



Mesoporous silica nanotubes coated with multilayered polyelectrolytes for pH-controlled drug release

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ABSTRACT

Two kinds of inorganic/organic hybrid composites based on mesoporous silica nanotubes (MSNTs) and pH-responsive polyelectrolytes have been developed as pH-controlled drug delivery systems via the layer by layer self-assembly technique. One system was based on alternatively loading poly(allylamine hydrochloride) and sodium poly(styrene sulfonate) onto as-prepared MSNTs to load and release the positively charged drug doxorubicin. The other system was synthesized by alternately coating sodium alginate and chitosan onto amine-functionalized MSNTs, which were used as vehicles for the loading and release of the negatively charged model drug sodium fluorescein. Controlled release of the drug molecules from these delivery systems was achieved by changing the pH value of the release medium. The results of *in vitro* cell cytotoxicity assays indicated that the cell killing efficacy of the loaded doxorubicin against human fibrosarcoma (HT-1080) and human breast adenocarcinoma (MCF-7) cells was pH dependent. Thus, these hybrid composites could be potentially applicable as pH-controlled drug delivery systems.

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1. Introduction

In recent years much work has focused on controlled drug release from polymeric materials in response to specific stimuli, such as electric [1] or magnetic [2] fields, exposure to ultrasound [3], light [4], enzymes [5], saccharides [6] or antigens [7] and changes in pH [8], temperature [9] or redox state [10]. Since the human body exhibits variations in pH along the gastrointestinal tract from the stomach (pH 1.0–3.0), to the small intestine (pH 6.5–7.0), to the colon (pH 7.0–8.0) [11] and also in some specific areas like tumoral tissues (pH 6.5–7.2) and subcellular compartments, such as endosomes/lysosomes (pH 5.0–5.5) [12], one very important system group is those sensitive to the pH of their surroundings. In this context pH-sensitive polyelectrolyte polymers have been found or designed as new drug carriers for controlled delivery [13,14]. These polymers contain relatively ionizable groups at levels ranging from a few mol. to 100% of the repeating units. They undergo controllable volume changes in response to small variations in pH of the external environment, which facilitate drug delivery control. To date, pH-sensitive polyelectrolyte polymers based on hollow microcapsules prepared by the layer by layer (LBL) self-assembly of polyelectrolytes on colloidal particles have been extensively investigated [15–23]. Möhwald and co-workers prepared hollow

poly(allylamine hydrochloride) and sodium poly(styrene sulfonate) (PAH/PSS) microcapsules and confirmed the controlled encapsulation and release of several kinds of species, such as dyes [18], enzymes [19], dextran [20] and DNA [21], from the capsules by changing the pH of the release medium. Using the same method Ye et al. achieved the pH-controlled encapsulation and release of insulin from hollow alginate (ALG) and chitosan (CHI) microcapsules [22]. Caruso and co-workers prepared poly(L-lysine) and poly(L-glycolic acid) microcapsules by sequentially coating mesoporous silica spheres and accomplished the controlled encapsulation and release of catalase [23]. However, these hollow capsules are not mechanically strong and easily collapse in the course of drying and the removal of colloidal templates [24]. Therefore, some smart inorganic/organic composites have been developing for pH-controlled drug delivery [24,25]. Sukhorukov and co-workers synthesized pH-sensitive YF₃/polycyclic aromatic hydrocarbon (PAH), Fe₃O₄/PAH and hydroxyapatite/PAH composite capsules and demonstrated the controllable encapsulation and release of dextran molecules [25]. Zhu et al. used hollow mesoporous silica spheres as a container for drug molecules and PAH/PSS multilayer coatings as a pH-responsive switch [24]. It is encouraging that with these smart composites they not only achieved pH-controlled encapsulation and release of drug molecules, but also enhanced the mechanical strength of the polyelectrolyte capsules. Especially in the latter research, the drug storage capacity was greatly increased by mesoporous silica materials as drug vehicles. As is well known, mesoporous silica materials are ideal drug supports due to their

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non-toxic and biocompatible nature, adjustable pore size and high specific surface area with abundant Si–OH bonds [26,27]. These materials have been found to have promising applications for some oral drug formulations [28–30] and as implantable matrices for the regeneration of bone tissues [31]. Several research groups have reported the design of stimuli-responsive controlled drug delivery systems based on mesoporous silica materials. As examples, Fujiwara and co-workers successfully realized photo-controlled reversible release of drug molecules from coumarin-modified MCM-41 [32]. Lin and co-workers prepared a series of stimuli-responsive controlled delivery systems by capping removable CdS [33], Fe₃O₄ [34] or gold [35] nanoparticles in the channel of mesoporous silica spheres. In addition, thermo-responsive [36], glucose-responsive [37], enzyme-responsive [38] and dual stimuli-responsive [39] controlled drug delivery systems have also been developed on the basis of mesoporous silica materials with various morphologies, such as SiO₂–Au nanoshells, mesoporous silica nanospheres and MCM-41 nanoparticles.

