification has little impact on the specific surface area and pore size distribution of ZIF-8. The drug release of ZIF-8/cystamine/paclitaxel was studied under different pH and glutathione concentrations. The cytotoxicity was investigated with human gastric cancer cells. Higher glutathione (GSH) concentration and lower pH were favorable to the release of paclitaxel from ZIF-8/cystamine/paclitaxel, and the drug release platform provided a higher tumor-killing effect than free paclitaxel solution.

1. Introduction

Cancer has been a significant threat to human health. Currently, chemotherapy is a widely used treatment for most cancers [1–5]. However, the disadvantages of chemotherapy, such as poor targeting to tumor cells, side effects to healthy tissues and organs, and low stability, have limited its performance for cancer treatment [6]. To solve this problem, medical researchers have developed various drug delivery systems (DDSs), to encapsulate chemotherapy drugs for accurate delivery to tumor cells, and precise release of the drugs [7–10]. Because of the enhanced permeability and retention (EPR) effect, the chemotherapy drugs could have higher concentration at tumor sites than healthy tissues [11–14]. For more precise drug delivery, stimuli-responsive DDSs have been developed to increase the release of the anti-tumor drugs at the tumor sites by an external stimulus (such as light, heat, or ultrasonication) or internal stimuli (such as pH, enzyme, or redox reaction) [15]. Thanks to the low pH, and high glutathione (GSH) concentration at the tumor sites, this environment could be used to speed up the drug release at the tumor site by the smart design of DDSs [15–17].

Metal-organic frameworks (MOFs) are a category of material with metal ions as nodes, bridged by organic ligands within the frameworks. Due to their high chemical resistance, physical stability, large surface area, and various surface active sites, MOFs have been widely used for catalysis, dye encapsulation, environment protection, and H2 production [18–22]. As a novel material, the benefits of MOFs could also be applied for drug delivery. Firstly, the size could be tuned at the nanoscale, which provides a large surface area for drug loading and accessible transportation through cell membranes [23–26]. Secondly, the toxicity of the materials could be minimized by selecting biocompatible precursors [27]. Besides, MOFs could be further externally modified by...
various stimuli-responsive composites for smart drug delivery. For example, ZIF-8 has been used as drug delivery carriers to deliver anti-tumor drugs to tumor sites, and the drug release was triggered by the acidic environment of the tumor cells [28]. Besides, Abdelhamid has also applied ZIF-8 for gene delivery [29, 30]. UiO-type MOFs have been used to deliver the drugs to the tumor side, and the drug release was achieved by light stimuli [31].

Generally, the stimuli-responsive drug delivery system includes four parts, including the drug delivery vehicle, surface modification linker, stimuli-responsive material, and drug [32–35]. The surface modification linker is working as a bridge to conjugate the rest two components to the drug delivery vehicle surface. For example, Zhang et al synthesized LA-AuNR/ZIF-8@DOX (LA: lactobionic acid; AuNR: gold nanorod) for drug delivery [36]. In this system, ZIF-8 is the drug delivery vehicle, Au NR is the stimuli-responsive material, LA is the surface modification linker, and the DOX is the model drug. Due to the various components in the drug delivery system, the synthesis procedures become complicated and less cost-effective. Therefore, it has been a great interest and desire to develop a simple synthesis process for the drug delivery system. In the paper, we combined the surface modification linker and stimuli-responsive material into one material. Specifically, cystamine, which includes amine functional groups (–NH₂) at both ends of its molecular chain, and disulfide bond (S–S) in the middle of the chain, plays dual roles of a linker and responding to redox stimuli [37]. Amine functional groups have been widely used in the previous study for surface functionalization to link the anti-tumor drug to the surface of the drug delivery vehicle [38]. Meanwhile, the disulfide bond could be cleaved by GSH, so that the release of the drug could be achieved [39]. In this paper, ZIF-8 is used as the drug delivery vehicle (due to its exceptional biocompatibility), cystamine is used as the linker and redox-sensitive material, and paclitaxel (PTX) is selected as the anti-tumor drug. The drug release of ZIF-8/cystamine/paclitaxel is studied under different pH and GSH concentrations, and its toxicity is investigated with AGS human gastric cancer cells.

2. Material and methods

2.1. ZIF-8 metal framework fabrication

ZIF-8 was synthesized by a wet process. Briefly, Zn(NO₃)₂ · 6H₂O (Sigma Aldrich, 99%, 1 g, 3.3 mmol) and 2-methylimidazole (VWR, 99.5%, 10 g) were mixed in 50 ml DI water with magnetic stirring for 6 h at room temperature. The product was separated with a high-speed centrifuge, cleaned with DI water for 5 times.

