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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.

Keywords

Porous silicon; Small molecule drug delivery; Nanotechnology; Photonic crystal; Cancer; Protein therapy

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

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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 pay-loads, 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 nmto 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 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 substrate with a procedure commonly referred to as "electropolishing" or "lift-off." The etching electrolyte is replaced with one containing a lower concentration of HF and a current pulse is applied for several seconds. The lower concentration of HF results in a diffusion limited situation that removes silicon from the crystalline Si/porous Si interface faster than pores can propagate. The result is an under-cutting of the porous layer, releasing it from the Si substrate [37]. The freestanding porous Si film can then be removed with tweezers or a vigorous rinse. The film can then be converted into microparticles by ultrasonic fracture. Conventional lithography [44,45] or microdroplet patterning [46,47] methods can also be used if particles with more uniform shapes are desired.

2.2. Stain etching

Stain etching is an alternative to the electrochemical method for fabrication of porous Si powders. The term stain etching refers to the brownish or reddish color of the film of porous Si that is generated on a crystalline silicon material subjected to the process [48]. In the stain etching procedure, a chemical oxidant (typically nitric acid) replaces the power supply used in the electrochemically driven reaction. HF is a key ingredient, and various other additives are used to control the reaction [49]. Stain etching generally is less reproducible than the electrochemical process, although recent advances have improved the reliability of the process substantially [50]. Furthermore, stain etching cannot be used to prepare stratified structures such as double layers or multilayered photonic crystals. However, porous Si powders prepared by stain etch are now commercially available (http://vestaceramics.net), and a few additional vendors are poised to enter the market. For the biomedically inclined researcher this eliminates the need to set up a complicated and hazardous electrochemical etching system, and it should stimulate the growth of the field.

3. Chemistry of porous Si

3.1. Biocompatibility and reactions of biological relevance

Silicon is an essential trace element that is linked to the health of bone and connective tissues [51]. The chemical species of relevance to the toxicity of porous Si are silane (SiH_4) and dissolved oxides of silicon; three important chemical reactions of these species are given in Eq. (1)–(3). The surface of porous Si contains Si–H, SiH_2, and SiH_3 species that can readily convert to silane [52,53]. Silane is chemically reactive (Eq. (1)) and toxic, especially upon inhalation [54,55]. Like silane, the native SiH_x species on the porous Si surface readily oxidize in aqueous media. Silicon itself is thermodynamically unstable towards oxidation, and even water has sufficient oxidizing potential to make this reaction spontaneous Eq. (2). The passivating action of SiO_2 and Si–H (for samples immersed in HF solutions) make the spontaneous aqueous dissolution of Si kinetically slow. Because of its highly porous nano-structure, oxidized porous Si can release relatively large amounts of silicon-containing species into solution in a short time. The soluble forms of SiO_2 exist as various silicic acid compounds with the ortho-silicate (SiO_4^{4-}) ion as the basic building block (Eq. (3)), and these oxides can be toxic in high doses [56–58]. Because the body can handle and eliminate silicic acid, the

important issue with porous Si-based drug delivery systems is the rate at which they degrade and resorb [12,14,15,59,60]. The work of Bayliss, Canham, and others established the relatively low toxicity of porous Si in various cellular and live animal systems [21,61–66]. The low toxicity, degradation properties, and solubility of the degradation byproducts of porous Si have generated much interest in its use in controlled drug delivery systems.

There are many conditions that affect the lifetime of biomaterials *in vivo*. In order to be a successful candidate, porous Si must be able to perform reproducibly and retain the physical and chemical properties needed for the particular application under the harsh biological conditions of the body (salinity, pH, and enzymatic activity). The chemistry of the nanomaterial is therefore of utmost importance.

$$SiH_4+2H_2O \rightarrow SiO_2+4H_2 \quad (1)$$

$$Si+O_2 \rightarrow SiO_2 \quad (2)$$

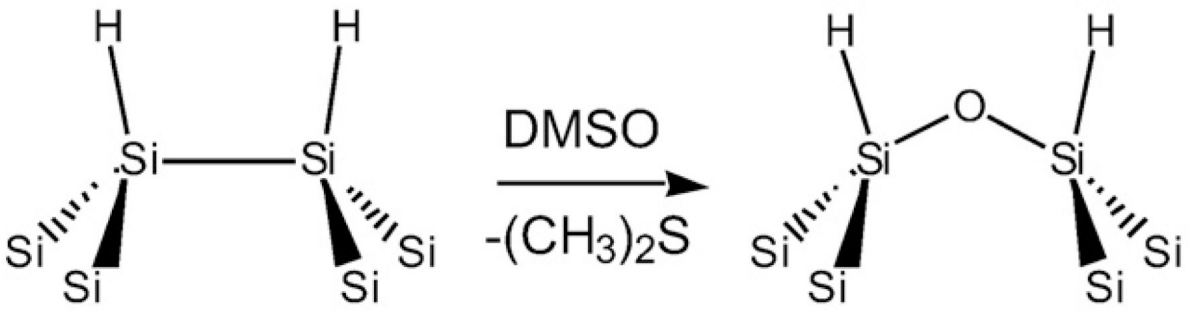
$$SiO_2+2H_2O \rightarrow Si(OH)_4 \quad (3)$$

Surface chemistry plays a large role in controlling the degradation properties of porous Si *in vivo*. Immediately after Si is electrochemically etched, the surface is covered with reactive hydride species. These chemical functionalities provide a versatile starting point for various reactions that determine the dissolution rates in aqueous media, allow the attachment of homing species, and control the release rates of drugs. The two most important modification reactions are chemical oxidation (Eq. (2)) and grafting of Si–C species.

3.2. Oxidation of porous Si

With its high surface area, porous Si is particularly susceptible to air or water oxidation. Once oxidized, nanophase SiO_2 readily dissolves in aqueous media [10], and surfactants or nucleophiles accelerate the process [67,68]. Si–O bonds are easy to prepare on porous Si by oxidation, and a variety of chemical or electrochemical oxidants can be used. Thermal oxidation in air tends to produce a relatively stable oxide [69], in particular if the reaction is performed at >600°C [70]. Ozone oxidation, usually performed at room temperature, forms a more hydrated oxide that dissolves quickly in aqueous media [10]. Milder chemical oxidants, such as dimethyl sulfoxide (DMSO, Eq. (4)) [71] benzoquenone [72], or pyridine [73] can also be used for this reaction. Mild oxidants are sometimes preferred because they can improve the mechanical stability of highly porous Si films, which are typically quite fragile.

The mechanical instability of porous Si is directly related to the strain that is induced in the film as it is produced in the electro-chemical etching process [74], and the volume expansion that accompanies thermal oxidation can also introduce strain. Mild chemical oxidants presumably attack porous Si preferentially at Si–Si bonds that are the most strained, and hence most reactive [16]. As an alternative, nitrate is a stronger oxidant, and nitric acid solutions are used extensively in the preparation of porous Si particles from silicon powders by chemical stain etching [75].

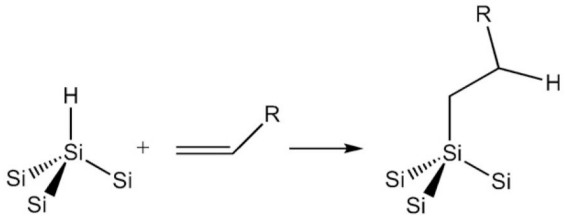


(4)

Slow oxidation of the porous Si surface by dimethyl sulfoxide (DMSO), when coupled with dissolution of the newly formed oxide by HF, is a mild means to enlarge the pores in porous Si films [16]. Aqueous solutions of bases such as KOH can also be used to enlarge the pores after etching [76]. Electrochemical oxidation, in which a porous Si sample is anodized in the presence of a mineral acid such as H_2SO_4, yields a fairly stable oxide [77]. Oxidation imparts hydrophilicity to the porous structure, enabling the incorporation and adsorption of hydrophilic drugs or biomolecules within the pores. Aqueous oxidation in the presence of various ions including Ca^{2+} generates a calicified form of porous Si [12,15] that has been shown to be bioactive and is of particular interest for *in vivo* applications. Calcification can be enhanced by application of a DC electric current [14].

