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Polydopamine-based surface modification of mesoporous silica nanoparticles as pH-sensitive drug delivery vehicles for cancer therapy

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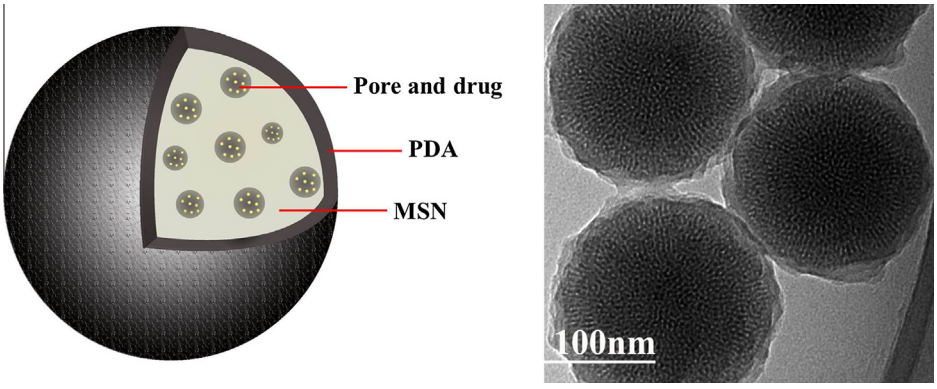
HIGHLIGHTS

- A pH-sensitive drug delivery system of mesoporous silica nanoparticles was prepared.
- MSNs were surface modified by polydopamine for controlled release of desipramine.
- The nanocarriers have good cytotoxicity and ASM inhibit efficiency.
- The novel drug delivery system is promising for cancer therapy.

GRAPHICAL ABSTRACT



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ABSTRACT

A novel pH-sensitive drug delivery system of mesoporous silica nanoparticles (MSNs) which were modified by polydopamine (PDA) for controlled release of cationic amphiphilic drug desipramine (DES) was prepared. MSNs–DES–PDA were characterized in terms of size, size distribution, surface morphology, BET surface area, mesoporous size and pore volume, drug loading content and *in vitro* drug release profile. MSNs–DES–PDA had high drug loading content and pH sensitivity. The DES release profiles of MSNs–DES and MSNs–DES–PDA were totally different, and the drug release of MSNs–DES–PDA accelerated with increasing acidity. MSNs–DES–PDA can be internalized into cells. *In vitro* experiments demonstrated that MSNs–DES–PDA had higher cytotoxicity and inhibitory effects on acid sphingomyelinase than those of free DES. This drug delivery system was beneficial for controlled release and cancer therapy.

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1. Introduction

Cancer has become one of the most serious global health problems in recent years, and millions of people die of cancer every year [1]. Nowadays, cancer is mostly treated by conventional approaches like chemotherapy, surgical resection and radiotherapy. However, these methods are highly aggressive, non-specific,

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and often accompanied by significant side effects, because they also show conspicuous toxicity to normal cells and tissues [2,3]. Having lower toxicity as well as higher efficiency and stability than those of conventional dosage forms, nanoparticles allow sustained and controlled delivery of anticancer agents, and also can be used to deliver drugs by altering signal transduction or modulating the tumor microenvironment [4–6]. Nanoparticulate drug delivery systems have been used to targetedly deliver drugs, to control the release of drugs, and to improve bioavailability and stability [7–9]. As delivery systems for drugs, nanoparticles preferentially accumulate and remain in tumors, unlike free drugs or small molecules that rapidly undergo renal filtration. As to the enhanced permeability and retention (EPR) effect, the retention time of drugs packed in nanoparticles is ten times that of free drugs at the tumor site [10,11]. Till now, nanoparticles have been widely used in drug delivery for cancer therapy.

Mesoporous silica-based nanomaterial MCM-41 was discovered in 1992 [12]. Mesoporous silica nanoparticles (MSNs) contain a complex 'worm-like' network of channels throughout the interior, so they have large surface areas and extraordinarily high drug loading capacity. MSNs remain stable over broad ranges of temperature and pH, and can be used to deliver large doses of drug in a controlled manner [13,14]. In addition, the size, surface chemistry, shape, and mesoporous or hollow structure of MSNs can be controlled. MSNs also have high *in vitro* and *in vivo* biocompatibility, and can eventually be excreted from the body. For cancer therapy, MSNs are obviously superior to other nanoparticulate drug delivery systems [15,16].

MSNs, as drug delivery systems, have been used for delivery of chemotherapeutic drugs, therapy genes or co-delivery [17–19]. To block drug molecules inside the pores of MSNs and to control drug release, some "gatekeepers" are required on the surface of MSNs [20–22]. Polydopamine (PDA) is a biomimetic polymer which can form on a wide range of materials including polymers, ceramics, noble metals, and semiconductors through self-polymerization of dopamine in an aqueous solution [23,24]. PDA coating, which is a well-documented gatekeeper on the surface of MSNs, is highly sensitive to pH. With this coating, drug molecules are blocked in MSNs at neutral pH and released at lower pH [25,26].

