Hindawi Publishing Corporation
Journal of Nanomaterials
Volume 2012, Article ID 830503, 15 pages
doi:10.1155/2012/830503

Review Article

Nanoporous Silicon as Drug Delivery Systems for Cancer Therapies

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Received 13 January 2012; Revised 10 May 2012; Accepted 18 May 2012

Academic Editor: Krasimir Vasilev

Porous silicon nanoparticles have been established as excellent candidates for medical applications as drug delivery devices, due to their excellent biocompatibility, biodegradability, and high surface area. The simple fabrication method by electrochemical anodization of silicon and its photoluminescent properties are some of the merits that have contributed to the increasing interest given to porous silicon. This paper presents the methods of fabrication, which can be customized to control the pore size, various chemical treatments used for the modification of silicon surfaces, and the characterization and pore morphology of silicon structures. Different approaches used for drug loading and the variety of coatings used for the controlled released are revised. The monitoring of the toxicity of silicon degradation products and the in vivo release of a drug in a specific site are described taking into account its significance on medical applications, specifically on cancer therapy.

1. Introduction

Nanotechnology has revolutionized engineering designs in a range of materials and applications. Biotechnology, pharmaceutics, food technology, and semiconductors among others are some of the various scientific fields that have benefitted from this technology.

Among some of the numerous applications, the fabrication of nanostructures has been envisioned as drug delivery systems. These have the potential of reducing side effects by delivering the exact amount of drugs into a specific site rather than the common systemic delivery, which diffuses across tissues and organs [1–3]. Special efforts are required on the design and development of a new drug delivery system. Identification of the target and management of the release over time are important issues to consider in order to achieve maximum treatment. Nanoporous structures with pore size of less than 100 nm have been fabricated in different materials such as titanium oxide (TiO_2), aluminum oxide (Al_2O_3), and silicon (Si) [4, 5]. Porous silicon (pSi) has been and still being investigated in both bulk crystalline and as nanostructure for applications as diverse as optics [6–8], chemical sensors [9–11] and biosensors [12–16], radiotherapy [17], tissue engineering [18], cell culture [19], biotechnology, gas separation, catalyst and microelectronics [20]. pSi with pore size 2–50 nm has played a significant role as a carrier in pharmaceutical technology for its drug loading and controlled release properties [1, 2, 21–23].

Uhlir first discovered pSi in the Bell laboratories in 1950s when cleaning and polishing Si surfaces [24], and interest in pSi increased during 1970s–1980s due to its high surface area, which made it useful as a model in spectroscopic studies [25, 26]. During the 1990s, after its photoluminescence properties were discovered, pSi fascination increased and it was used later as a biomaterial, when covered with hydroxyapatite [27]. pSi pore dimensions can be precisely controlled depending on fabrication parameters. This useful feature enables a range of bioactive species to be loaded and the desired rate of drug release to be easily obtained [28]. Additionally, pSi presents properties such as a high surface area

(400–1000 m^2/g) [29], and the ability to degrade completely in aqueous solutions into nontoxic silicic acid, the major silicon form in the human body [27]. Silicic acid is known to be absorbed by the gastrointestinal tract and then secreted through the urine [30, 31]. However, other results have found pSi to be bioinert, bioactive or biodegradable depending on the porosity and pore size [32]. Subcutaneous injection of mesoporous silicates in rats showed no toxicity effects, but intraperitoneal and intravenous injections resulted in death or euthanasia. This was reported as a consequence of the formation of thrombus and hence further modifications of the structures were suggested [28]. Pore sizes together with surface treatments have been considered to play a major role in cell-particle interactions and hence determine toxicity of the material [33]. In an in vitro cytotoxicity study, the smallest particles were reported to be the most toxic, and the surface chemistry treatment the key factor regarding the toxicity aspect [34]. Nevertheless, there is still a need for more reports in cytotoxicity or biocompatibility of silicon structures for biotechnological applications.

Microfabricated pSi particles as drug delivery systems have shown to enhance paracellular delivery of insulin [21] and the permeability of griseofulvin [35] across intestinal Caco-2 cell monolayers. They have also been used as excellent carriers of clorgyline across the blood brain barrier as a treatment for central nervous system diseases such as Parkinson and Alzheimer [36]. Loading and release of various drugs have been investigated in vitro such as common oral drugs (antipyrine, ibuprofen, griseofulvin, ranitidine, and furosemide) [37, 38] or dexamethasone for cancer treatment [39]. The capability of pSi to carry up to 80% excess of load has been demonstrated in various studies with protein [40], anticancer drugs [41], and other types of drugs [37, 39].

The scope of this paper is to review the fabrication and characterization of pSi nanoparticles for application as drug delivery devices. With that in mind, surface modification, drug loading and controlled release methods are also revised. A special interest is given to these structures for application in cancer therapies.

2. Fabrication of Porous Silicon

Silicon is a biomaterial, one of the most frequent elements in the earth's crust [42]. A range of methods can be applied for the fabrication of porous Si, chemical stain etching, chemical vapor etching, laser-induced etching, metal-assisted etching, spark processing and reactive ion (plasma) etching. However, the most recurrent methods are electrochemical anodization and stain etching. A recent review discusses the various Si porosification methods and the numerous parameters (electrolyte composition and pH, current density, etching time, temperature, wafer doping and orientation, lighting, magnetic field, and ultrasonic agitation) that influence the process [43].