3.3. Hydrosilylation to produce Si–C bonds

Carbon directly bonded to silicon yields a very stable surface species. First recognized by Chidsey and coworkers [78], Si–C bonded species possess greater kinetic stability relative to Si–O due to the low electronegativity of carbon. Silicon can readily form 5- and 6-coordinate intermediates, and an electronegative element such as oxygen enhances the tendency of silicon to be attacked by nucleophiles. Si–C bonds are usually formed on hydride-terminated porous Si surfaces by hydrosilylation (Eq. (5)), a reaction first demonstrated on porous Si by Buriak [79–81] and extensively studied by Boukherroub, Chazalviel, Lockwood, and others.[60,82–88] Hydrosilylation involves reaction of an alkene (usually terminal) or alkyne with a Si–H bond. On porous Si, the reaction can be thermal [85], photochemical [89,90], or Lewis acid catalyzed [80,81].



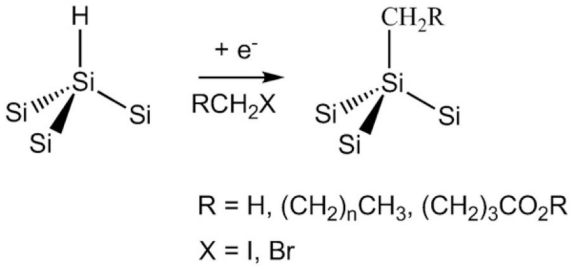
(5)

Thermal hydrosilylation provides a means to place a wide variety of organic functional groups on a crystalline Si or porous Si surface [80]. The main requirement of the reaction is that the silicon surface contains Si–H species so they can react with a terminal alkene on the organic fragment. Thus it is important to use freshly etched porous Si and to exclude oxygen and water

from the reaction mixture. Conventional Schlenk or vacuum line techniques should be employed [91].

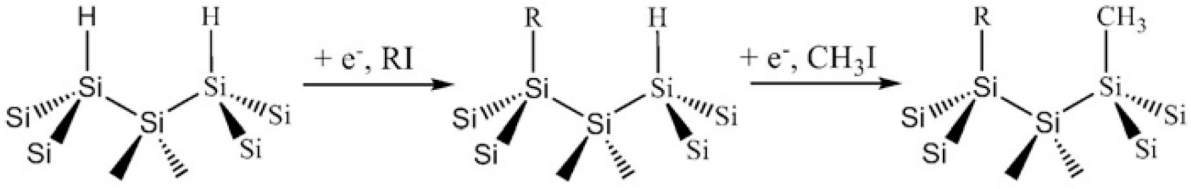
3.4. Chemical or electrochemical grafting of Si–C bonds

As an alternative to hydrosilylation, covalently attached layers can be formed on porous Si surfaces using Grignard and alkyl- or aryllithium reagents [78,92–98]. Electrochemical oxidation of methyl-Grignards [99] on porous Si and electrochemical reduction of phenyldiazonium salts [100] on single crystal Si have been shown to yield dense monolayers of methyl and phenyl groups, respectively. Electrochemical reduction of organohalides (Eq. (6)) has also been demonstrated as an effective grafting technique [101]. The electro-chemical approach allows the attachment of a methyl group to the Si surface, which is not possible with the hydrosilylation route. Because of their ease of application and dramatic improvements in stability, hydrosilylation and electrochemical grafting of alkyl halides are useful reactions for the preparation of biointerfaces.



(6)

It is important to note that porous Si modification reactions do not provide 100% surface coverage; they merely decorate the surface with the functional group. Thus infrared spectra show a large amount of surface Si–H groups remaining after hydrosilylation or electrochemical grafting reaction. The electrochemical method allows one to minimize residual Si–H species by “endcapping” the surface with small methyl groups following modification with a functional species (Eq. (7)) [102]. The endcapping reaction can also be performed on a hydrosilylated porous Si surface. The doubly modified (methyl endcapped) surfaces exhibit the greatest stability in aqueous media [102]. It is still an open question as to why the modification reactions impart such stability to the material; for example Buriak's hydrosilylation reaction makes porous Si stable to hydroxide solutions of pH>10 [81]. Unmodified (exclusively H-terminated) porous Si dissolves rapidly under such conditions. The stability probably derives from a combination of two factors: the Si–C bond is kinetically inert due to the low electronegativity of carbon and the attached organic species (typically a hydrocarbon chain 8 or more carbons long) is sufficiently hydrophobic that aqueous nucleophiles are excluded from the vicinity of their Si atom target.



(7)

Reaction of porous Si with gas phase acetylene generates highly carbonized porous Si that is possibly the most stable form of Si–C modified porous Si [103–105]. This material is referred to as thermally carbonized porous Si, or TCPSi [30]. It has been extensively investigated by Salonen and coworkers, with many publications of relevance to drug loading and delivery [20,30,31,106–109].

3.5. Conjugation of biomolecules to modified porous Si

Carbon grafting stabilizes porous Si against dissolution in aqueous media, but the surface must still avoid the non-specific binding of proteins and other species that can lead to opsonization or encapsulation. Reactions that place a polyethylene glycol (PEG) linker on a porous Si surface have been employed to this end (Fig. 3) [110,111]. A short-chain PEG linker yields a hydrophilic surface that is capable of passing biomolecules into or out of the pores without binding them strongly [112]. The distal end of the PEG linker can be modified to allow coupling of other species, such as drugs, cleavable linkers, or targeting moieties, to the material [110, 112].

The oxides of porous Si are easy to functionalize using conventional silanol chemistries [76, 110,113]. When small pores are present (as with p-type samples), monoalkoxydimethylsilanes ($RO–Si(Me)_2–R'$) can be more effective than trialkoxysilanes ($(RO)_3Si–R'$) as surface linkers [113]. This is because trialkoxysilanes oligomerize and clog smaller pore openings, especially when the reagent is used at higher concentrations.

Whereas Si–C chemistries are robust and versatile, chemistries involving Si–O bonds represent an attractive alternative two reasons. First, the timescale in which highly porous SiO_2 is stable in aqueous media is consistent with many short-term drug delivery applications— typically 20 min to a few hours. Second, a porous SiO_2 sample that contains no additional stabilizing chemistries is less likely to produce toxic or antigenic side effects. If it is desired that the porous Si material be stable *in vivo* for long periods (for example, an extended release formulation or an *in vivo* biosensor), Si–C chemistries such as hydrosilylation with endcapping [102] or thermal carbonization with acetylene [30] is preferred. If a longer-lived oxide matrix is desired, silicon oxides formed at higher temperatures (>700 °C) are significantly more stable in aqueous media than those formed at lower temperatures or by ozone oxidation [114].

4. Loading and controlled release of drugs with porous Si

Providing a controlled and localized release of therapeutics within the body are key objectives for increasing efficacy and reducing the risks of potential side effects [115–119]. The low toxicity of porous Si and porous SiO_2, the high porosity, and the relatively convenient surface chemistry has spurred interest in the use of this system as a host, or “mother ship” for therapeutics, diagnostics, or other types of payloads. Various approaches to load a molecular payload into a porous Si host have been explored, and they can be grouped into the following general categories: covalent attachment, physical trapping, and adsorption.

4.1. Incorporating a payload within the porous nanostructure by covalent attachment

Covalent attachment provides a convenient means to link a biomolecular capture probe to the inner pore walls of porous Si for biosensor applications [85,110], and this approach can also be used to attach drug molecules. As was pointed out in the previous section, linking a biomolecule via Si–C bonds tends to be a more stable route than using Si–O bonds due to the susceptibility of the Si–O species to nucleophilic attack.

