Journal of Colloid and Interface Science 434 (2014) 1–8

Contents lists available at ScienceDirect

Journal of Colloid and Interface Science

www.elsevier.com/locate/jcis

Responsive delivery of drug cocktail via mesoporous silica nanolamps

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ARTICLE INFO

Article history:
Received 30 April 2014
Accepted 18 July 2014
Available online 2 August 2014

Keywords:
Controlled release
Drug cocktail
Image-guided therapy
Mesoporous silica
Quantum dots

ABSTRACT

After a substantial advancement in single drug nanocarrier, nanomedicine now demands an integration of nanotechnology with combination therapy to achieve synergistic therapeutic effects. In this respect, a smart and multiple drug shuttling nanotheranostic system is developed which transport diverse kinds of anticancer drugs to cancer cells in a controlled and responsive manner respectively. Synthetically, a significantly high dose of hydrophobic camptothecin (CPT) is first loaded into the porous structure of quantum dots (CdS) coupled mesoporous silica nanocomposite. Subsequently, fluorescent doxorubicin (DOX) molecules are exclusively anchored onto the surface of CdS; as a result, the fluorescence of both CdS and DOX is quenched. Upon exposing to mildly acidic conditions, the fluorescence of both species is recovered, such fluorescent "on–off" states provides an added opportunity to real time sense drug release. In-vitro cell experiment reveals an excellent anticancer efficacy of drug cocktail, merely 3 μg/ml concentration of multiple drugs loaded nanocarrier reduces the cell viability to 30%. Furthermore, confocal imaging indicates a successful release of both therapeutic entities. We visualize that our newly fabricated multifunctional double drug-carrying nanoparticles can be a valuable addition to next generation of materials that simultaneously deliver cocktail of drugs with imaging functionality.

1. Introduction

Despite phenomenal advancement in molecular genetics, tumour biology and therapy, adequate treatment of cancer is far from satisfactory because of delayed diagnosis, indiscriminate strikes of potent cytotoxic drugs and development of chemoresistance [1,2]. Advent and integration of nanotechnology with biological systems has offered researchers a wealth of new avenues to solve this intractable health issue [3–8]. To date, variety of nanoparticle based drug delivery systems have been developed, including polymeric conjugates [9,10], micelles [11], liposomes [12], dendrimers [13], carbon nanotubes [14] and inorganic nanoparticles [15], to transport drugs in a controlled and targeted fashion [16]. While comparing drug nanocarriers, unlike liposomal and polymer-based nanoparticles, more robust and extremely stable mesoporous silica has recently emerged as one of the impressive nanotherapeutic platform [17–20]. Mesoporous silica nanoparticles (MSN) enjoy some exclusive properties, such as ease of synthesis, excellent biocompatibility, facile functionalization, tuneable pore structure and large surface area, which render them highly suitable for effective cell specific chemotherapy [21–24]. MSN with various functionalities have so far been successfully demonstrated to efficiently shuttle diverse kind of therapeutic agents and imaging probes into various cells, without causing any cytotoxic effects [25]. It has particularly been used to develop stimuli responsive or "smart" drug delivery systems which can attain site-selective delivery of anticancer drugs [26–28]. Furthermore, it can also be used to ferry multiple drugs due to the existence of both interior pores and exterior surface. Simultaneous delivery of DNA/siRNA and drugs has been demonstrated via MSN [29], however, this exclusive feature of MSN has never been used to codeliver hydrophobic and hydrophilic anticancer drugs with an aim to target two different mechanisms for enhancing the efficacy of cancer treatment.

Besides drug delivery, the focus of nanomedicine is now increasingly shifted towards the development of multifunctional nanoparticles to simultaneously achieve diagnosis with therapy. When considering different imaging modalities, optical imaging is currently a widely used diagnostic tool to non-invasively detect

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http://dx.doi.org/10.1016/j.jcis.2014.07.024
0021-9797/

disease and its progression. Quantum dots (QDs) have proficiently been applied as optical probes for real-time visualization of tumours and lymphatic system owing to their high brightness and photo-bio stability [30–32]. Few therapeutic entities have also been conjugated with quantum dots for simultaneous tumour imaging. Bagalkot et al. first developed a complex image-guided therapeutic system by conjugating targeting functionality (RNA aptamer) and doxorubicin with quantum dots (QD-Apt (DOX) [33]. The resulting system not only delivered DOX to the targeted prostate cancer cells, but also sensed the release of DOX by activating the fluorescence of the QDs presumably due to FRET phenomenon. In another report they coupled quantum dots with zwitterionic amphiphilic polymers for real-time observation of siRNA cell uptake, endosome escape, and separation from nanoparticle carrier [34]. QDs-incorporated liposomes have also been studied as nonviral drug vehicles, wherein QDs were encapsulated into the lipid bilayer of liposome to serve as fluorescence trackers [35]. Yamomoto's group has attached captopril to the QD surface to monitor its therapeutic response and pharmacokinetics in hypertensive rats [36].