2.1. Electrochemical Anodization. PSi can be prepared by electrochemical anodization of a single crystalline silicon wafer using a solution of hydrofluoric acid (HF) [44]. The method itself does not present any complication, but a tight control of the porous structures is challenging since it depends on several factors. Current density, concentration of hydrofluoric acid, electrolyte stirring, type of dopant (*p*-type and *n*-type), orientation of the crystalline Si, resistivity and temperature, the etching time and the illumination and wavelength during the etching process are key factors that affect the outcome of the Si nanoporous structures [45].

Typically, the electrochemical anodization consists in applying a constant current between two electrodes immersed in an electrochemical cell containing an aqueous solution of hydrofluoric acid and ethanol, where ethanol acts as surfactant to reduce hydrogen bubble formation [44, 46] (Figure 1). Other methods present some variants such as the use of H_2O_2 in the wet etching bath, with a high etching current [47] or by means of pulsed current anodic etching [48] and the use of ultrasound to further enhance the electrochemical etching [49].

A constant current is applied between the anode (Si wafer) and the cathode (platinum electrode) immersed in an electrochemical aqueous solution of hydrofluoric acid, where the following reactions take place:

$$\text{Pt} : 2H^+ + 2e^- \longrightarrow H_2 \tag{1}$$

$$\text{Si} : \text{Si} + 6F^- + 2H^+ + 2e^- \longrightarrow {SiF_6}^{2-} + H_2 \tag{2}$$

Pore formation in the Si wafer follows the mechanism shown in Figure 2, where (1) due to the low polarization between the hydrogen and silicon atoms, the fluoride ion of the HF-based electrolyte solution attacks the hydrogen-saturated silicon surface as long as there is absence of electron holes; (2) Si–F bond is formed by nucleophilic attack on a Si–H by a fluoride ion if a hole reaches the surface; (3) the polarization due to Si–F bond influences the second fluoride ion attack, replacing the remaining hydrogen bond and injecting two hydrogen atoms of one electron into the substrate; (4) after polarization, the Si-F bonds reduce the electron density of the Si–Si back bonds, and these make it liable to be attacked by HF or H_2O; (5) the highly stable SiF_6 fluoroanion is the reaction product of the tetrafluoride molecule with HF [50].

The porosity of Si structures can be defined as a percentage of empty hole volume, ranging between 20% and 80%, causing the difference in morphology. Pore morphology depends on the type of substrate and other anodization conditions. Increasing the etching time increases the overall size and thickness of the pSi layer [51].

In order to separate the porous layer from the substrate, an electropolishing process or lift-off method at a critical value of current density is required following the formation of pSi. Electropolishing processes occur at potentials higher than the peak potential of pSi formation. Pore diameter increases, in general, with increasing potential and decreasing HF concentration, while the amount of chemical dissolution increases with immersion time and decreasing HF concentration [52]. Hence, the etched Si is immersed in a different HF electrolyte solution, and secondary current pulses are applied [53]. During lower concentration of HF electrolyte, it is considered that the process occurs under

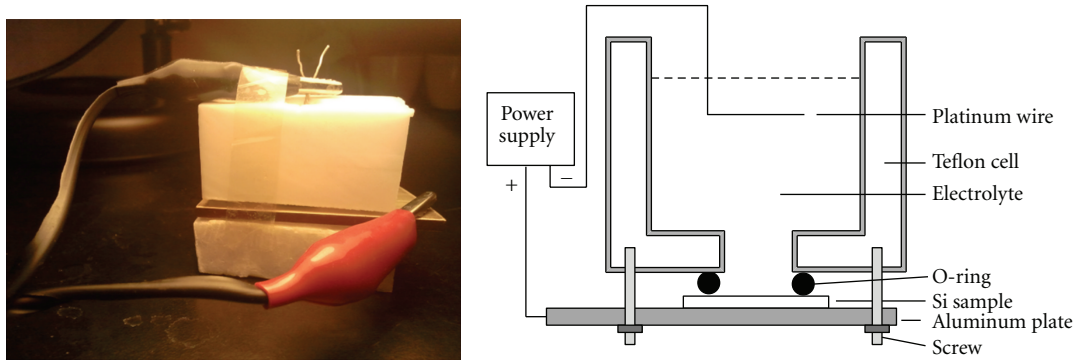


Figure 1: Setup for electrochemical etching of porous silicon. (a) Teflon cell containing the silicon wafer (anode) and the platinum wire (cathode). (b) Sketch of the Teflon cell illustrating the components of the setup.

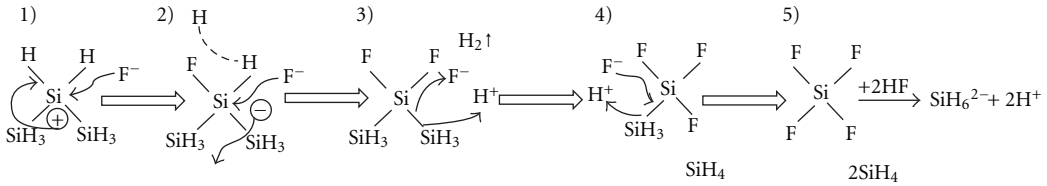


Figure 2: Mechanism of pore formation. (1) F ion attacks the hydrogen saturated silicon surface; (2) Si–F bond is formed by nucleophilic attack on a Si–H by a F ion; (3) the second F ion attack replaces the remaining hydrogen bond; (4) HF or H_2O attacks the Si–Si back bond due to the reduced the electron density; (5) the tetrafluoride molecule reacts with HF producing the highly stable SiF_6 fluoroanion.

diffusion-limited conditions and the propagation of pores is slower than the removal of Si from the interface between Si substrate and pSi layer [54]. However, the HF concentration, current densities, and immersion time have been found to vary among groups [36, 55], which suggests that an accurate balance between immersion time, HF concentration and current pulses is required. Once the porous layer is released from the Si substrate, it can be converted to microparticles using ultrasonic fracture (Figure 3).