2.2. Cystamine coated ZIF-8 fabrication

To functionalize the surface of ZIF-8, cystamine (CA) was coated. Briefly, ZIF-8 (50 mg) was dispersed in tris hydrochloride (Sigma Aldrich, >99%, NH₂C(CH₂OH)₃·HCl, 10 mmol l⁻¹, 100 ml) with the aid of ultrasonication for 10 min. Then, cystamine (Sigma Aldrich, 96%, CH₃H₂N₂S₂, 20 mg) was introduced into the dispersion with ultrasonication for another 4 h. The cystamine coated ZIF-8 (ZIF-8/CA) was separated with centrifuge and cleaned with DI water for 3 times.

2.3. PTX loading on ZIF-8/CA

Paclitaxel (PTX) was loaded to ZIF-9/CA with the following procedures. PTX stock solution was prepared in ethanol, and ZIF-8/CA was prepared in chloroform. The PTX solution (5 mmol l⁻¹, 2 ml⁻¹) and ZIF-8/CA dispersion (10 mg ml⁻¹, 5 ml⁻¹) were mixed in a vial and ultrasonicated for 1 h. After that, the particles were collected by high-speed centrifuge and cleaned with DI water to remove the unbound PTX. The PTX loaded sample was noted as ZIF-8/CA@PTX.

2.4. Materials characterization

The as-synthesized particles were characterized by Transmitting Electron Microscope (TEM, Hitachi HT8500, accelerating voltage: 200 kV) for surface morphology and x-ray Diffraction (XRD, Bruker D8, with irradiation source of Copper kα = 0.154 nm, operating at 40 kV and 30 mA) for crystal structure. The specific surface area was determined by a Brunauer–Emmett–Teller (BET) method on a surface analyzer (3P, Mesos 400) through liquid N₂ adsorption/desorption isotherms at 77 K. Before that, the sample (0.5 g) was introduced into the apparatus for degassing (Vacuum: ~5 mm Hg; temperature: 383 K) for 10 h to remove volatile surface residues. The pore size distribution of the particles was studied by using the N₂ desorption data through Barrett-Joyner-Halenda (BJH) method. The surface functional groups were studied by FT-IR (Newport, 80351) spectroscopy, and the thermal analysis was conducted by a thermogravimetric analyzer (TGA, PerkinElmer, TGA 8000). The UV–vis spectroscopy was determined by a spectrophotometer (PerkinElmer, Lambda XLS). The Zeta potential was determined by a Zeta potential analyzer (Malvern Panalytical, Zetasizer Ultra).
2.5. Drug release testing
To study the PTX release behavior, ZIF-8/CA@PTX (5 mg) was dispersed in a buffer solution (1 ml) with controlled pH, which was then transferred into a dialysis bag with molecular weight cutoff (MWCO) of 3500 Da, which was immersed in the corresponding buffer solution (100 ml) with magnetic stirring at 37 °C. The PTX concentration in the release medium was monitored by UV–vis spectrometer (ThermoFisher, GENESYS 40) at defined time intervals, and fresh medium was added at each time point.

2.6. Cytotoxicity testing
The cytotoxicity of ZIF-8, ZIF-8/CA, free PTX solution, and ZIF-8/CA@PTX was studied by MTT assay with AGS human gastric cancer cells. MTT refers to a yellow dye of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide, which could be reduced by the cellular enzyme into a blue product. Briefly, the cells were seeded within a 96-well plate with a density of ∼1 × 10^4 cells/well for 24 h under 37 °C and 5% of CO₂ environment. After that, the cell medium was replaced with different concentrations of ZIF-8, ZIF-8/CA, free PTX, and ZIF-8/CA@PTX dispersion. For free PTX, it was dissolved in ethanol and Tween 80 (1:1). The incubation time was 48 h, and the cell viability was studied by Glomax 96-well luminometer (Promega, Wisconsin, USA).

To further study the cell survival rate, the above-cultured cells were further stained with calcein-AM (2.0 μM) and Propidium Iodide (PI, 2 μM) for live and dead cells, respectively. The corresponding conformal images were obtained by a fluorescence microscope (Olympus, BX 2000).

3. Results and discussion
The TEM images of as-synthesized ZIF-8 are presented in figures 1(a), and (b). It can be seen that the particles are hexagonal, which is consistent with the previous report [40]. ZIF-8 has a ZnN₄ tetrahedra unit combined with imidazole linkers. The ZIF-8 has a porous sodalite cage structure with an aperture diameter of 0.34 nm [41]. The crystal structure of ZIF-8 is provided in figure 1(c). The hydrogen atoms are not shown in the structure. The black, blue, and green balls refer to carbon, zinc, and nitrogen atoms, respectively. After the surface functionalization with cystamine (CA), the corresponding TEM images of ZIF-8/CA are shown in figures 1(d), and (e). It is observed that the particle surface becomes rough after surface modification, and the particles still maintain similar hexagonal shape compared with pure ZIF-8. As a reference, the molecular structure of CA is presented in figure 1(f), and the amine groups (two ends) and disulfide bond (in the middle) are presented.