The versatility of the hydrosilylation reaction for preparing functional porous Si surfaces was recognized early in the history of porous Si surface chemistry [80]. One of the more common approaches is to graft an organic molecule that contains a carboxyl species on the distal end

of a terminal alkene as was presented above in Fig. 3 [85]. The alkene end participates in the hydrosilylation reaction, bonding to the Si surface and leaving the carboxy-terminus free for further chemical modification. A favorite linker molecule is undecylenic acid, which provides a hydrophobic 10 carbon aliphatic chain to insulate the linker from the porous Si surface [85, 120]. The drug payload can be attached directly to the carboxy group of the alkene, or it can be further separated from the surface with a PEG linker as shown in Fig. 3 [110]. Due to the stability of the Si–C bond, hydrosilylation is one of the most robust means of attaching a payload to porous Si. The payload is only released when the covalent bonds are broken [112] or the supporting porous Si matrix is degraded. For drug delivery this introduces a complication in that the drug may not release from the linker, resulting in a modified version of the drug being introduced into the body. In addition, a drug may be susceptible to attack by silane generated during the degradation of the porous Si scaffolding [52] or by residual reactive species on the porous Si material itself [31]. Any studies involving porous Si (or with nanomaterials in general) need to incorporate activity assays to ensure that the released drug has not become inactivated.

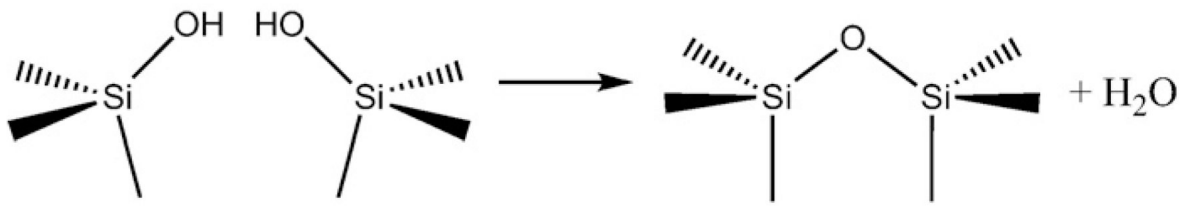
4.2. Trapping a payload by oxidation

If the species to be trapped is relatively robust, it can be locked into place by oxidation of the porous Si host matrix. The locking procedure takes advantage of the fact that when porous Si is oxidized to SiO_2 there is a volume expansion to accommodate the extra oxygen atoms, Fig. 4. This volume expansion serves to shrink the pores, trapping anything that happens to be in them at the time. Iron oxide (Fe_3O_4) nanoparticles have been loaded and locked into the porous nanostructure in this fashion, using aqueous ammonia to induce oxidation [121]. The high pH and nucleophilic nature of ammonia enhance oxidation of freshly etched porous Si in aqueous solutions [122]. Similar oxidation can be induced by vapor phase pyridine [123]. Nucleophilic groups present on drug payloads may also participate in this reaction [20], as can oxidizing species such as quinones [72].

The silicic acid generated during dissolution Eq. (3) can participate in sol–gel type reactions —essentially reprecipitation of the silicic acid, but in the form of various inorganic silicates. Common ions such as Ca^{2+} and Mg^{2+} in solution can participate in silicate precipitation reactions Eq. (8), and these types of precipitates are known to be bioactive [125–127].

$$Si(OH)_4 + 2Ca^{2+} \rightarrow Ca_2SiO_4 + 4H^+ \quad (8)$$

Once formed, mild thermal treatments can be used to dehydrate the oxide or silicate matrix. Heating tends to densify and rigidify the structure by forming strong Si–O–Si linkages (Eq. (9)).



(9)

4.3. Concentrating a payload by spontaneous adsorption

As-formed porous Si has a hydride-terminated surface that is very hydrophobic. Oxidized porous Si is hydrophilic, and chemically modified porous Si surfaces can be hydrophobic, hydrophilic, or both (amphiphilic), depending on the specific functional group(s) attached. The nature of the surface plays a critical role in determining the amount of drug that can be loaded and the rate at which it is released. Silicon oxide surfaces tend to present a negative surface charge to an aqueous solution due to the low pK_a of SiO_2 [128]. Often referred to as "electrostatic adsorption," attractive coulombic forces from this negative surface provide a means to extract positively charged ions from solution and concentrate them at the interface. Whereas covalent attachment and oxidative trapping approaches described above tend to trap their payloads fairly irreversibly, electrostatic adsorption represents essentially an ion exchange mechanism that holds molecules more weakly. Electrostatics is a useful means to effect more rapid drug delivery, as opposed to covalent or physical trapping approaches that release drug over a period of days, weeks, or months [43,60].

The affinity of a porous Si particle for a particular molecule can be controlled with surface chemistry. The surface of oxidized porous Si has a point of zero charge at a pH of around 2 [128,129], and so it presents a negatively charged surface to most aqueous solutions of interest, as depicted in Fig. 5. At the appropriate pH, porous SiO_2 spontaneously adsorbs positively charged proteins such as serum albumin [130,131], fibrinogen [132], protein A [70,114,133], immunoglobulin G (IgG) [134], or horseradish peroxidase [25], concentrating them in the process. For example, a 0.125 mg/mL solution of the monoclonal antibody bevacizumab (trade name Avastin, an anti-cancer drug) spontaneously concentrates in suitably prepared porous SiO_2 by a factor of >100 (unpublished results).

Porous Si can also be made hydrophobic, and hydrophobic molecules such as the steroid dexamethasone or serum albumin can be loaded into these nanostructures [16,135]. Hydrophilic molecules can also be loaded into such materials with the aid of the appropriate surfactant [21]. The native hydride surface of porous Si is hydrophobic. Though it is not particularly stable in aqueous media, it has been used for short-term loading and release studies [21,31]. Because water is excluded from these hydrophobic surfaces, aqueous degradation and leaching reactions tend to be slow. The grafting of alkanes to the surface by hydrosilylation is commonly used to prepare materials that are stable in biological media; this stability derives in large part from the ability of the hydrophobic moieties to locally exclude water or dissolved nucleophiles, as was discussed above in the chemistry section [43,60].

5. Composites of porous Si and polymers

Hybrid materials, in which the payload consists of an organic polymer or a biopolymer, forms an additional class of host/payload systems. Composites are attractive candidates for drug delivery devices because they can display a combination of advantageous chemical and physical characteristics not exhibited by the individual constituents. Advances in polymer [136] and materials [137] chemistries have greatly expanded the design options for nanomaterial composites in the past few years, and synthesis of materials using nanostructured templates has emerged as a versatile technique to generate ordered nanostructures [138]. Templates consisting of microor mesoporous membranes [139,140], zeolites [141], and crystalline colloidal arrays [142–144] have been used, and many elaborate electronic, mechanical, or optical structures have resulted.

5.1. Porous Si as a template

Porous Si is an attractive candidate for use as a template because of the tunability of the porosity and average pore size. Additionally, elaborate 1, 2, and 2.5-dimensional photonic crystals are

readily prepared in porous Si [145]. Porous Si composites show great promise for improving the mechanical stability and control over release rates of a delivery system. Polymers that have been incorporated into porous Si include polylactide [146], polydimethylsiloxane [147], polyethylene [146], polystyrene [146], polycaprolactone [148], zein (a biopolymer derived from maize) [149], and poly(N-isopropylacrylamide) [150]. Either the composite itself or a nanostructure derived from the composite by removal of the porous Si template can be used (Fig. 6) [146]. Porous Si combined with a biocompatible polymer has been shown to yield improved control over drug release kinetics and improved stability in aqueous media [146], and the use of biopolymers that are selectively cleaved by specific proteases [112,149] provides the possibility of tissue-specific action.

Removal of the porous Si or porous SiO_2 template from a polymer or biopolymer imprint can sometimes be achieved by chemical dissolution using aqueous KOH or HF, respectively, providing a freestanding porous polymer film with the optical characteristics of the master. Whether or not the process replicates the nanostructure of the master is highly dependant on the processing conditions and the type of polymer used. Also, the ability of the polymer to release from the master is highly dependant on the interfacal chemistry and tortuosity of the pore network.