2.2. Stain Etching. Unlike electrochemical anodization, stain etching, which gets this name due to the brownish or reddish color formed on the surface of the Si, is a simpler method [56, 57]. It depends on the chemical reaction, and no addition of current is needed. Typically, HNO_3 and HF are used and the product of the cathodic reaction (NO) serves as a hole injector, enabling Si to dissolve [44, 58]. The disadvantage of this method is that the etching outline is not uniform, presenting both cathodic and anodic sites randomly but constantly distributed on the Si surface. Reproducibility and the pSi layer formed are quite limited in stain etching compared with anodization [44]. More recently, other aqueous solutions have been used producing brilliantly luminescent pSi and reproducible homogeneous thick films compared with those of nitrate/nitrite-based methods [59–61].

3. Morphology of Porous Si

The IUPAC defines a pore as a cavity, channel, or interstice with depth exceeding its width. pSi is classified into three types in terms of its pore size: microporous silicon ≤ 2 nm, mesoporous silicon 2–50 nm, and macroporous silicon ≥ 50 nm (IUPAC classification of pore size). The porosity, pore size and volume, thickness and shape of the porous layer determine the optical properties of pSi, making the material interesting for a range of applications in the biomedical field, especially controlled drug delivery devices [45, 62]. The control over all these characteristics depends on the various fabrication factors stated before. The diverse types of pSi have been classified into three groups: (1) space-charge layer control, (2) substrate resistance control, and (3) photocarrier control. The first extends to all pSi formed, except the macropores formed from *p*-type, and the micropores formed under illumination. The second involves macroporous Si formed in low-doped *p* type Si, and the third covers all micropores formed under illumination [63, 64]. Doping type, HF concentration, and applied voltage determine the size and geometry of the pores. In general, smoothness and pores size increase by decreasing the concentration of the electrochemical solution, using ethanol as a diluting agent or by increasing the current density [54]. However, increasing the pore size decreases the interpore connection and the degree of branching [44]. For the development of nanoporous materials, it is necessary to control the pore size, shape, and distribution, since the rate of degradation increases with the porosity of the material. An excellent summary of all manifestations of pores in silicon is reviewed by Föll et al., where pores from 1 to 10 nm are reported to be the typical dimension of the sponge-like perfection and cylindrical face morphology [65]. In addition, samples

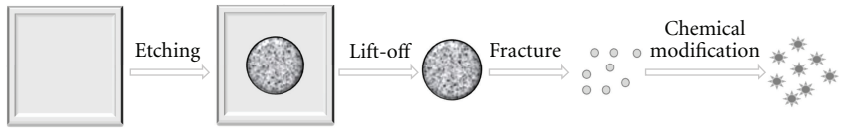
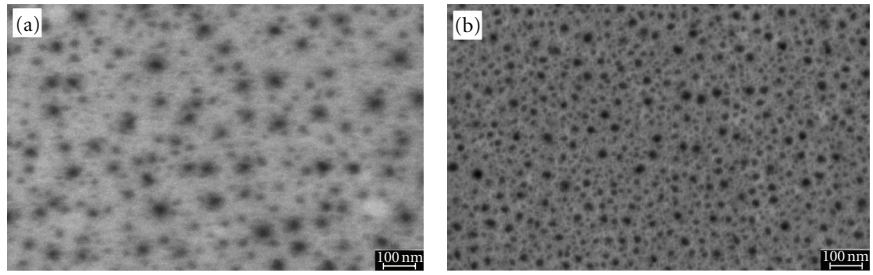


Figure 3: Schematic representation of the fabrication of pSi. Following the electrochemical anodization of the silicon wafer, the porous layer can be separated from the substrate by a secondary current pulse. Ultrasonic fracture is the common method for the conversion of the pSi layer in microparticles that can then be subsequently treated by chemical modification methods.



(a) (b)

Figure 4: Field emission-scanning electron microscopy images of porous silicon samples following anodization with current densities of (a) 5 mA and (b) 10 mA.

with higher porosity have shown to possess higher surface area and consequently cover larger groups of Si-Hx [66]. Morphology and pore size of Si structures are typically characterized by field emission-scanning electron microscopy (FE-SEM) as shown in Figure 4.

4. Porous Si Surface Modification

Surface chemistry of silicon is an area of strong interest, not only for the possibility of exciting technological application but also from a basic perspective. pSi bulk crystalline and nanostructure forms are used in a range of biomedical applications such as tissue engineering, cell culture, biosensing and as drug delivery device. The material's surface plays an important role during the degradation of this in vivo. As such, the stability of porous Si in aqueous medias is affected by the surface chemistry, its compatibility with tissue, and its affinity for different biomolecular species [18]. The development of the concept of pSi surface modification occurred as it became evident that the material's surface was unstable without any chemical adjustment [67]. Typically pSi is oxidized in normal conditions of humidity, temperature, and composition of ambient air. The oxidation process changes the pSi surface from hydrophobic to hydrophilic due to the formation of an oxide monolayer [68]. At physiological pH and temperature, oxidation process is enhanced increasing further the formation of the silicon oxide monolayer. This property has been used to study the oxidation-induced release of attached fluorophore molecules such as the anticancer drug doxorubicin [69]. The semiconducting silicon matrix typically quenches the fluorescence of this drug, but the fluorescence intensity increases with the growth of the insulating silicon oxide layer (oxidation of silicon). The recovery of fluorescence and the molecule released can then be monitored in real time by fluorescence microscopy. Nevertheless, pSi surface modification is usually required in order to control pSi degradation rate and to increase stability and optical properties at the same time as modifying the character hydrophobic and hydrophilic of the surface [70–73].

