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Nanoassembles constructed from mesoporous silica nanoparticles and surface-coated multilayer polyelectrolytes for controlled drug delivery

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ABSTRACT

Carboxylated mesoporous silica nanoparticles (MSN-COOH), aminated MSN (MSN-NH_2) and hollow MSN (H-MSN), were preloaded with doxorubicin hydrochloride (DOX), and further surface-assembled with polyelectrolytes, such as polycations, 1,4-butanediamine (BDA) and 1,2-ethanediamine (EDA) modified linear or star-shaped polyglycerol methacrylate (PGOHMAs), and polyanion, poly(acrylic acid) (PAA) by layer-by-layer (LbL) self-assembly technique to obtain MSN-polyelectrolytes nanoparticles (MSNPENs). The loading capacity of MSNPENs based on negatively charged MSN-COOH is superior to that based on positively charged MSN-NH_2 owing to its electrostatic interaction with positively charged DOX. Meanwhile, H-MSN with hollow cavity and more free volume inside the nanoparticles also exhibited high loading capacity. Therefore, MSN-COOH and H-MSN were used to deliver DOX in a controlled release fashion. Loading process was characterized by dynamic light scattering (DLS), fourier transform infrared spectroscopy (FT-IR), thermo-gravimetric analysis (TGA), and X-ray diffraction spectroscopy (XRD). Nanoassembles constructed from star-shaped polymers exhibited better loading capacity and sustained release. Cytotoxicity assay revealed that MSNPENs were biocompatible and comparatively safe for drug delivery. *In vitro* release test showed that drug release accelerated at acidic condition but remained within MSNPENs at neutral pH values. These formulations show great potential for safe pH-responsive anti-cancer drug delivery.

1. Introduction

During the past decades, a series of nanoparticles have been employed for drug delivery applications [1], which include organic materials, i.e., liposomes, micelles, viruses, capsules and carbon nanomaterials, and inorganic nanoparticles, i.e., mesoporous silica nanoparticles (MSNs) and gold nanoparticles [2,3]. Currently, MSNs have drawn much attention as attractive candidates for drug delivery and biosensors [4–6], owing to their unique characteristics, such as high surface area-to-volume ratio allowing for drug adsorption, being free from various biochemical attacks and bioerosions, high loading capacity, sustained release profile, good thermal stability, etc. [7]. It is also well demonstrated that MSNs can be degraded in simulated body fluid and is truly biocompatible [8,9]. However, MSNs without appropriate surface functionalization, especially gating components, are unable to accomplish on demand drug release in a targeted and controlled manner [10].

MSNs possessing a high specific surface area and functional groups allow for effective surface functionalization, so that therapeutic agents and drugs can be easily integrated into their regular pores by supramolecular interactions such as hydrogen bonding and electrostatic interactions [11], with an enhanced loading capacity. In addition, hollow MSNs (H-MSNs) with penetrating mesoporous channels and hollow cavities exhibit a much higher drug loading capacity as compared with conventional MSNs and well-sustained release properties in drug storage and release [12]. During the past two decades, a series of control release systems based on MSNs have been designed and tested. One of the relevant research in the field of MSN-based nanocontainers focuses on the development of new strategies emphasizing on the on/off switching of their nanopore entrances for effective loading/storage of cargos with zero premature release and ideal controlled release effects [13–16]. Therapeutic agents trapped in their pores of MSNs gated by various entities, such as inorganic nanoparticles, organic molecules, biomacromolecules and supramolecular systems [17,18], can be released in response to a range of external stimuli

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including enzyme [19,20], redox [21–25], pH [26–39], competitive binding [40], light [15,41–44], and so on [45,46].

Layer-by-layer (LbL) self-assembly allows the creation of highly tunable, functional thin films with nanometer-level control over the structure, composition and properties, which has been widely used as a simple, yet versatile method for constructing functional nanostructures [47,48]. Notably, MSN-polyelectrolytes nanoparticles (MSNPENs) constructed from LbL deposition of oppositely charged polyelectrolytes on the outer surface of MSNs can provide an alternate approach for payload encapsulation [3]. The release of cargo molecules can be controlled by the permeability and structural stability of the outer polyelectrolyte multilayers [49]. Active materials could be loaded within porous nanoparticles, such as silica [50] and calcium carbonate [51] that can be subsequently LbL-coated [52]. Shi and co-workers [53] coated multilayers of poly(allylamine hydrochloride)s and sodium salts of poly(styrene sulfonate)s on the surface of ibuprofen-loaded MCM-41, where the release of payload was achieved under extremely acidic condition (pH = 1.4) and high ionic strength. These assembles combined the advantages of hard material (silica composition) and soft material (polyelectrolytes), endowing the nanoparticles fascinating new properties. However, to our best knowledge, there is no report on MSNPEN assemblies based on star-shaped polymers so far.

Based on our previous study, amino poly(glycerol methacrylate)s (PGOHMAs) and poly(acrylic acid) (PAA) are reactive, inexpensive, hydrophilic, biocompatible and hypotoxic [54]. Their pH-responsive and targeted release properties made them attractive candidates for drug delivery application. Amino PGOHMA/PAA LbL-coated silica nanoparticles have shown promising results as doxorubicin hydrochloride (DOX) carriers [55]. However, hydrofluoric acid has to be applied to etch the template. To simplify the procedure, avoid using the etching process and incorporating new entities for cargo storage, different MSNs, carboxylated mesoporous silica nanoparticles (MSN-COOH), aminated MSN (MSN-NH_2) and H-MSN, were used as templates for MSNPEN assembly and as reservoirs for drug storage and protection to result in MSNPEN1, MSNPEN2 and MSNPEN3, respectively. Herein, anti-cancer drug, DOX, was pre-loaded into the mesoporous interior of the MSNs or H-MSN, and then released along with the permeability of the outer LbL coatings under a certain external stimuli.

