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Porous silicon in drug delivery devices and materials ☆

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ABSTRACT

Porous Si exhibits a number of properties that make it an attractive material for controlled drug delivery applications: The electrochemical synthesis allows construction of tailored pore sizes and volumes that are controllable from the scale of microns to nanometers; a number of convenient chemistries exist for the modification of porous Si surfaces that can be used to control the amount, identity, and *in vivo* release rate of drug payloads and the resorption rate of the porous host matrix; the material can be used as a template for organic and biopolymers, to prepare composites with a designed nanostructure; and finally, the optical properties of photonic structures prepared from this material provide a self-reporting feature that can be monitored *in vivo*. This paper reviews the preparation, chemistry, and properties of electrochemically prepared porous Si or SiO_2 hosts relevant to drug delivery applications.

Contents

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1. Introduction

Porous Si has been investigated for applications in microelectronics, optoelectronics, [1–4] chemical [5,6] and biological [7–10] sensors, and biomedical devices [11]. The *in vivo* use of porous Si was first promoted by Leigh Canham, who demonstrated its resorbability and biocompatibility in the mid 1990s [12–15]. Subsequently, porous Si or porous SiO_2 (prepared from porous Si by oxidation) host matrices have been employed to demonstrate *in vitro* release of the steroid dexamethasone [16], ibuprofen [17], cis-platin [18], doxorubicin [19], and many other drugs [20]. The first report of drug delivery from porous Si across a cellular barrier was performed with insulin, delivered across monolayers of Caco-2 cells [21]. An excellent review of the potential for use of porous Si in various drug delivery applications has recently appeared [20].

An emerging theme in porous Si as applied to medicine has been the construction of microparticles ("mother ships") with sizes on the order of 1–100 μm that can carry a molecular or nanosized payload, typically a drug. With a free volume that can be in excess of 80%, porous Si can carry cargo such as proteins, enzymes [22–29], drugs [16–20,30,31], or genes. It can also carry nanoparticles, which can be equipped with additional homing devices, sensors, or cargoes. In addition, the optical properties of nanocrystalline silicon can be recruited to perform various therapeutic or diagnostic tasks—for example, quantum confined silicon nanostructures can act as photosensitizers to produce singlet oxygen as a photodynamic therapy [32–35]. A long-term goal is to harness the optical, electronic, and chemical properties of porous Si that can allow the particles to home to diseased tissues such as tumors and then perform various tasks *in vivo*. These tasks include detecting, identifying, imaging, and delivering therapies to the tissue of interest. In this work we review the chemistry of porous Si that allows the incorporation of drug payloads, homing devices, optical features for imaging, and sensors for detection of various physical changes.

2. Preparation of porous Si

2.1. Electrochemical etching

Porous Si is a product of an electrochemical anodization of single crystalline Si wafers in a hydrofluoric acid electrolyte solution. Pore morphology and pore size can be varied by controlling the current density, the type and concentration of dopant, the crystalline orientation of the wafer, and the electrolyte concentration in order to form macro-, meso-, and micropores [36]. Pore sizes ranging from 1 nm to a few microns can be prepared.

The mechanism of pore formation is not generally agreed upon, but it is thought to involve a combination of electronic and chemical factors [37]. The type of dopant in the original silicon wafer is important because it determines the availability of valence band holes that are the key oxidizing equivalents in the reaction shown in Fig. 1. In general the relationships of dopant to morphology can be segregated into four

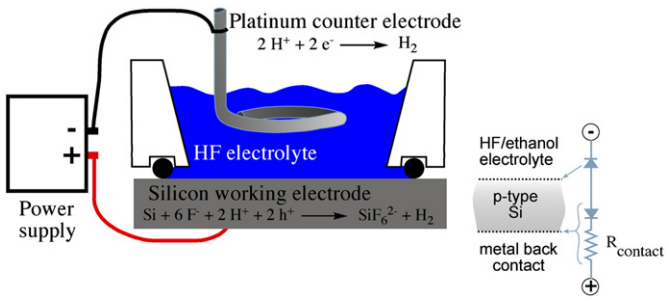

Fig. 1. Schematic of the etch cell used to prepare porous Si. The electrochemical half-reactions are shown, and the equivalent circuit for etching of a p-type Si wafer is shown at right.