Following electrochemical anodization, the surface of pSi presents hydrogen-terminated compounds (Si-H, Si-H_2, and Si-H_3) [74], fluorine species, and oxygen impurities from the storage in ambient air [32]. pSi surfaces are typically modified by oxidation in gas phase [75, 76], hydrosilylation [77], thermal carbonization [78], and grafting [18]. These have shown to significantly improve the capabilities of pSi as a controlled and localized drug delivery device [79]. Few reviews have covered extensively the surface modification of pSi [32, 54, 80].

4.1. Oxidation. Typically during oxidation, the hydrogen atoms are replaced by oxygen atoms, and the surface character changes from hydrophobic to hydrophilic. This newer attraction for water provides a more convenient environment for substances dissolved in water such as drugs, converting porous Si in an ideal drug delivery device under physiological conditions [44].

Both thermal and chemical oxidations are common methods. Typically, thermal oxidation produces Si–O bonds following oxidation for few hours at 300°C, and pSi appears completely oxidized at around 750–800°C [18]. Chemical oxidation is also used for surface stabilization, using reagents that contain nitrogen such as nitric acid and pyridine [75, 81, 82] or other reagents like ozone hydrogen peroxide, halogen and dimethyl sulfoxide (DMSO) [83, 84]. DMSO is employed for slow oxidation of pSi at room temperature (Figure 5), which generates a stable oxide layer, and to

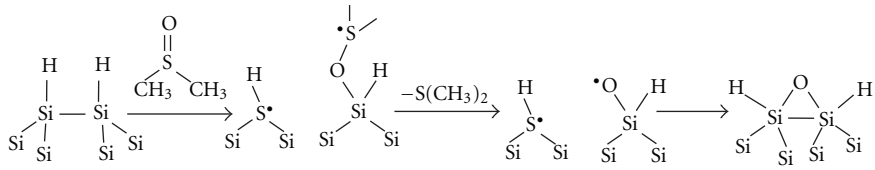


Figure 5: Mechanism of oxidation of pSi by dimethyl sulfoxide. The nucleophilic attack of the sulfoxide occurs at the most reactive Si–Si bonds, forming two radical structures that then react with each other forming a more stable Si–O bond.

expand the porous for loading dexamethasone [39]. Anodic oxidation and photonic oxidation are also sometimes used, but thermal and chemical oxidation are more easily implemented [44].

Oxidation of pSi has been investigated at different temperatures and during exposure to humid and dry air, water, vapors with pyridine and other solutions. Thermal oxidation is a simple method since no chemicals are required. Several groups have shown the suitability of thermal treatments for drug delivery devices, where the stability is increased [85], chemical reactions with the load prevented [29], and cell damage reduced [34] without significant effects on the electrical properties [9]. However, chemical oxidation confers a further improved stability against environmental aging and a good electronic surface passivation to allow chemical functionalization [82]. Other surface chemical treatments include thermally hydrocarbonized [34, 86] and carbonized with acetylene [87]. Few studies have investigated in vitro the effect of surface chemical treatment. Santos et al. used with this purpose a human colon carcinoma cell line [34]. Thermally carbonized pSi was found to enhance the kinetics of furosemide release and to decrease the pH dependence of dissolution behavior [38]. Others have investigated the amount of ibuprofen loaded on pSi to observe the effect of surface treatment by thermal oxidation and thermal carbonization during different periods of storage at 30°C [33].

4.2. Hydrosilylation. Hydrosilylation of pSi was first demonstrated by Buriak et al. [88] and extensively studied since then [89–91]. Long hydrophobic alkynes and alkenes attack the hydride terminated pSi surfaces to produce Si–C bonds by either photochemical reaction, mediated by excitation [92], or by chemical reaction, catalyzed by Lewis acid [88]. The low electronegativity of C confers a greater stability to Si–C bonds compared with Si–O, which is easily attacked by nucleophiles. Freshly prepared pSi (with abundant Si–H bonds) must be used during hydrosilylation methods, and Schlenk tubes and vacuum techniques are required to eliminate the formation of Si–O bonds by oxidation of the surface [54]. In the effort to develop a chemical method that provides stabilization of the pSi without significant loss of the photoemissive properties, Stewart and Buriak succeeded using a white light-promoted reaction that enabled the hydrosilylation [92]. De Smet et al. proposed a mechanism of the formation of Si–C bonded monolayers on silicon by reaction of alkenes with hydrogen-terminated pSi surfaces, via the same radical chain process as at single-crystal surfaces [93].

Alternatively, microwave irradiation has been used to chemically modify hydrogen-terminated pSi in an attempt to simplify common hydrosilylation methods, typically performed in the Schlenk tube under vacuum conditions for up to 1 hour. The microwave technique not only produces highly stable organic monolayers, but also allows the introduction of different functional groups and greatly reduced reaction times (approximately 10 minutes). Furthermore, the rate of the hydrosilylation reaction was increased, and a higher surface coverage obtained with the use of microwaves as an energy source [94]. Common organic compounds used during hydrosilylation techniques are dodecene, undecylenic, methoxy, trimethylsiloxy, and folate [76, 95–97].

