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Porous silicon-cyclodextrin based polymer composites for drug delivery applications

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ABSTRACT

One of the main applications of porous silicon (PSi) in biomedicine is drug release, either as a single material or as a part of a composite. PSi composites are attractive candidates for drug delivery systems because they can display new chemical and physical characteristics, which are not exhibited by the individual constituents alone. Since cyclodextrin-based polymers have been proven efficient materials for drug delivery, in this work β-cyclodextrin–citric acid *in-situ* polymerization was used to functionalize two kinds of PSi (nanoporous and macroporous). The synthesized composites were characterized by microscopy techniques (SEM and AFM), physicochemical methods (ATR-FTIR, XPS, water contact angle, TGA and TBO titration) and a preliminary biological assay was performed. Both systems were tested as drug delivery platforms with two different model drugs, namely, ciprofloxacin (an antibiotic) and prednisolone (an anti-inflammatory), in two different media: pure water and PBS solution. Results show that both kinds of PSi/β-cyclodextrin–citric acid polymer composites, nano- and macro-, provide enhanced release control for drug delivery applications than non-functionalized PSi samples.

1. Introduction

Porous silicon (PSi) is an excellent biomaterial due to its high surface area (Bisi, Ossicini, & Pavesi, 2000), biocompatibility (Martin-Palma, Manso-Silvan, & Torres-Costa, 2010), biodegradability (Tanaka et al., 2010) and bioresorbability (Hernández-Montelongo, Muñoz-Noval, Torres-Costa, Martín-Palma, & Manso-Silvan, 2012). In view of these properties, different PSi bioapplications have been developed such as: biosensing (Dhanekar & Jain, 2013a), tissue engineering (Coffer et al., 2005), tumor imaging (Martin-Palma et al., 2010), bioreactor platform (Stewart & Buriak, 2000) and drug delivery (Anglin, Cheng, Freeman, & Sailor, 2008). When PSi is used as a drug delivery system, drugs are loaded into its porous matrix or immobilized on its surface after a proper surface derivatization (Stewart & Buriak, 2000). However, when combined with biopolymers, it works as substrate for composite materials, providing new advantageous chemical and physical characteristics, which are not exhibited by the individual constituents, such as an improved control over drug release kinetics and improved stability in aqueous solution (Anglin et al., 2008). Indeed, PSi has been previously combined with biopolymers such as polylactide, polydimethylsiloxane, polyethylene, polystyrene, polycaprolactone and poly(N-isopropylacrylamide) for that purpose (Anglin et al., 2008; Mukherjee et al., 2006; Segal et al., 2007).

Herein, we focus on the functionalization of PSi by β-cyclodextrin (βCD). Cyclodextrins (CDs) are cyclic oligosaccharides with a hydrophilic outer surface (C–OH groups) and a hydrophilic apolar cavity (C–O–C and C–H bonds) (Davis & Brewster, 2004) (Fig. 1). Because of their characteristic cavity and their ability to form reversible complexes with drugs, CDs have been used as efficient delivery carriers (Leprêtre et al., 2009). CDs have also been crosslinked, yielding a three-dimensional polymer network suitable for drug delivery applications. Such volume structure presents

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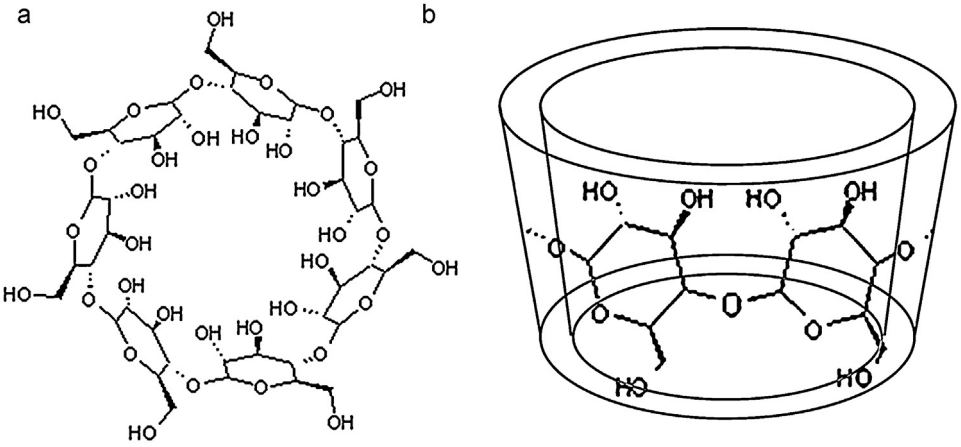


Fig. 1. (a) Chemical structure of β-CD, and (b) its toroidal shape.

extended interactions with drugs, prolonging residence time in the medium and/or increasing efficiency and specificity towards targeted sites (Trotta, Zanetti, & Cavalli, 2012). Some examples used crosslinkers used to polymerize CDs are alginate (Izawa et al., 2013), poly(ethylene oxide) (Liu et al., 2011; Li, Ni, & Leong, 2003), camptothecin (Davis, 2009), epichlorohydrin (Davis & Brewster, 2004), and citric acid (Martin et al., 2013), which is the one used here, amongst others. In addition, CD-based polymers have been used to functionalize different biomaterials for drug release applications, such as vascular prostheses (Blanchemain et al., 2012), polypropylene (Degoutin et al., 2012), polyamide inguinal plates (El Ghoul et al., 2008), hydroxyapatite (Leprêtre et al., 2009) and hip prostheses (Taha et al., 2013).