The concept of placing a polymeric material within a porous Si matrix was first demonstrated in the early 1990s [151]. Two synthetic approaches have emerged: either the polymer is synthesized within the porous matrix [151–154], or a pre-formed polymer is infused into the matrix by melt- or solution-casting [46,47,146,147,155]. For drug delivery applications, it is important to use a biocompatible polymer, and hydrogels are of particular interest [29,150]. Hydrogels are commonly used in ophthalmologic devices, biosensors, biomembranes, and controlled drug delivery [156].Water-swollen, crosslinked polymeric networks can undergo volume phase transitions in response to environmental changes such as pH [157,158], ionic strength [159], temperature [160], or electric fields [161]. Materials responsive to pH changes have been investigated extensively because they are applicable to many drug delivery and biosensing schemes.

5.2. Locking the polymer in a porous Si template

Since porous Si consists of a delicate matrix of nanocrystalline domains, its mechanical stability is an issue, especially for applications in which the material is thermally cycled or subjected to mechanical stresses. Chemical crosslinking of a porous Si template can be achieved with the correct choice of polymerization conditions. First demonstrated in 2003 [152], such methods take advantage of the reactivity of the hydride-terminated porous Si surface. For example, porous Si treated with a ruthenium ring-opening metathesis polymerization catalyst followed by norbornene produces a flexible, stable composite in which poly(norbornene) is covalently attached to the porous Si matrix (Fig. 7). The method follows the procedure of Lewis and Grubbs to graft polymers onto crystalline Si surfaces using a ring-opening metathesis polymerization catalyst [162,163].

The ring-opening metathesis polymerization (ROMP) reaction acts on rings containing double bonded carbon, and the C=C double bonds are conserved through the process [162]. A significant amount of this unsaturated polymer becomes covalently attached by hydrosilylation with the Si–H species on the porous Si surface. If oxidized porous Si is used in the reaction, the lack of Si–H surface groups eliminates the possibility of covalent Si–C bond formation between the polymer and the template. Composites with lower mechanical and chemical stability result [152]. Thus both the weaving of a soft polymer network into the pores and the covalent attachment of this polymer to the matrix combine to provide the robust chemical and mechanical properties. Hydrosilylation can also be induced via a radical mechanism, and the

radical initiators used to set a hydrogel polymer probably induce similar covalent attachment reactions between these polymers and their porous Si hosts [150].

6. *In vivo* monitoring using the optical properties of porous Si

Many material hosts have been developed for drug delivery, but few can 'self-report' on the amount of drug loaded or released. It is important to know these quantities when determining the efficacy of a treatment to identify when it is time to administer a new dose. The unique optical properties that can be engineered into porous Si provide a mechanism to perform such assays *in vivo*. Incorporation of molecules into a porous Si layer alters its index of refraction, and the spectrum obtained from a thin film or multilayer structure provides a measure of loading in the nanostructure. Primarily exploited for molecular binding assays [7,9,10,22,70,149, 164–173], the optical spectrum can be monitored *in vivo*, allowing it to indicate the quantity of drug that has diffused out of the film [16] or the degree of degradation of the porous matrix [10]. The optical spectrum also provides a convenient means to characterize and quantify various drug loading or release concepts *ex vivo*. Detailed descriptions of the optical interference spectra and their interpretation appear elsewhere [6]; a brief summary will be presented here.

6.1. Principles of optical detection in porous Si films

The reflectivity spectrum of a thin film (Fig. 8) displays Fabry–Pérot interference frin1ges that correspond to constructive and destructive interference from light reflected at the different boundaries in the layered structure. The thickness of the layer and the refractive index (RI) contrast at each interface (air/porous Si and porous Si/crystalline Si) can be extracted from the fast Fourier transform (FFT) of this spectrum. Theoretically, a layered structure will yield a single peak in the FFT spectrum. The amplitude of the peak is related to the index contrast at each of the interfaces, and the position of a peak yields the product of optical thickness, or nL (where n is refractive index and L is thickness) [113]. Since the refractive index can be related to the mass loading of a layer by application of the Bruggeman effective medium model [174], this method can be used to monitor molecular in- or exfiltration. We refer to this method as RIFTS, for Reflective Interferometric Fourier Transform Spectroscopy [70,114,175].

More complicated structures, such as rugate filters, Bragg stacks, and microcavities can be prepared, but the basic principle of detection remains the same: a shift in the characteristic optical reflectivity spectrum corresponds to a change in refractive index of the porous layer, which is related to its composition. Shifts in the spectrum occur when molecules are transported into or out of the layer. A shift can also occur when the porous Si film oxidizes. Porous Si has a refractive index of approximately 2.1, and the index of oxidized porous Si ranges from this value down to a value of ~ 1.6, depending on the degree of oxidation. In an aqueous system, molecules removed from the pores are replaced by water. Since water has an index of 1.33 and most biomolecules have an index of 1.5–1.7, release of molecules from the pores results in a blue shift in the spectrum. For the same reason, dissolution of the porous Si matrix also results in a blue shift of the spectrum. The sensitivities of the various optical structures (Fabry–Pérot, rugate, Bragg stack, microcavity), in terms of spectral shift vs analyte concentration in the pores, are similar [176].

6.2. Monitoring a porous Si fixture in vivo

The optical interference spectrum used to assess loading can be measured with inexpensive and portable instrumentation such as a CCD spectrometer or a diode laser interferometer [177,178]. This is useful, for example, in monitoring porous Si particles in the vitreous of rabbit eyes for ocular drug delivery (Fig. 9) [146]. Removal of drug or dissolution of the particle results in a change in the refractive index of the porous film that is observed as a wavelength

shift in the reflection spectrum. In clinical situations, we have shown that this color change can be qualitatively followed with the use of a fundus camera or quantitated by spectroscopy in the living eye. The presence of DNA [9,179], human IgG [10], bovine serum albumin [130], dexamethasone [16], caffeine [146], and many other molecules has been detected (in *ex vivo* systems) using this methodology. The high surface area and optical interferometric means of detection lead to sensitivities comparable to surface plasmon resonance (SPR) for many of these systems [173,176].

The optical spectrum of a porous Si photonic crystal can be read through human tissue (up to 1 mm in thickness), demonstrating the feasibility of the *in vivo* self-reporting system [146]. The optical method is particularly useful for monitoring of intraocular drug release either in the form of porous Si particles or composite films (Fig.10). The porous Si microparticles displayed in Fig. 9 demonstrate their potential as self-reporting drug delivery devices for treatment of diseases such as age-related macular degeneration, where there is an important need for long acting intraocular drug delivery systems [180].

7. Medical applications of porous Si

The suitability and efficacy of various forms of porous Si are being assessed for medical applications, and some are currently in clinical trials. The incorporation of anti-cancer therapeutics [19,181], anti-inflammatory agents [16,31], analgesics [31], and medicinally relevant proteins and peptides has been demonstrated [21]. The oral administration of porous Si to provide a dietary supplement of silicon [182] has also been assessed [183]. Porous Si drug delivery devices have taken the form of particles [25,184,185], films [16], chip implants [186,187], composite materials [146,150], and microneedles [188,189]. Much work has focused on microparticle systems [21,25,30,31,106–108,190–193] due to their relative ease of fabrication, administration, and their compatibility with existing drug delivery concepts.

7.1. Particle formulations

Particles have the potential for percutaneous or intravenous administration depending on their size. Foraker et al. have demonstrated delivery of insulin across Caco-2 cell monolayers [21], while Salonen and coworkers have investigated the drug release kinetics from porous Si microparticles for applications in oral delivery [31]. The latter workers have investigated the interactions between various drugs with the different porous Si surface chemistries in detail [20]. The incorporation of superparamagnetic iron oxide nanoparticles, of interest for Magnetic Resonance Imaging (MRI) has been demonstrated [25,121], and remote RF heating (by Néel relaxation) of such structures has been reported [185]. The amount of drug that can be loaded into a porous Si microparticle is large due to its relatively large free volume. For example, a single cubic particle 10 μm on an edge and with a porosity of 80% yields a maximumfree volume of 0.8 pL [25]. Because they can concentrate molecules within their nanostructure and protect them from the body's natural immunological responses, the particles can potentially carry a much higher dose than could be allowed with a free drug injection. The particles can also be manufactured with well-defined shapes and dimensions, allowing the reproducible loading and release of precise quantities [44–46].