4.3. Chemical or Electrochemical Grafting of Si–C Bonds. Grafting by covalent attachment is another way for chemically modifying the surface using Grignard, alkyl, or aryl lithium reagents [98]. Dense monolayers are prepared on the silicon surface by 1-alkene or 1-alkynes and diacylperoxides [99], followed by oligoethyleneglycol (OEG), polyethylene glycol (PEG), or other chemical species employed to graft the pSi surface. Activated ester monolayers have also been covalently attached to modify pSi surfaces [100]. OEG has been grafted on pSi surface through thermal hydrosylilation reaction with different alkenes species [84, 91]. PEG can be covalently attached onto pSi by Si–C bonds, increasing the hydrophilic character of the Si surfaces [54, 101]. Higher hydrophilic character has shown a stronger ability of the Si surface to admit sucrose and bovine serum albumin (BSA) [101], or other species such as drugs [102].

Typically, two steps are involved in the modification by covalent attachment of Si surfaces, the production of an intermediate surface, which acts as an attachment site for another molecule and the attachment of the molecule itself [103, 104].

In general, surface modification establishes the surface chemistry at the same time that it provides the exact chemical structure required [88]. Electroluminescent properties of pSi were stabilized using thermal oxidation treatments, where the Si–H bonds on the Si surface were replaced by more stable silicon-carbon (Si–C) and silicon-oxygen (Si–O–C) bonds [9].

5. Biocompatibility and Biodegradability

Nanostructures, capable of circulating in the body, are potentially the ideal solution for many diagnostic and therapeutic applications. Nontoxic, noncarcinogenic, nonantigenic

and nonmutagenic are the requirements of biocompatible materials [5]. pSi has exhibited extraordinary qualities for application in biological field as a drug delivery system due to its biocompatibility and biodegradability [78], low toxicity and solubility [54]. Nanomaterials for medical application require inoffensive disposal from the body, once they have reached their diagnostic or treatment goal, following a reasonable time after implantation [78, 86]. Biocompatibility, the ability of a biomaterial to remain in the human body without causing any undesirable effect, is one of the main advantages of pSi, together with its bioresorbability [39]. Safe intravenous administration of Si nanoparticles was reported with no change in plasma levels of renal and hepatic biomarkers as well as 23 plasma cytokines [106]. Orthosilicic acid ($Si(OH)_4$), a nontoxic, soluble silicon degradation product, is naturally found in numerous tissues and can be absorbed by the human body [79]. Some studies reported an excess of silica acid in urine samples excreted from the subjects monitored [41, 78, 107]. The complete dissolution and nontoxicity of a Si-implanted structure was investigated in vivo in the eye of a living rabbit as intraocular drug delivery device [74]. The low toxicity of Si structures was also reported in human colon carcinoma and murine microphage cells, suggesting these to be a suitable candidate for oral drug delivery application [76]. The slow degradation of Si in physiological fluid and the capability of this to be controlled with the porosity of the Si structure (biodegradable with porosity >70% and bioactive with porosity <70%) explain the extremely low concentration of silicic acid during in vivo studies [44]. Lumeniscent pSi nanostructures in a mouse model self-destructed into particles that could be cleared by the kidneys in relatively short period and without causing any toxicity effect [78]. This is extremely important for chronic use, where unlike most of the optically active materials (carbon nanotubes, gold nanoparticles and quantum dots), that cannot be metabolized or self-destructed, there is no need for excretion or surgical removal after their administration.

Alternatively, a purification procedure has recently been reported, capable of reducing the concentration of residual impurities to levels acceptable for biomedical applications while preserving the required photoactivity of the Si particles [108]. Wesselinova has discussed further some of the toxicity features in a recent review [109].

6. Drug Loading with Porous Silicon

Drugs loaded into pSi nanostructures have the potential to deliver the appropriate concentration at the appropriate location to minimize side effects. In general, the process of loading the drug in the nanoporous structure is performed through capillary action by dropping the drug solution on the device surface or by immersing the device in the drug solution [5, 21, 110]. Typically, sonication of the solution is required to enhance the intake of the drug by the device. The three most common methods for loading drugs into pSi implant are described in this section: covalent attachment, physical trapping, and spontaneous adsorption.

6.1. Covalent Attachment. Covalent attachment is the most robust approach for loading drugs into porous matrix. Typically, organic molecules that contain carboxyl species on the distal end of terminal alkenes are used during grafting. The hydrosilylation reaction between the end of alkenes and Si surface leaves the carboxyl terminal free, where the drug payload can be directly attached, or alternatively, this is attached via the PEG linker [91, 101]. Typically, acid and succinimidyl functional groups are added on the porous Si surface. The reaction of hydrogen-terminated surface with undecylenic acid under thermal condition results in an organic monolayer covalently joined to the surface through Si–C bonds and terminal COOH functional group [91]. The pSi surface modified by thermal hydrosilylation promotes the attachment of different-size molecule such as proteins and enzyme to the surface [111, 112]. Aminoacids and anticancer drugs such as doxorubicin, covalently attached onto pSi matrix, have been investigated in vitro [69, 113, 114]. While this method arguably presents the strongest attachment, the release of the drug requires breaking the covalent bonds or degrading the porous matrix. Hence, it is necessary to perform activity assays to ensure that the active principle of the drug is still effective following the disentanglement process [54].