To realize a responsive combinatorial dug nanocarrier with imaging functionality, we report, for the first time, the development of luminescent CdS@MSN nanocomposite to codelivers two cytotoxic drugs simultaneously into cancer cells, in response to mildly acidic lysosomal environment (Scheme 1).

2. Materials and methods

2.1. Materials

Chemical reagents used in this study are of analytical grade and used as received. Cetyltrimethylammonium bromide (CTAB), 3-[4, 5-dimethylthialzol-2-yl]-2, 5-diphenyltetrazolium bromide (MTT) were purchased from Sigma–Aldrich. 3-mercaptopropyltriethoxysilane (MPTES), 3-aminopropyltriethoxysilane (APTES), mercaptopropionic acid (MPA), Camptothecin (CPT), 1-(3-(dimethylamino) propyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl), tetraethyl orthosilicate (TEOS, 99.98%), absolute ethanol, dimethyl sulfoxide (DMSO) and toluene were obtained from Aladdin reagent company. Doxorubicin hydrochloride was obtained from Yuancheng tech. development Co. Wuhan.

2.2. Synthesis of cadmium sulfide (CdS) quantum dots

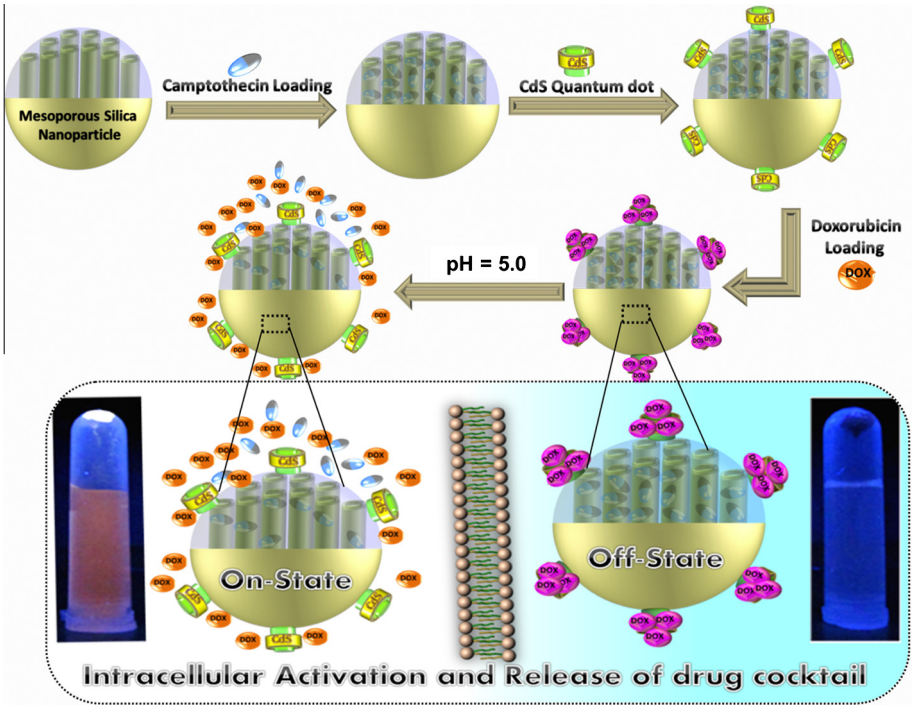
Following a literature approach, CdS QDs were prepared using a previous method with a slight modification [37]. Firstly, 3-mercaptopropionic acid (0.2 mmol) as stabilizing agent was introduced into 36 mL of water. After stirring for five minutes, 3 mL of Cd $(NO_3)_2$ (40 mmol) was slowly dropped into the MPA solution with constant stirring. pH of the solution was adjusted to 10–12 with tetrapropylammonium hydroxide base solution. Next, 5 mL of Na_2S (20 mmol) was rapidly introduced into the system and allowed the growth of CdS nanocrystals for 10 min followed by the addition of another 5 mL of Cd $(NO_3)_2$ solution. The resulting CdS nanocrystals were separated from the solution by adding acetone. The precipitate was centrifuged and redispersed in water.

2.3. Synthesis of mesoporous silica nanosphere

First of all, CTAB surfactant (1.0, 1.37 mmol) was dissolved in 240 mL of distilled water. Aqueous solution of sodium hydroxide (2.00 M, 1.75 mL) was then added to the CTAB solution and the temperature of the mixture was raised to 80 °C. Later, TEOS (2.50 mL) and APTES (250 μL) were successively added dropwise into the above surfactant solution under moderate stirring. The mixture was allowed to stir for 2 h to produce a white precipitate. The resulting solid crude product was centrifuged, washed with water and ethanol, and later dried at 60 °C.

2.4. Synthesis of amine functionalized MSN (MSN-NH_2)

In order to maximize the quantity of amine group, as-synthesized MSN were suspended in 50 mL of dry toluene containing 500 μL of APTES. The solution was stirred under reflux for



Scheme 1. Schematic illustration of synthetic and operational mechanism of image-guided and responsive delivery of drug cocktail.