7.2. Cancer treatment

Some of the most advanced clinical studies have been performed by pSiMedica, inc. using porous Si as a brachytherapy device for the treatment of cancer [11,186,187]. In this work, percutaneous implants of porous Si particles (on the order of 20 μm in size) containing radioactive ^{32}P provide local radiation to the tumor. The radioactive isotope is synthesized in the porous Si material by elemental transmutation of Si, induced by exposure to high energy neutrons emanating from a nuclear reactor. After delivery of the radiation dose, the device

resorbs into the body as the Si implant hydrolyzes to silicic acid (Eqs. (2) and (3)), thereby requiring no further surgery to recover the device. Although silicic acid can be cytotoxic [56–58,64,65], apparently the resorption rate is slow enough under physiologic conditions that the concentration of free silicic acid does not reach toxic levels.

Anti-cancer therapeutics have been successfully incorporated into porous Si. Delivery of cis-platin, doped into calcium phosphate/porous Si films has been demonstrated in simulated body fluid [194], and doxorubicin loaded porous Si films have shown cytotoxic effects towards human colon adenocarcinoma cell lines [19]. In addition, photoexcitation of quantum confined silicon nanostructures in aqueous aerated media has been shown to produce singlet oxygen [32–35]. The ability of the porous Si nanostructure to degrade into relatively harmless silicic acid byproducts makes porous Si an attractive alternative to molecular (typically porphyrin-based [195]) sensitizers for photodynamic therapy [196,197].

8. Summary and prospects

Porous Si microparticles offer a number of properties of interest for controlled drug delivery: First, nanostructured materials based on silicon are promising platforms for pharmaceutical applications because they provide low toxicity. Their ability to degrade in the body presents fewer challenges for chronic use than, for example, carbon nanotubes which are not metabolized and so must be excreted after administration.

Second, the electrochemical means of fabrication allows one to “dial in” the properties of surface area, free volume, and pore size. Pores can be generated anywhere from a few nanometers to several hundreds of nanometers in diameter.

Third, the surface of freshly prepared porous Si is easily modified via convenient chemistry with a large range of organic or biological molecules (drugs, peptides, antibodies, proteins, etc.), allowing flexibility in the engineering of release profiles.

Fourth, the optical properties of porous Si provide a useful dimension for *in vivo* sensing or therapeutics. Porous Si can display fluorescence deriving from Si quantum dot structures that are produced during the etch [1], and it can be prepared with unique optical reflectivity spectra. These features allow porous Si to exhibit a signal that is affected in a predictable way when exposed to environmental changes, presenting possibilities for the development of advanced functional systems that incorporate sensors for diagnostic or therapeutic functions.

Finally, the ease with which porous Si can be integrated into well-established Si microelectronics fabrication techniques could also lead to more sophisticated, active devices for medical applications [65,89,198]. The possibility of placing active electronic circuit components into the silicon-based particles is another feature of silicon that is yet to be exploited for *in vivo* use.

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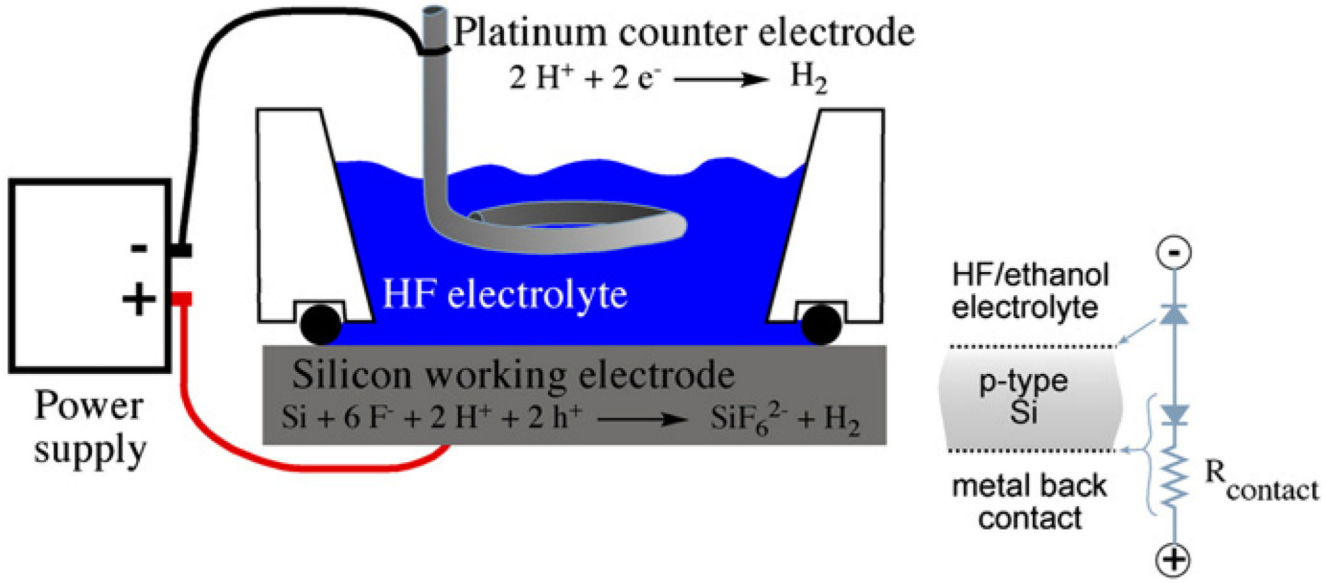

Fig. 1.
Schematic of the etch cell used to prepare porous Si. The electrochemical half-reactions are shown, and the equivalent circuit for etching of a p-type Si wafer is shown at right.