6.2. Physical Trapping by Oxidation. The oxidation process causes Si to expand to accommodate the extra volume of O atoms and hence the pores shrink, trapping the drug molecules inside those. In recent years, the oxidation of pSi has been the subject of extensive studies since deliberated oxidation increases the stability of pSi surface [82]. Oxidation of freshly prepared Si surfaces has been induced by a range of solutions such as ammonia and pyridine [82, 115]. IR-spectroscopy and photoluminescence have been used to study the influence of the etching of the oxide matrix of porous nanocomposite Si/SiOx structures by HF vapors, which cause a significant decrease in the volume of a film and a partial additional oxidation of its surface [116].

6.3. Spontaneous Adsorption. Spontaneous adsorption of the drug molecules into the matrix pores consists of a simple immersion of the porous Si structure into the drug solution. Loading of drug molecules such as ibuprofen, gentamicin, and BSA onto mesoporous silicon has been investigated [37, 40]. pSi isoelectric point is found at pH of 2, so it is generally negatively charged with most of the solutions used [117]. At the appropriate pH, pSi spontaneously adsorbs various positively charged molecules such as immunoglobulin G (IgH) [118] and protein A [119]. The hydrophobic surface can be extremely advantageous for the adsorption and delivery of small hydrophobic molecules such as doxorubicin [41], dexamethasone [39], porphyrins [120], or BSA [40]. The surface chemistry can control the affinity of pSi particles for a particular molecule, and hence the amount of drug loaded and the rate of release. Adsorption is recognized as an optimal technique for drug loading since it does not require high mechanical energy [120]. This can be performed at room temperature without exposing the drug to harsh chemical conditions, and the nanoparticles are recovered

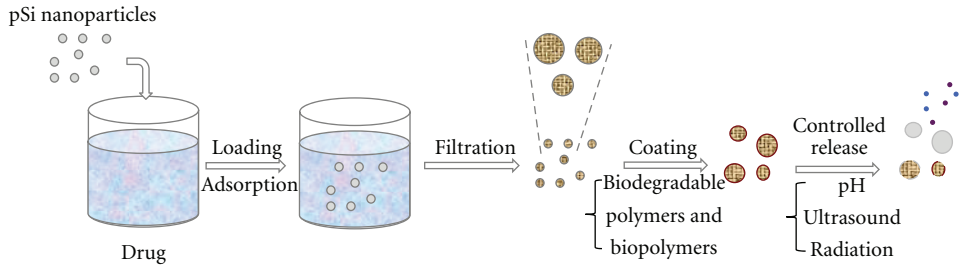


Figure 6: Schematic representation of drug loading and coating of pSi. Spontaneous adsorption of the drug molecules into the matrix pores consists of a simple immersion of the pSi structure into the drug solution. The particles are then recovered by filtration and coated with a range of biodegradable polymers for controlled release.

with basic filtration procedures [121] (Figure 6). However, it is not feasible for long release periods, since the attachment is weaker than covalent or physical trapping. Electrostatic adsorption is typically used when rapid drug delivery rates are required as this increases with time at alkaline pH and temperatures of 37°C [122]. However, in a recent review a monoclonal antibody bevacizumab (Avastin), spontaneously adsorbed on the nanostructure, provided a sustained release over a period of one month, and the electrostatic adsorption allowed bevacizumab to be concentrated [123].

7. Coating Nanoporous Silicon for Drug Release Control

Surface coatings offer an effective method to control the drug release from porous materials. These materials can be coated with films that surround the drug and control its release rate due to the diffusion process of the drug through the film [22]. In general, nanoparticles as drug delivery devices are coated with hydrophilic polymers/surfactants and biodegradable copolymers with hydrophilic segments [5]. Some of the materials used for coating are polyethylene glycol, polyethylene oxide, poloxamer, and poloxamine, polysorbate and lauryl ethers [124, 125]. Porous layers oxidize rapidly and degrade in short time, hence coating increases the stability of the material and improves the drug release [126]. Hydroxyapatite coatings have shown to increase the bioactivity of pSi [127]. Silica gel has been used for coating pSi substrates, which enhances the photoluminescence properties, and can then be used for in vivo monitoring of the delivery systems [128]. Silica xerogel coatings proved to be easy, flexible, and an efficient way for the controlled release of vitamin B1 from mesoporous silicon structures [22]. Other studies demonstrated the benefits of silica xerogel as controlled release material for the treatment of bone infection [129], and recently, it has been suggested as a coating for metallic implantable materials [130]. Other coatings used for in vitro studies include polymeric matrix of dextran for the release in vitro of two types of anticancer drugs, dacarbazine and bleomycin [105], chitosan polysaccharides to slow down the release of insulin [120] and BSA for capping the antibiotic vancomycin from pSi [131]. The use of biopolymers that are cleaved by specific proteases such as zein (derived from maize) can be potentially used as a highly selective drug delivery system for specific tissues or organs (Figure 6) [124, 132, 133].

Alternatively, since pores size can be controlled by varying fabrication factors, pSi has been used as a template for other materials. pSi composites have shown to improve the mechanical stability and the control release rate [124]. Polymers selected to form the Si composite must be biocompatible and biodegradable. In some cases the composite itself is used as a carrier [125], whereas in others only the polymer (formed with Si template, which is then removed) is the drug delivery system [124]. Some of the polymers used are polycaprolactone and poly(N-Isopropylacrylamide) [134]. Metals or metal oxides encapsulated into pSi have also been used, typically to generate a potential magnetic resonance imaging contrast agent [114, 135–138].