All these features make CDs interesting for combining with PSi for further drug delivery applications. In this work, the functionalization of nanoporous and macroporous PSi (nPSi and mPSi, respectively) by β-CD–citric acid (CTR) *in-situ* polymerization has been investigated. In order to test their viability as drug delivery systems (Thrimawithana, Young, Bunt, Green, & Alany, 2011), these composites have been loaded with two model drugs: ciprofloxacin (CFX, an antibiotic) (Oliver, Strube, Mohan, & Slomovic, 2005; Ravindran et al., 2009) and prednisolone (PDN, an anti-inflammatory) (Lane & Holland, 2012; Struck & Bariszlovich, 2001), in two media: pure water and PBS solution.

2. Materials and methods

2.1. Porous silicon preparation

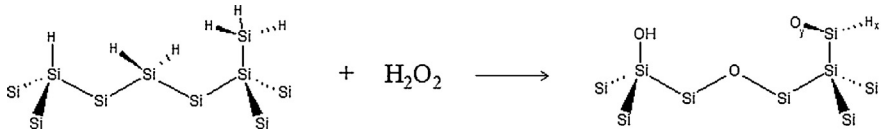
2.1.1. Nanoporous silicon

Nanoporous silicon (nPSi) was fabricated by electrochemical etching of p^+ type silicon wafers (boron-doped, orientation ⟨1 0 0⟩, resistivity 0.01–0.02 Ω cm) in a HF:EtOH (1:2) solution, HF at 48 wt%. A current density of 60 mA cm^{-2} was applied for 90 s under illumination with a 150 W halogen lamp (Hernández-Montelongo et al., 2012). Afterwards, nPSi was chemically oxidized (nPSi-CO_x) by H_2O_2 (30%, v/v) for 2 h (Naveas et al., 2012), rinsed with EtOH and dried with a nitrogen flow. A porosity of 60% for these samples was calculated by gravimetric analysis.

2.1.2. Macroporous silicon

Macroporous silicon (mPSi) was fabricated by electrochemical etching of p^+ type silicon wafers (boron-doped, orientation ⟨1 0 0⟩, resistivity 29–31 Ω cm) in a HF:DMF (1:6) solution, HF at 48 wt% (Föll, Christophersen, Carstensen, & Hasse, 2002). In this case, the applied current density was 20 mA cm^{-2} for 600 s under illumination with the same 150 W halogen lamp. The mPSi samples were also chemically oxidized (mPSi-CO_x) by H_2O_2 (30%, v/v) for 2 h, rinsed with EtOH and dried with nitrogen. In these samples a 40% porosity was determined by gravimetric analysis.

As-prepared (fresh) PSi surface is mainly composed of Si–H bonds (Bisi et al., 2000; Mawhinney, Glass, & Yates, 1997; Tolstoy, Chernyshova, & Skryshevsky, 2003). The chemical post-treatment of PSi by H_2O_2 is an oxidation process involving different reactions; Si–H bonds can be transformed to Si–OH, Si–O–Si or $-O_ySi-H_x$. The oxidation process is represented by Eq. (1) (Dhanekar & Jain, 2013b; Naveas et al., 2012):



(1)

2.2. PSi functionalization with modified β-cyclodextrin

The proposed method to functionalize both kinds of PSi is straight forward and accessible (Fig. 2). A monomer solution was prepared with 10 g β-cyclodextrin (Roquette, Lestrem France), 3 g $NaH_2PO_2{\cdot}H_2O$ (Aldrich, Saint Quentin Fallavier, France) as catalyst and 10 g citric acid (Aldrich, Saint Quentin Fallavier, France) in 100 mL of distilled water. nPSi-CO_x and mPSi-CO_x samples were immersed in this solution for 15 min while stirring. Afterwards, the excess of monomer solution was carefully removed by capillarity using a soft cellulosic tissue, leaving a thin film on the top. The samples were dried, first at room temperature, and later at 90 °C for 1 h in each case. The βCD–CTR polymerization (Martel, Ruffin, Weltrowski, Lekchiri, & Morcellet, 2005) in PSi samples was carried out at 140 °C for 25 min, thereby obtaining the nPSi-CD and mPSi-CD samples. Afterwards, they were washed with distilled water for 15 min while stirring, rinsed with EtOH and dried at 90 °C for 1 h.

The polymerization achieved between βCD and CTR may be explained by a polyesterification mechanism between hydroxyl groups of βCD and carboxylic groups of CTR, which contains three carboxylic groups as detailed in the following equation (Eq. (2)) (Martel et al., 2005). The resulting polymer was named polyCTR–βCD.