Recently, our group has successfully synthesized a novel kind of mesoporous silica nanotubes (MSNTs) with a very spacious hollow core and a tubular shell with a mesoporous framework, as well as a tunable pore size distribution and shell thickness [40]. This material has been studied as a carrier to load and release various active species, such as drugs [41], enzymes [42] and so on. However, the cargo-loaded tube material suffers from the drawback of uncontrolled release of active species from the carrier upon being exposed to external surroundings such as various pH media. Here we attempt to introduce polyelectrolytes onto the surface of the preformed silica tubes as a pH switch in the hope of obtaining novel pH-responsive MSNTs. In view of this, two kinds of inorganic/organic composites based on MSNTs and polyelectrolytes, including the synthetic pair PAH/PSS and the natural pair ALG/CHI, were developed for pH-controlled drug delivery. The PAH/PSS pair is the most researched polyelectrolyte and presents very good pH-responsiveness [18–21]. ALG and CHI are biocompatible and biodegradable polysaccharides and, more importantly, they are very

economical, because they can be obtained from brown algae and crustacea, respectively, which are both widespread in nature [22]. pH-controlled release of model drugs, including doxorubicin hydrochloride (DOX) and sodium fluorescein (FLU), from these composites has been investigated in detail. In addition, *in vitro* cell cytotoxicity assays of the loaded DOX against tumoral cells were carried out in different pH culture media. The fabricated pH-responsive MSNTs are anticipated to be applicable as oral drug formulations for local drug delivery or implantable matrices in the treatment of bone disease.

2. Experimental

2.1. Materials

PAH (M_w 70,000) and PSS (M_w 70,000) were obtained from Aldrich. ALG (M_w 12,000–80,000) was obtained from Sigma, Canada. CHI (M_w 30,000) was obtained from Primex Biochemicals, Norway. DOX (M_w 580, $pK_a = 6.5$ [43]) was purchased from Meiji Pharmaceuticals, China. FLU (M_w 376, $pK_{a1} = 4.3$, $pK_{a2} = 6.4$ [44]) was obtained from Sinopharm Chemical Reagent, China. For reference, the chemical structures and charges of PAH, PSS, CHI, ALG, DOX and FLU are shown in Fig. 1. 3-Aminopropyltriethoxysilane (APTS) was purchased from Fluka, Japan. Human fibrosarcoma (HT-1080) and human breast adenocarcinoma (MCF-7) cells were from the ATCC. All other chemicals used in the experiments were obtained from commercial sources as analytical reagents without further purification. Millipore water with a resistivity of 18.2 M Ω cm was used throughout the study.

2.2. Polyelectrolyte multilayer coating

MSNTs were fabricated according to the procedure in a previous report [41]. PAH/PSS multilayer coating was accomplished as follows. An aliquot of 25 ml of PAH (2 mg ml⁻¹ in 0.5 M NaCl) was

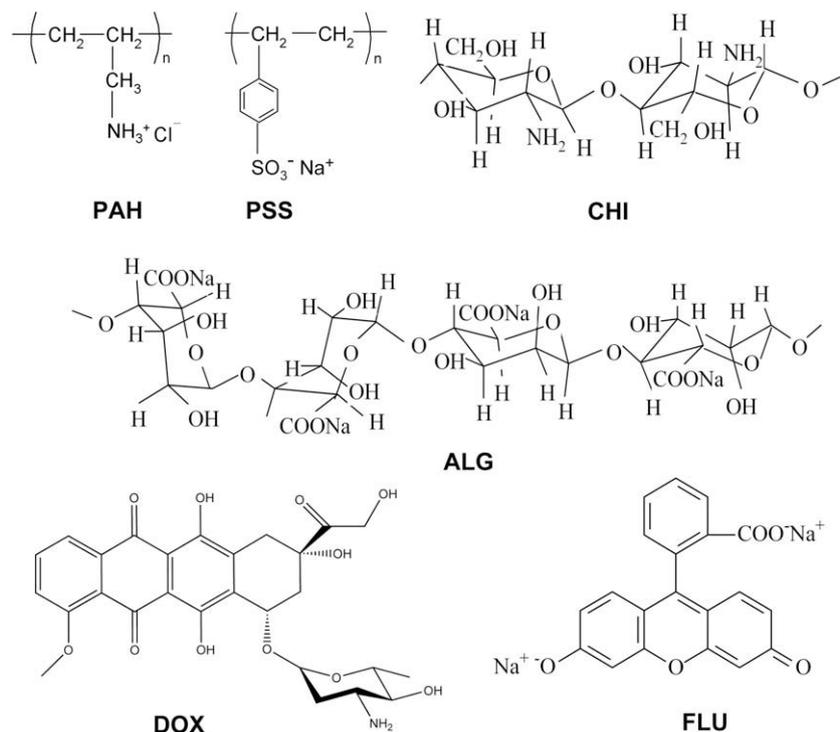


Fig. 1. Chemical structures of PAH, PSS, CHI, ALG, DOX and FLU.

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