Lysosomes, as dynamic acidic organelles that contain hydrolytic enzymes capable of degrading intracellular components, are involved in cell death pathways [27]. Lysosomes are excellent pharmacological targets for killing cancer cells. Cationic amphiphilic drugs (CADs), such as desipramine (DES), have been developed to treat depression, allergies and hypertension. CADs are also applicable to cancer therapy [28], long-term use of which is safe, especially when compared with existing chemotherapeutics. CADs display cancer-specific cytotoxicity *in vitro* and *in vivo*, and can surmount multidrug-resistant phenotype. CADs exhibit cytotoxic activity and reverse tumor multidrug resistance by inhibiting acid sphingomyelinase (ASM), which is essential for lysosomal stability and survival of cancer cells, as well as for multidrug-resistant phenotype [29]. Probably directly inhibiting ASM, CADs lead to a generally dysfunctional lysosomal lipid homeostasis that severely affects the physiology of this cellular compartment, increases lysosomal fragility and causes lysosome membrane permeabilization, triggering cell death via apoptosis and apoptosis-like pathways [30,31].

As we known, nanoparticles are mainly ingested by cancer cells through endocytosis, and degraded in lysosomes [13] in which ASM is also located. In this study, we designed a strategy for cancer treatment as Fig. 1A, using PDA-coated MSNs as pH-sensitive nanocarriers loading DES. Nanoparticles were targeted to tumor by the EPR effect, and DES was released quickly at low pH in lysosomes and delivered directly to the target ASM. The MSNs were characterized, and the antitumor effects of DES-loaded MSNs and free drug were evaluated *in vitro*. The DES-loaded MSNs displayed higher antitumor activity than that of free drug.

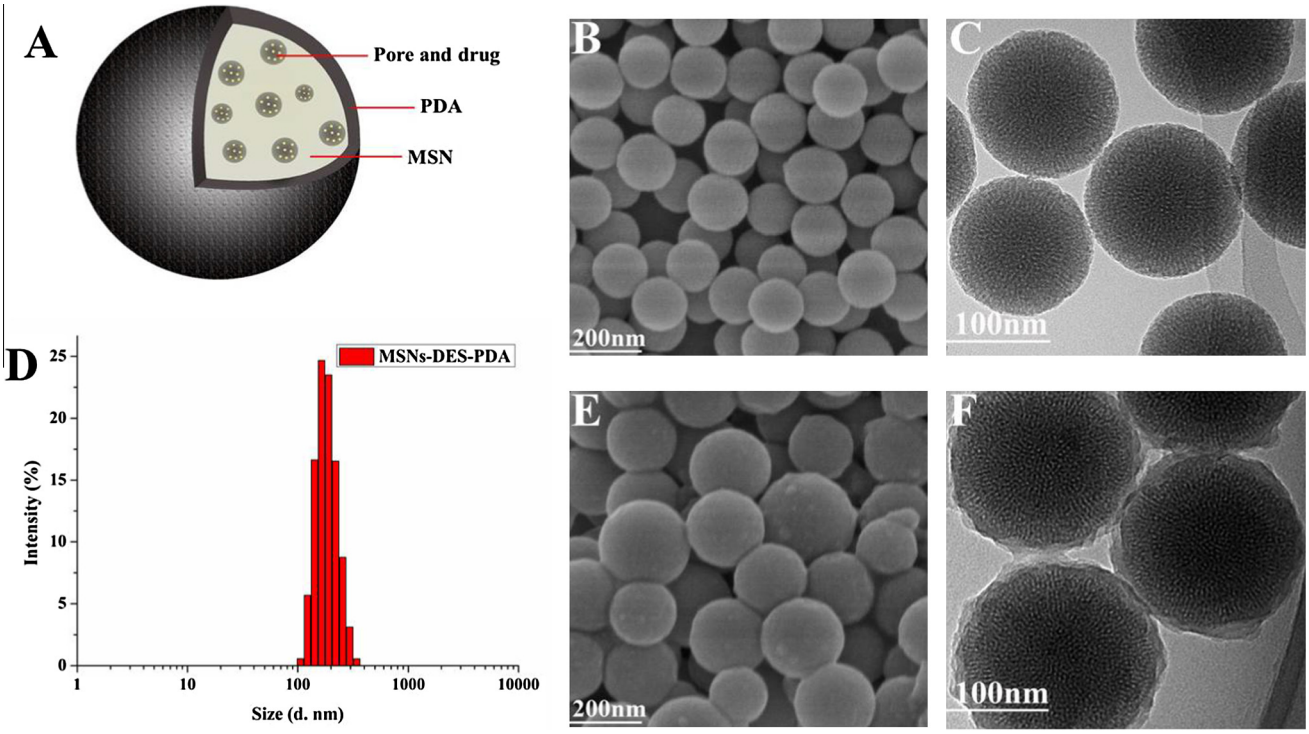

Fig. 1. (A) Schematic of MSNs–DES–PDA, (B) FESEM image of MSNs, (C) TEM image of MSNs, (D) DLS size distribution of MSNs–DES–PDA, (E) FESEM image of MSNs–DES–PDA, and (F) TEM image of MSNs–DES–PDA.

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