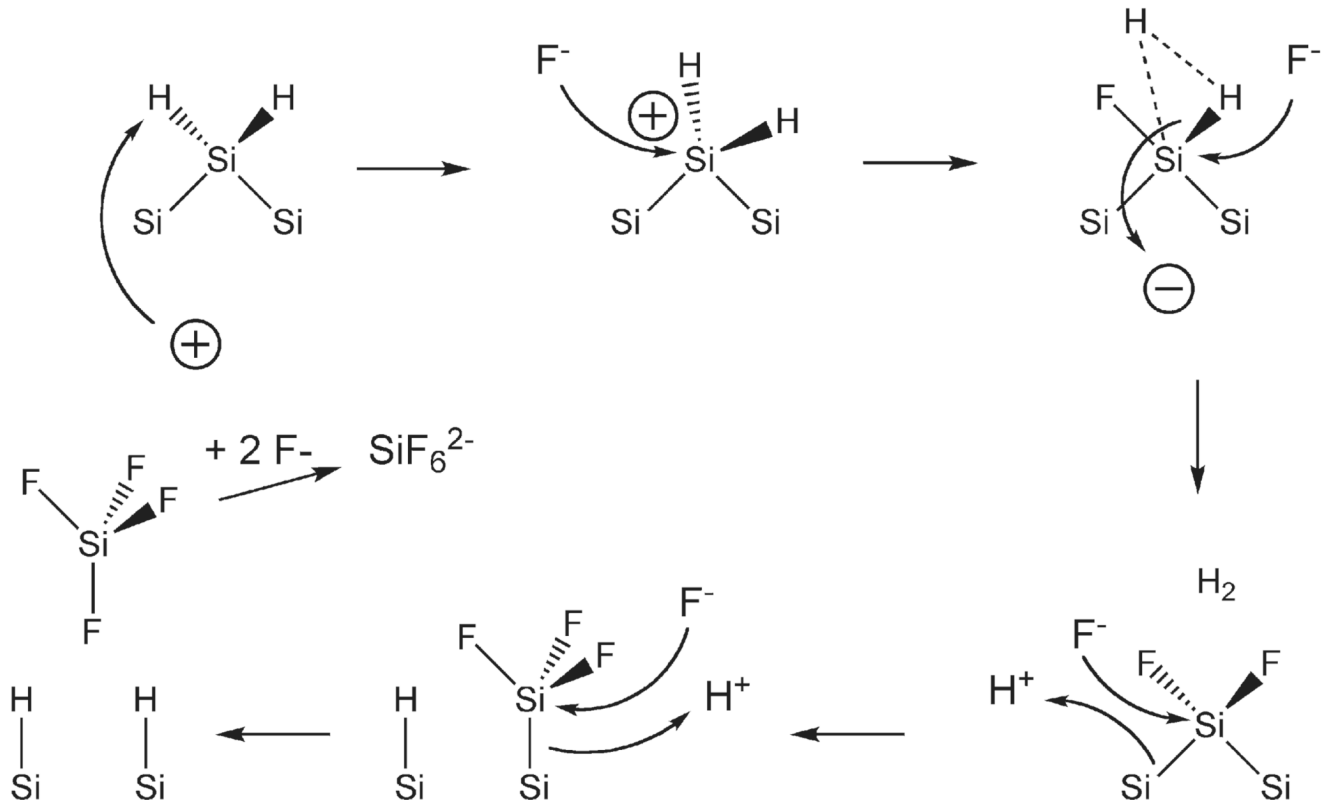

Fig. 2.
Mechanism of Si oxidation during the formation of porous Si (adapted from reference [38]).

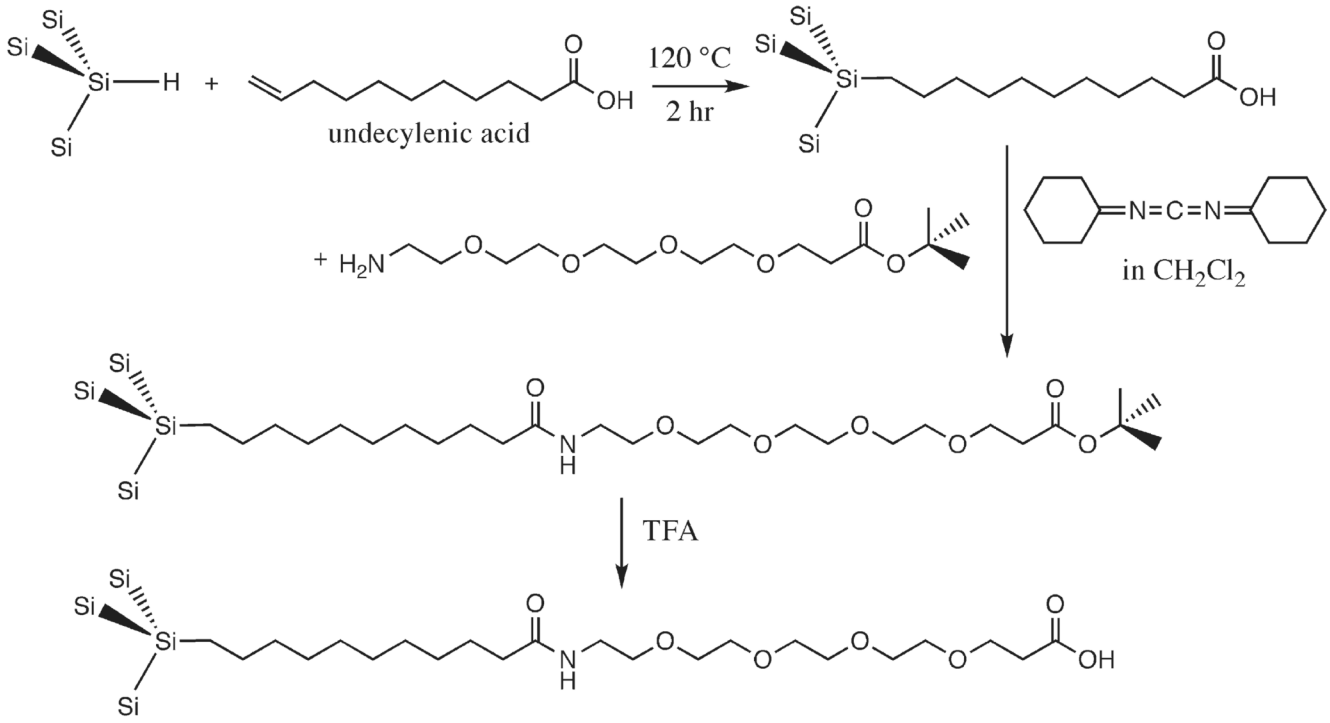

Fig. 3.

Adding a linker to porous Si via hydrosilylation. The short-chain PEG linker yields a hydrophilic surface that minimizes non-specific binding effects (adapted from reference [110]).

Fig. 4.

Building a bottle around a ship. A molecular or nanoparticle payload can be trapped by partial oxidation of the porous Si host layer. Oxidation produces a volume expansion (Si to SiO_2) that shrinks the pores, locking the payload in place. After [124]

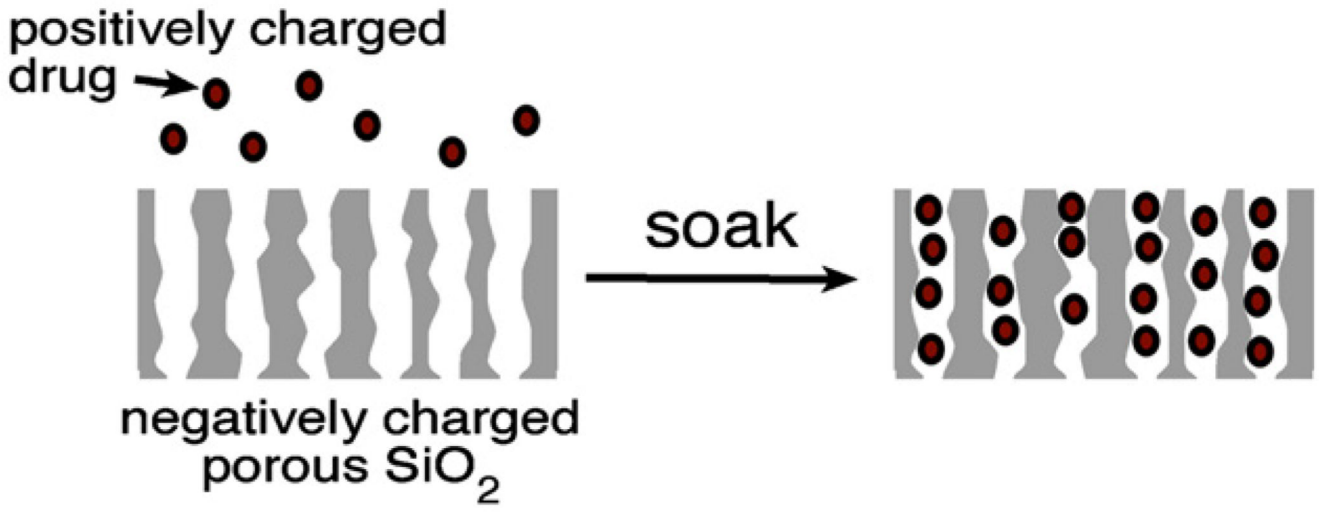

Fig. 5.

Trapping of a positively charged drug payload in a porous SiO_2 layer by ionic adsorption. Porous SiO_2 (oxidized porous Si) has a negative surface charge; molecules with positive charges will spontaneously adsorb to the inner pore walls and surface. This method is commonly used to load proteins [70,114,130,132–134]

Fig. 6.

Fabrication of a nanostructured composite from a porous Si template. A variety of solution- or melt-processible organic and biopolymers can be solution-cast or injection-molded into a porous Si or porous SiO_2 host. The composite can be used as-formed, or the template can be removed by chemical dissolution. If the template is removed, the polymer castings often replicate the nanostructure of the master. Use of these castings as vapor sensors, deformable and tunable optical filters, and as self-reporting, bioresorbable materials has been demonstrated [146].