2. Experimental section

2.1. Materials

PAA was purchased from Sigma Aldrich Co., Ltd. Glycidyl methacrylate (GMA), 2-bromoisobutyryl bromide, bipyridyl and CuBr were purchased from Adamas Reagent Co., Ltd. (Shanghai, China). 1,4-Butanediamine (BDA) was purchased from J&K Co., Ltd. (Beijing, China). DOX was purchased from Beijing Huafeng United Technology Co., Ltd. Cetyltrimethyl ammonium bromide (CTAB), didecyl adipate (DDA), polyvinyl pyrrolidone-10 (PVP-10) and 3-aminopropyltriethoxysilane (ATPES) were purchased from Aladdin Co., Ltd. (Shanghai, China). 1,2-Ethanediamine (EDA), tetraethyl orthosilicate (TEOS) and all other reagents were purchased from Tianjin Chemical Reagent Co., Ltd. Cell Counting Kit-8 (CCK-8) was obtained from Dojindo (Beijing, China), and all other biologic agents and consumable items were from Lifaxiang Reagent Co., Ltd. (Tianjin).

Amino-PGOHMAs were synthesized according to our previous reported procedures [56,57]. Briefly, linear poly(glycidyl methacrylate) (L-PGMA) and five-arm PGMA (S5-PGMA) were synthesized from GMA using atom transfer radical polymerization (ATRP) with different initiators, and post-modified with EDA and BDA to obtain L-BDA (L-B), S5-BDA (S5-B), as well as S5-EDA (S5-E) (L represents linear polymer, S5 represents 5-arm polymer).

2.2. Preparation of MSNs and H-MSN

MSN-COOH: CTAB (1.0 g) was dissolved in deionized H_2O (240 mL) and then aqueous NaOH solution (3.5 mL, 2 M) was added. The mixture was heated to 80 °C under stirring for 30 min to get pellucid solution. Then, TEOS (5.0 mL) and ICPTES (0.6 mL) were added dropwise *via* injection sequentially and rapidly. Following the injection, a white precipitation was formed during 15 min of stirring at 1500 rpm. The reaction mixture was heated at 80 °C for another 2 h, and the products were isolated by hot filtration and collected using centrifugation and washed with extensive amount of H_2O and MeOH. To remove the templating surfactants from the mesopores, the as-synthesized silica nanoparticles (1.0 g) was suspended in acidic MeOH (MeOH: 100 mL; conc. HCl: 1.0 mL), and then refluxed for 6 h. The solvent extracted nanoparticles were collected by centrifugation, washed with MeOH, and dried under vacuum to give MSN-COOH.

MSN-NH_2: MSN-NH_2 were obtained by using a base-catalyzed sol–gel method and refluxed in a solution of ATPES according to our previous reported procedure [15].

H-MSN: PVP-10 (0.50 g) was dissolved in a mixture of MeOH and H_2O (2:8 v/v) and the solution was heated to 30 °C under stirring. In another flask, DDA (1.30 g, 7 mmol) was dissolved in EtOH (5 mL) and added into the above solution. After 30 min of stirring, TEOS (5 mL) was slowly added into the reaction mixture, which was stirred for another 3 h. The product was collected by centrifugation and washed with EtOH. To remove the template from the nanoparticles, the as-synthesized product was suspended in EtOH and refluxed for 12 h. The solvent-extracted nanoparticles were collected by centrifugation, washed with EtOH, and dried under vacuum to give H-MSN.

2.3. Preparation of MSNPENs by LbL self-assembly

MSNs (10 mg) were dispersed into phosphate buffer solution (PBS, pH 8.0 or pH 5.0, 5 mL) and mixed with DOX solution (5 mL, 0.5 M). The mixtures were stirred for 5 h. Then, amino-PGOHMAs (8 mg) were added and stirred for another 15 min, followed by centrifugation/dispersion twice with PBS (pH 7.4, NaCl 0.5 mol/L) for 1 min. The nanocomposites were re-dispersed in PBS (pH 7.4) and coated with PAA and amino PGOHMA successively using the same method. These DOX-loaded MSNPENs were collected by centrifugation, rinsed with buffer and then lyophilized. DOX concentrations in the supernatant after each coating and rinse were determined by measuring the Ultraviolet–visible (UV) absorbance at 482 nm on a Shimadzu UV-2550 instrument, with the aid of calibration curve describing the absorbance-concentration relationship.

$$\mathrm{LC}(\%\mathrm{w/w}) = \frac{\text{Mass of loaded guest}}{\text{Mass of loaded nanoparticles}} \times 100\% \quad \mathrm{EE}(\%) = \frac{\text{Mass of loaded drug}}{\text{Initial of loaded drug}} \times 100\%$$

2.4. Characterization

Transmission electron microscopy (TEM) experiments were carried out on a JEM-200CX microscope. The samples were ultrasonically dispersed in PBS (pH 7.4), deposited on carbon-coated copper grid and dried in air. Field-emission scanning electron microscopy (SEM) on a JEOL JSM-6700F microscope, operating at an accelerating voltage of 300 kV, was conducted to observe the topology of the samples.

The Zeta-potential and particle size of the microspheres in the coating process were measured with a Zetasizer Nano ZS90