For controlled release, approaches such as pH-value-responsive release due to electrostatic interactions [136, 139] ultrasound to fracture and remove the porous layer [53, 140], and microwave radiation [141], are some of the current investigations. When porous Si matrix is oxidized, the release is also induced; however, these methods are limited to in vitro studies [69]. In general, drug release can easily be adjusted by changing pore properties [142].

8. Characterization and In Vivo Monitoring

Development of nanotechnology requires a high-quality characterization approach. Parameters such as pore distribution, diameter, and geometric shape of the pores determine the properties of pSi. In general, Si structures are characterized by imaging techniques, scanning electron microscopy (SEM), atomic force microscopy (AFM) [143–147], transmission Fourier transform infrared (FTIR) spectroscopy [148, 149], X-ray photoelectron spectroscopy (XPS), and contact angle measurements [18, 150, 151]. However, other techniques are required for monitoring drug loading and release.

Raman spectroscopy has been used during different steps of functionalization and protein grafting [112], while electrochemical impedance spectroscopy (EIS) and cyclic voltammetry measurements have been carried out to detect the electrochemical behavior of etched silicon surfaces [61, 113]. Drug loading has been monitored by optical interferometric measurements [123], differential scanning calorimetry

(DSC) [152] and high-pressure liquid chromatography (HPLC) which also determines the chemical purity of the loaded porous particles [105, 121].

During the etching process of Si, the optical properties can be adjusted with the variation of current density, tailoring in this way the refractive index of the nanostructures [102, 153]. The chemical treatment of Si surface also causes a change in optical properties, such as the strong decrease of the absorption in the visible spectrum observed in oxidized samples compared with nonoxidized ones. The excitons bound on these new Si–O bonds formed due to the oxidation are related to radiative transitions that can be measured by photoluminiscence [8]. The medium used also has been shown to affect the photoluminescence of nanoporous Si [154]. pSi have been long envisioned as integrated optoelectronic devices. The tunable light emission and room-temperature quantum efficiencies have led to the production of quantum dots structures that can display fluorescence [155]. This provides an advantage over other nanoparticles for in vivo sensing and therapeutic applications. Detailed description of the optical properties of pSi can be found elsewhere [156, 157], but basically consist of changes of refractivity and reflectivity index of the pSi layer. Spectrometers and interferometers are used to measure the reflectivity spectrum that can be resolved by fitting the reflectivity data by fast Fourier transform (FFT). Photonic crystals can be prepared by forming multiple pSi layers, known as rugate filters, which at predetermined wavelengths provides an intensive reflectivity peak to the pSi particles. A shift in the FFT peaks may indicate the loading or release of various biomolecules [119].

Degradation and drug delivery can also be monitored by digital imaging or spectroscopic techniques. Spectroscopic ellipsometry has been used during studies of adsorption of oxidized pSi [158]. Wu et al. used ultraviolet absorption spectroscopy to monitor the release of daunorubicin. The strong reflectivity peak generated by the pSi photonic crystal provides a distinctive color to the particles that evolved as the drug was released [159]. Others have followed in vitro antibody bevacizumab (Avastin) drug release profiles by enzyme-linked immunosorbent assay (ELISA), confirming that the antibody was released in its active, VEGF-binding form [123].

In case of in vivo studies, other techniques are required depending on the tissue itself. For example, the stability and toxicity of different chemically modified pSi particles injected into rabbit vitreous were studied by indirect ophthalmoscopy, biomicroscopy, tonometry, electroretinography and histology and showed no toxicity effects for a period up to 4 months [140]. Accumulation and degradation of luminescent pSi nanoparticles carrying a drug payload could be monitored in vivo in a mouse model due to the intrinsic near-infrared photoluminescence of these particles [78]. The near-infrared region of pSi reflectivity spectrum was used for the surveillance of the particles up to thickness of 1 mm through human tissues, which accounts for the advantage of these nanoparticles as in vivo self-reporting systems [124]. Alternatively, Fe_3O_4 nanoparticle, radiolabels or particles with intrinsic luminescence are embedded in pSi nanoparticles to be able to track them by near-infrared photoluminescence or positron emission tomography [53, 78, 114, 135, 160]. Nevertheless, there is still a need for further studies to overcome the physical barrier presented by the body such as blood vessel walls, organs' physical entrapment and phagocytic cells removal. Ideally, nanoparticles for drug delivery should not only overcome these barriers, but also allow real-time visualization, detection, and selectivity as well as rapid accumulation at damaged tissue and effective therapy [161].

9. Application in Cancer Therapies

Nanoscale devices are smaller than human cells, but similar in size to large biomolecules such as enzymes and receptors. Devices smaller than 50 nm can easily enter most of the cells, and when smaller than 20 nm they can move out of blood vessels while circulating through the human body [162]. This tissue accessibility is one of the most advantageous factors of nanomaterials in biomedical application. Nanoparticles for cancer therapies are particularly advantageous for their intrinsic properties as contrast agents, which can significantly improve diagnosis at the same time as delivering treatment agents [163]. Moreover, particles of certain size tend to accumulate more in cancer tissues than in normal tissues due to the leaky blood cells in tumors [164]. Approaches to deliver the nanoparticles specifically to the tumor site can be physical or mechanical, such as loading the nanoparticles with magnetic agents that can be directed by an external magnetic field (Figure 7). Chemical and biological approaches use molecules such as antibodies and enzymes that recognize the tumor cells since these express molecules on their surface that distinguishes them from normal cells [165]. This brings the possibility of delivering higher doses for longer periods of time, which allows the selective destruction of cancer cells without damaging the surrounding healthy cells.