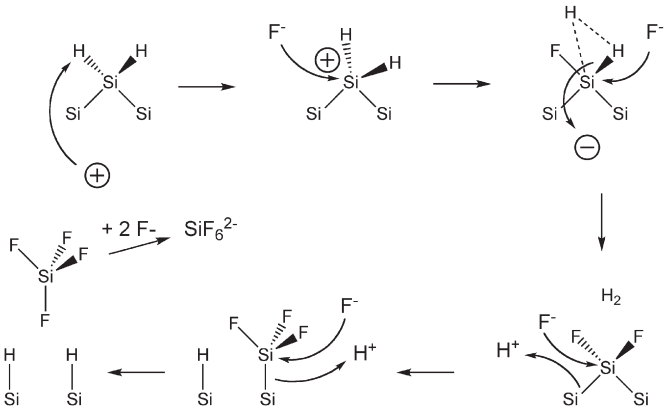

Fig. 2. Mechanism of Si oxidation during the formation of porous Si (adapted from reference [38]).

groups based on the type and concentration of the dopant: n-type, p-type, highly doped n-type, and highly doped p-type. By "highly doped," we mean dopant levels at which the conductivity behavior of the material is more metallic than semiconducting. For n-type silicon wafers with a relatively moderate doping level, exclusion of valence band holes from the space charge region determines the pore diameter. Quantum confinement effects are thought to limit pore size in moderately p-doped material. For both dopant types the reaction is crystal face selective, with the pores propagating primarily in the <100> direction of the single crystal. A simplified mechanism for the chemical reaction is shown in Fig. 2 [38,39]. The electrochemically driven reaction requires an electrolyte containing hydrofluoric acid. Application of anodic current oxidizes a surface silicon atom, which is then attacked by fluoride. The net process is a 4 electron oxidation, but only two equivalents are supplied by the current source. The other two equivalents come from reduction of protons in the solution by surface SiF_2 species. Pore formation occurs as Si atoms are removed in the form of SiF_4, which reacts with two equivalents of F^- in solution to form SiF_6^{2-}.

The porosity of a growing porous Si layer is proportional to the current density being applied, and it typically ranges between 40 and 80%. Pores form only at the Si/porous Si interface, and once formed, the morphology of the pores does not change significantly for the remainder of the etching process. However, the porosity of a growing layer can be altered by changing the applied current. The film will continue to grow with this new porosity until the current changes. This feature allows the construction of layered nanostructures simply by modulating the applied current during an etch. For example, one-dimensional photonic crystals consisting of a stack of layers with alternating refractive index can be prepared by periodically modulating the current during an etch [40–42].

The ability to easily tune the pore sizes and volumes during the electrochemical etch is a unique property of porous Si [37] that is very useful for drug delivery applications. Other porous materials generally require a more complicated design protocol to control pore size, and even then, the available pore sizes tend to span a limited range. With electrochemically prepared porous Si, control over porosity and pore size is obtained by adjusting the current settings during the etch. Typically, larger current density produces larger pores. Large pores are desirable when incorporating sizable molecules or drugs within the pores. Pore size and porosity is important not only for drug loading; it also determines degradation rates of the porous Si host matrix [43]. Smaller pores provide more surface area and expose more sites for attack of aqueous media. The smaller porous filaments within the film yield greater dissolution rates, providing a convenient means to control degradation rates of the porous Si host.

For *in vivo* applications, it is often desired to prepare porous Si in the form of particles. The porous layer can be removed from the Si