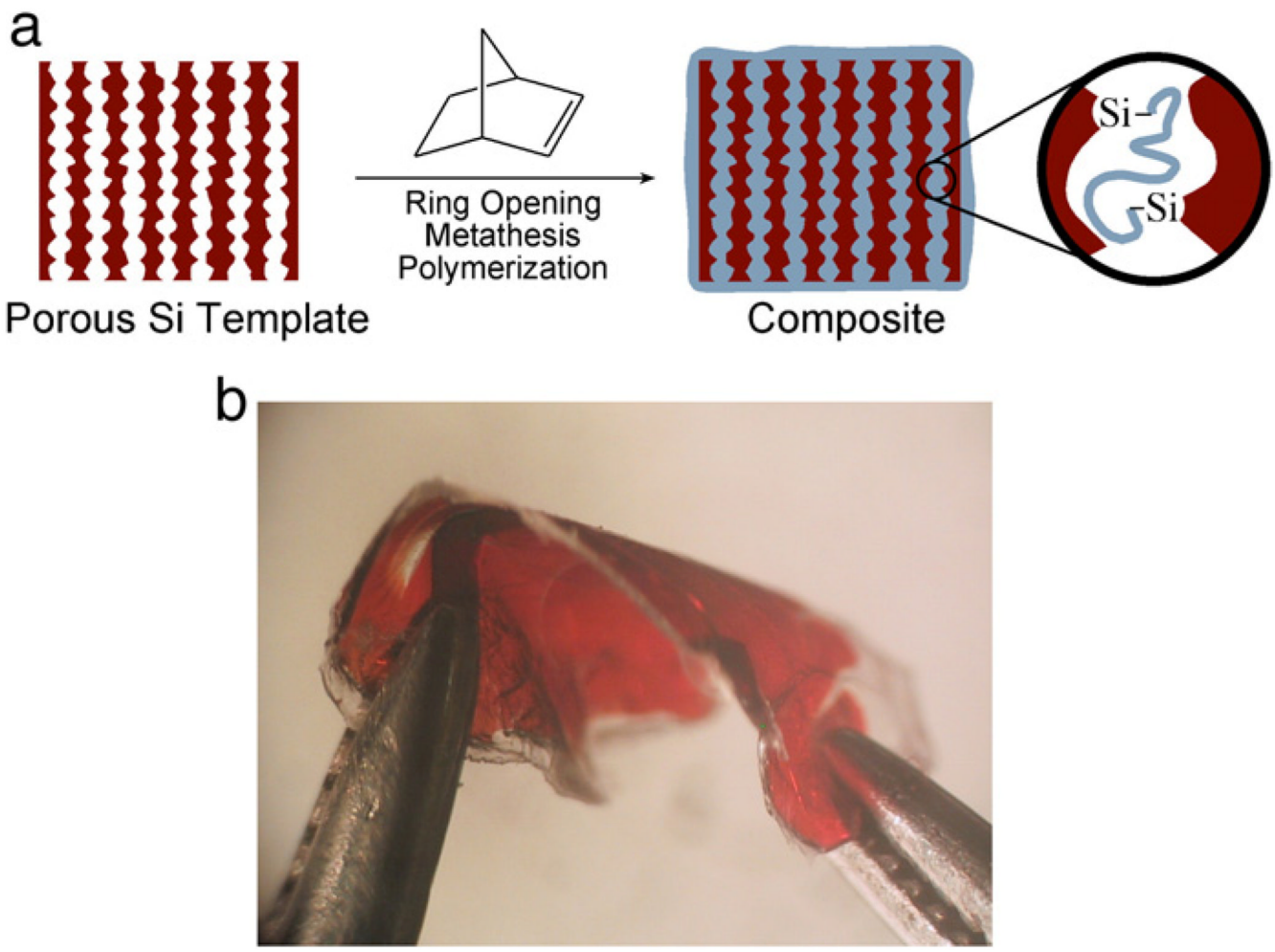

Fig. 7.

In-situ polymerization and crosslinking of a porous Si template. The catalyzed reaction generates a composite porous Si/polymer matrix in which the polymer is covalently attached to porous Si via Si–C bonds. The chemical and mechanical stability of the chemically crosslinked porous Si matrix is significantly improved relative to the porous Si film alone. After [152].

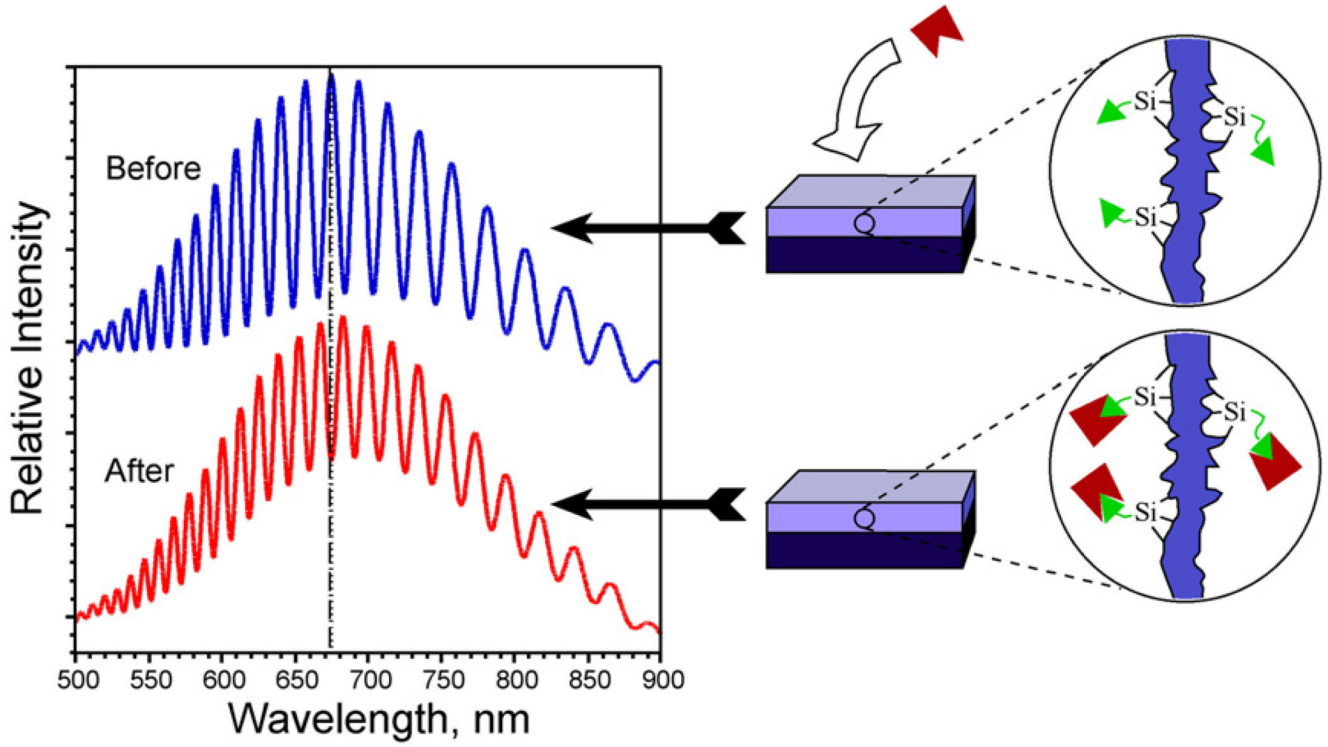

Fig. 8.

Schematic demonstrating the change in a reflectance spectrum from a single layer of porous Si upon introduction of a molecular species into the porous matrix. The change in refractive index of the composite film results in a red shift of the Fabry–Pérot interference fringes. The reverse process can also be monitored, yielding a blue shift in the spectrum.