The powder XRD patterns of ZIF-8 and ZIF-8/CA are represented in figure 2(a). For as-synthesized ZIF-8, the diffraction peaks are in agreement with the JCPDS card (No. 00-062-1030), indicating the high purity of the
crystallization. After the surface functionalization, all the characteristic peaks are still maintained, and little difference in the diffraction patterns is presented, attributing to the amorphous state of the organic coating material. The specific surface area is an essential evaluation for drug carriers. A larger one is always favorable so that more active sites are available for drug loading. The specific surface areas of ZIF-8 before and after CA functionalization are determined by the nitrogen adsorption–desorption isotherms, and the results are presented in figure 2(b). The specific surface areas are 258.7 m² g⁻¹ and 246.1 m² g⁻¹ for ZIF-8 and ZIF-8/CA, respectively. The corresponding pore size distributions for both samples are presented in figure 2(c). After the surface functionalization, the peak pore size is slightly shifted from 15.1 nm to 13.3 nm. The reduction in both specific surface area and pore size after surface functionalization could be ascribed to that CA partially blocks the holes within ZIF-8.

FT-IR spectroscopy is used to inspect the surface modification of ZIF-8, and the corresponding results are presented in figure 3(a). For the as-synthesized ZIF-8, two characteristic peaks at 3135 and 2929 cm⁻¹ are due to the stretching vibration of aromatic and aliphatic C-H, respectively [42]. After the surface modification, besides the absorption peaks from ZIF-8, two new peaks at 3368 and 3487 cm⁻¹ are detected, which are attributed to the vibration of N-H groups within CA [43], indicating that CA is successfully coated on ZIF-8 surface.

Zeta potential is used to evaluate the magnitude of repulsion or attraction between the particles [44]. The Zeta potential has an enormous impact on the stability of the particles. The Zeta potentials of ZIF-8 (12.5 mV) and ZIF-8/CA (47.3 mV) are presented in figure 3(b). It is observed that, after CA coating, the Zeta potential is increased. Generally, nanoparticles tend to agglomerate, because the attractive force between the nanoparticles exceeds the repulsion force, displaying a small Zeta potential [25]. While a surface coating could reduce the interaction, therefore, preventing the agglomeration, displaying an increased Zeta potential. The increased Zeta potential and decreased agglomeration are beneficial to drug delivery due to a better dispersion of the carriers.

Moreover, TGA in figure 3(c) is used to investigate the surface functionalization and drug loading. For ZIF-8, ZIF-8/CA, and ZIF-8/CA@PTA, a major weight loss happens at ~275 °C, due to the decomposition of the MOF at elevated temperature. Below 400 °C, the weight loss order follows ZIF-8/CA@PTA > ZIF-8/CA > ZIF-8, which could be attributed to more attachment of organic volatiles in ZIF-8/CA@PTA and ZIF-8/CA than pure ZIF-8. Specifically, the weight loss is 25.1%, 44.6%, and 57.3% at 400 °C, for ZIF-8, ZIF-8/CA, and ZIF-8/CA@PTA, respectively.

Direct observation of PTX loading on ZIF-8/CA could be studied by the UV–vis spectra in figure 3(d). As a reference, pure PTX is also presented. Compared to the pure PTX with a significant peak at ~230 nm, a similar peak is observed from ZIF-8/CA@PTX, while this peak is absent from ZIF-8/CA, indicating that PTX has been successfully loaded to ZIF-8/CA.

To investigate the redox-responsive drug release from ZIF-8/CA@PTX, the in vitro drug release profiles are presented under different concentrations of GSH. It can be seen in figure 4(a) that a higher concentration of GSH is favorable to increase the PTX release. For example, when the GSH concentration is increased from 0 mM to 15 mM, the cumulative PTX release is increased from 10.9% to 48.8%. This is because a higher concentration of GSH is beneficial to cleave the disulfide bond (S-S bond) within the linker of CA. Therefore, PTX drug release from the drug carrier is accelerated. When the GSH concentration is further increased from 15 mM to 20 mM, a negligible PTX release is observed. This could be due to that GSH has reached its cleaving limit under the environment.

Moreover, it is known that the tumor cell environment is more acidic (pH ~ 5.0–6.5) than healthy tissues (pH ~ 7.4). Therefore, the PTX release with GSH (15 mM) at different pH is investigated, and the result is presented in figure 4(b). It is observed that the acidic environment is more favorable for PTX release, indicating a higher responsive capacity at the tumor environment. For example, when the pH is decreased from 7.4 to 5.5,
the PTX cumulative release increased from 48.8% to 78.6%. As a comparison, the PTX cumulative release (%) reported in previous publications are summarized in table 1.