Si nanoparticles optoelectronic properties are the reason for its use as biological interfaced devices [166]. This has made possible the incorporation of anticancer drugs in pSi devices for the specific release in tumor sites. Cisplatin combined with layers of hydroxyapatite on a pSi delivery device was tested in simulated body fluid for treatment of bone cancer [167] and the delivery of doxorubicin into human colon showed cytotoxic effects towards the carcinoma cells [41]. Chondroitin sulphate (a sulphated glycosaminoglycan), lactoferrin (globular protein with antimicrobial activity), and N-butyldeoxynojirimycin (an iminosugar that inhibits the growth of the CT-2A brain tumour) showed a significant decrease in tumoral cells density [114]. A recent study demonstrated the remarkable capability of a single drug-loaded porous nanoparticle modified with a targeting peptide that specifically binds to human hepatocellular carcinoma to kill a drug-resistant human carcinoma [168]. Superparamagnetic iron oxide nanoparticles and the anticancer drug doxorubicin loaded in pSi microparticles were delivered under the guidance of a magnetic field to in vitro human cervical cancer cells [53]. Particle sizes and magnetic properties have shown the ability to enhance the oncolytic

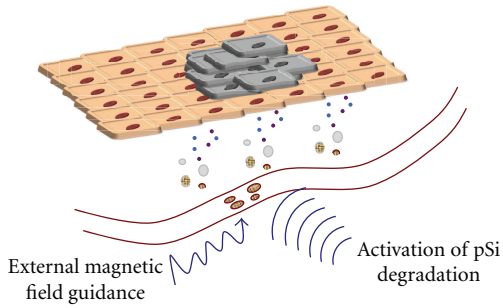


Figure 7: Schematic representation of targeted release on tumor cells. The pSi nanoparticles loaded with magnetic agents can be guided by external magnetic fields to the specific site and the drug released via photothermal activation.

potency of adenovirus [138] and magnetic mesoporous nanocomposites to produce magnetic hyperthermia, a very promising result for application as thermoseeds for cancer treatment [137].

The photothermal capacity of pSi nanoparticles in combination with a near-infrared laser has been employed to efficiently destroy cancer cells selectively without damaging the surrounding healthy cells during in vivo animal studies [169–171]. This same property has allowed researchers to treat cancer cells with pSi prepared as photosensitizers, exhibiting a 45% cell death rate compared with 10% in control experiments [172]. The inhibition of the proliferation of cancer cells when placed on pSi with 10–100 nm nanostructures and the complete destruction of these during additional ultrasonic exposure was demonstrated [173], leading to new possibilities for the application of Si as photo- and sono-sensitizers for cancer therapy [174] (Figure 7). The attachment and long-term viability of the three types of human cancer cell lines onto nanostructured oxidized pSi substrates are also being investigated [175]. A synergistic effect of combined chemo- and photo-thermotherapy was found at moderate power intensity of near-infrared irradiation based on the doxorubicin release and the photothermal effect of gold magnetic core/mesoporous silica shell nanostructure [136].

Other studies showed the endocytosis process of Si nanoparticles releasing their content into the cells in response to lysosomal acidity during in vitro human pancreatic carcinoma studies [176] and the therapeutic efficacy of liposomal encapsulated silicon-RNA [177]. Fluorescent polymers encapsulated inside silica-shell and recovered with folic acid have recently shown to enhance significantly the uptake by breast cancer cells, conferring a great potential for early detection of cancer [178].

10. Future Trends

pSi has shown its superiority in a wide range of technological applications over the last 50 years. More recently Si nanoparticles have been proposed for applications in biomedical and pharmaceutical fields as drug delivery and sensing systems. The simplicity of its fabrication and surface modification methods, its low cytotoxicity and its optical properties have put these at the forefront of implantable drug delivery devices [179]. The optical properties of porous Si provides an advantage over other nanoparticles, since these can be detected in vivo with imaging techniques, without the need for a label. Furthermore, its optical reflectivity can be used for the development of sensing devices. In fact, Si has been used extensively for electronics and micro- and nanochips have been fabricated for biosensign applications [80, 132, 180]. Biocompatibility issues with the biorecognition molecule and the metals of some of the components of the sensors are currently slowing down the implementation of this in vivo. Membranes that impart permeability and decrease biofouling of the electrodes are investigated and porous Si provides again an interesting solution [181, 182]. Microfluidic devices to deliver small volumes of fluids have also seen the advantageous properties of porous Si [183]. Aptamer-incorporated nanoparticles have been envisioned as delivery systems where the drug release is controlled via aptamer molecular gates [184]. With the advance of science and technology, closed-loop systems are seen as the next generation of therapeutic devices, where sensing mechanisms would trigger and control the release of the drug at a specific site or when reaching a certain threshold.

The diversity of pSi allows the combination of microfluidics, microarray biosensors, drug delivery [185], and high-resolution imaging techniques that can provide detailed images of cancerous cells and lesions [186], thus creating systems with incredible synergetic capabilities for therapeutic and diagnosis applications.

Acknowledgments

The authors acknowledge the support of the Material Innovations and Nano-Electronics (MINE) and Biosignal Processing (BSP) Research Groups and the financial funding of Ministry of Higher Education of Malaysia and Universiti Teknologi Malaysia for this paper.

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