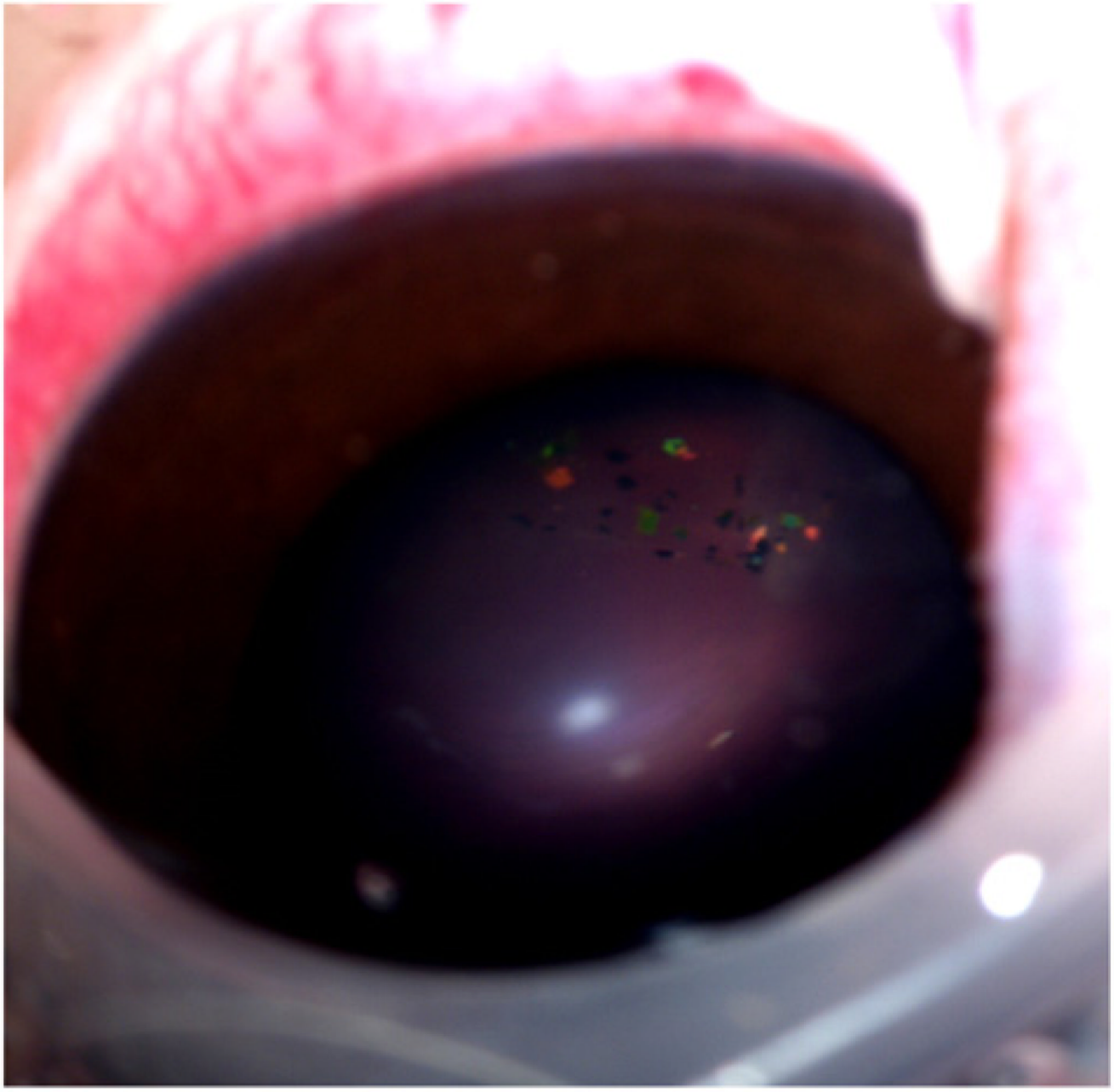

Fig. 9.
Photograph of porous Si microparticles in a live rabbit eye. The particles were prepared as multilayered photonic crystals (rugate filters), and they appear as brightly colored flecks that can be seen floating the vitreous. The color of the microparticles shifts to the blue as the particles degrade *in vivo*, providing a predictive metric to the clinician.

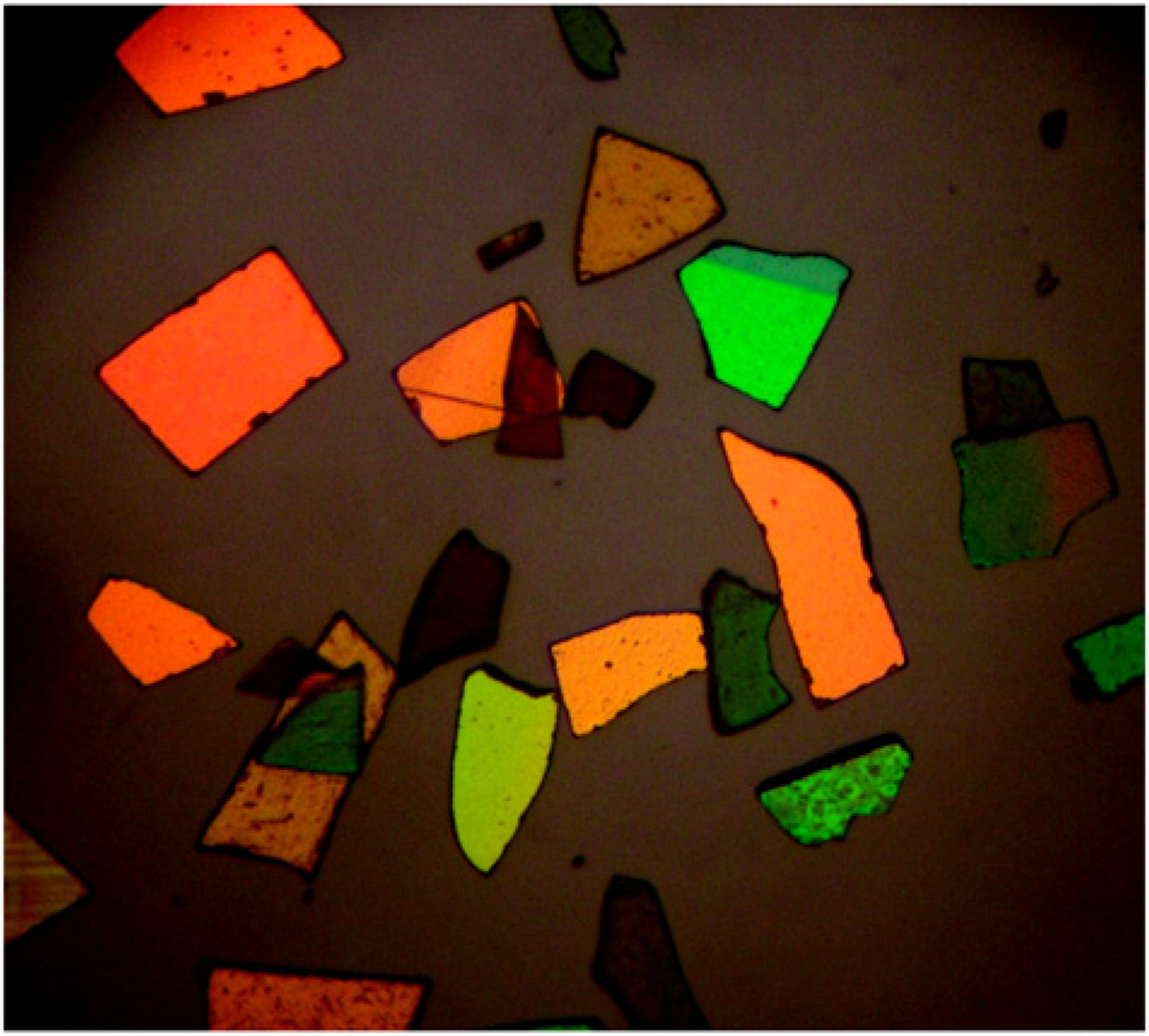

Fig. 10.
Light microscope image of porous Si microparticles. These particles were prepared as multilayered photonic crystals (rugate filters) and display various spectral colors depending on the periodicity of their layered nanostructure. Nominal particle size is 50 μm.