The cytotoxicity and biocompatibility of the composites are evaluated with AGS human gastric cancer cells. Firstly, cancer cells are cultured with different concentrations of ZIF-8 and ZIF-8/CA for 48 h, and the cell viability is counted and presented in figure 5(a). It can be seen that after 48 h, the cell viability is maintained at over 80%, indicating that both ZIF-8 and ZIF-8/CA have limited toxicity to the cells. The cells are further

Figure 3. (a), FT-IR spectra for ZIF-8 and ZIF-8/CA; (b), Zeta potentials for ZIF-8/CA, and ZIF-8/CA@PTX. (c), TGA curves for ZIF-8, ZIF-8/CA, and ZIF-8/CA@PTA; (d), UV–vis spectra for ZIF-8, ZIF-8/CA, and ZIF-8/CA@PTA;

Figure 4. (a). Drug release dynamics of ZIF-8/CA@PTA in PBS with different concentrations of GSH (pH = 7.4); (b). The cumulative release of PTX under different pH (GSH concentration: 15 mM).
cultured with different concentrations of PTX from free PTX solution and ZIF-8/CA@PTX for 48 h, and the cell viability is presented in figure 5(b). Firstly, it is observed that the cell viability is mostly dependent on the PTX concentration, and higher concentration results in lower cell viability. Moreover, it is also observed that ZIF-8/CA@PTX also has a higher tumor cell killing effect than free PTX, which could be attributed to two reasons. Firstly, the PTX is a hydrophobic, and it is hard to be involved in the cell metabolism, while the PTX released from ZIF-8/CA@PTX is attached with ammonium functional groups, which increases its hydrophilicity in the cell environment. Secondly, the PTX from ZIF-8/CA@PTX is released gradually, as shown in figure 4(b), instead of flooding from free PTX solution. The drug killing effect from ZIF-8/CA@PTX could be maintained for a longer them than the free PTX in the solution.

To further study the cancer cell killing effect of ZIF-8/CA@PTX, AGS human gastric cancer cells cultured 40 μg ml⁻¹ PTX from free PTX, and ZIF-8/CA@PTX are stained with calcein-AM and PI for live and dead cells, which are displayed green and red fluorescence, and the corresponding confocal images are shown in figures 5(c), and (d). When the cells are treated with free PTX, only a small amount of dead cells are observed, featured by red fluorescence. However, when the cells are treated with ZIF-8/CA@PTX, most of the cells display red fluorescence, indicating that most of the cells are killed. This image indicates that the ZIF-8/CA@PTX has presented a more significant therapeutic effect against tumor cells, and the results are also consistent with the cell viability presented in figure 5(b).

Table 1. The PTX cumulative release (%) compared with previous publications.

| No. | Drug delivery carrier | pH   | Cumulative release (%) | Drug | Release time | References       |
|-----|-----------------------|------|------------------------|------|--------------|------------------|
| 1   | CA-CDEP               | 5.0  | 52%                    | PTX  | 80 h         | [45]             |
| 2   | CS/PLGA               | 5.5  | 76%                    | PTX  | 48 h         | [46]             |
| 3   | RGD-PEG-Chol          | 5.5  | 58%                    | PTX  | 96 h         | [47]             |
| 4   | PEG-β-PLGA            | 5.0  | 78%                    | PTX  | 48 h         | [48]             |
| 5   | ZIF-8/CA              | 5.5  | 78%                    | PTX  | 48 h         | This research    |

Figure 5. (a). AGS human gastric cancer cell viability under different concentrations of ZIF-8 and ZIF-8/CA; (b). AGS human gastric cancer cell viability under different concentrations of PTX from free PTX and ZIF-8/CA@PTX; (c) and (d): confocal images of AGS human gastric cancer cells stained under free PTX and ZIF-8/CA@PTX treatment.
4. Conclusions

Redox responsive ZIF-8/CA@PTX composite was synthesized by using CA as both linker and redox stimuli, and ZIF-8 as the drug delivery vehicle. The FT-IR spectrum and UV–vis spectrum indicated that CA and PTX were successfully conjugated to the ZIF-8 surface. The drug release of ZIF-8/cystamine/paclitaxel was studied under different pH and GSH concentrations. The cytotoxicity was investigated with AGS human gastric cancer cells. The study showed that a higher GSH concentration and lower pH were favorable to the release of PTX. ZIF-8 based drug release platform could provide a higher tumor-killing effect than free PTX solution, which was confirmed by cytotoxicity study and cell stain technology.

Disclosure

The authors report no conflicts of interest in this work.

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