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Chemical Engineering Journal 137 (2008) 162–172

Chemical Engineering Journal

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Fabrication and chemical surface modification of mesoporous silicon for biomedical applications

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Received 30 May 2007; received in revised form 31 August 2007; accepted 3 September 2007

Abstract

Mesoporous silicon (PSi) is an attractive choice when considering the utilization of mesoporous materials in biomedical applications. The size of the pores, morphology and the surface chemistry of the pore walls can be easily changed and controlled making PSi a versatile material. So far, PSi has not been widely applied in commercial products, but as the knowledge of biocompatibility and toxicity is increased by further *in vivo* studies, the possibilities of PSi are wide in medical treatments and diagnostics. In this review, we will focus on the fabrication and chemical modifications of porous silicon for biomedical applications, but a wide variety of biomedical applications will be discussed also.

Keywords: Mesoporous materials; Porous silicon; Surface modifications; Biomedical applications; Drug delivery

1. Introduction

The modern medical diagnostics and treatments normally endeavour to adopt the latest technologies and scientific innovations as quickly as it is technologically and regulatorially possible. History of mankind is full of these success stories mainly starting at the beginning of the last century. Such scientific breakthroughs as radioactivity and X-rays introduced several important applications into medical diagnostic, and the applications derived including electron microscopy, positron emission, lasers and magnetic resonance imagining complete an impressive list of these applications. Based on this background, it is not surprising that nanotechnology has attained a lot of interest for its potential biomedical applications. The continuously increasing knowledge of biological processes in the human body has also gained the understanding what is needed to improve and develop the current treatment methods and practices. The quick progress of nanotechnology during the last few decades has aroused hopes of obtaining new treatments or diagnostic technologies. Indeed, nanotechnology has many potential advantages for future medical treatments.

The physical size of the nanoparticles enables new routes for the drug delivery previously excluded due to the size of the particles and for the new techniques to functionalize the nanoparticles to mimic the biological processes enabling the targeted drug delivery. The applications of nanotechnology are not restricted to therapeutic delivery. A wide range of potential application starting from the sensing of the biomolecules to *in vitro* and *in vivo* diagnostic techniques has been proposed and has already been demonstrated in practice.

Although the vision of independent, complex and *in vivo* applicable nanoelectronic devises with many advantageous functions integrated into them is exciting and attractive, nanotechnology can also exhibit much simpler and straightforward approaches. In many cases, the inorganic mesoporous materials can be exploited to obtain new beneficial functions arising from the nanoscale size of the pores. These applications usually fulfill all the essential definitions of nanotechnology [1], since the fabrication of the inorganic mesoporous materials can be controlled on an atomic or molecular scale in many cases. In the case of synthetic molecular sieve materials, this can be done with a proper choice of molecules for synthesis and, in the case of PSi, with fabrication parameters. The large specific surface area resulting from the mesoporosity, and the pronounced role of the surface chemistry, render the inorganic mesoporous materials an interesting alternative for many biomedical applications.

Although PSi was first reported over 40 years ago by Uhlir [2], the current interest in porous silicon (PSi) results primarily from the demonstration of efficient visible photoluminescence of PSi, which was first reported by Prof. Leigh Canham in 1990

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doi:10.1016/j.cej.2007.09.001

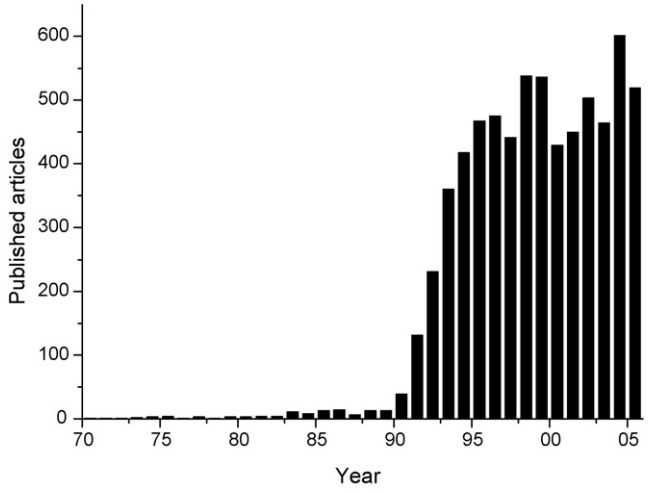

Fig. 1. Articles published on porous silicon research. The result based on the search of the articles in Thomson ISI Web of Knowledge database with the key word "porous silicon".

[3]. The possibility to produce light emitting structures of Si with a simple and straightforward method fascinated researchers around the world and the number of articles published on PSi increased drastically (Fig. 1). After the first 5 years, the number of publications has leveled to the average of 500 articles per year.

Ever since Leigh Canham reported the biocompatibility of PSi in 1995 [4], the biological properties and possible applications of PSi have been intensively studied. During the last decade, many of these properties have been utilized and a lot of interesting biomedical applications based on PSi has been reported. A wide range of the potential applications from biomedical sensors [5] to the culture of neurons [6] and brachytherapy applications [7] has expanded the biomedical research of PSi and increased the focus on the research.

In the present review, we will concentrate on the two major factors affecting biomedical applications of PSi, namely the fabrication of PSi and the surface chemistry of PSi. The porosity, pore sizes and pore morphology of PSi can be easily varied by changing the fabrication parameters and the well studied chemistry of the Si surface could be directly integrated into PSi applications. These two adjustable factors enable the versatile production of PSi with desired properties for the certain applications. In the last chapter of the review, these different applications which utilize different type of PSi, will be shortly introduced and described.

2. Fabrication and pore morphology of porous silicon

2.1. Electrochemical anodization

The most frequently used method to fabricate PSi is electrochemical anodization of Si in hydrofluoric acid (HF) based solutions. The anodization is performed by monitoring either the anodic current or voltage. The constant current method is preferable as it allows better control of the porosity and thickness and it also results in better reproducibility.

In the simplest setup to anodize PSi, a piece of Si and a cathode material are dipped into HF solution and an etching current is applied between the two electrodes (Fig. 2). The porous layer is formed on the surfaces of the Si, which is used as the positive anode. Usually the cathode is made of platinum and the fabrication cell has to be made of HF-resistant material, for example, Teflon (PTFE) or polyvinylidene fluoride (PVDF). Dilute HF solutions are generally used as electrolytes. To reduce the formation of hydrogen bubbles and to improve the electrolyte penetration in the pores, which results in the uniformity of the PSi layer, ethanol or another surface tension reducing agent is added to the electrolyte [8].

In the case of n-type Si substrates, in which electrons are the charge carriers (holes in p-type Si), an additional illumination during anodization is needed to generate photo-excited holes on the surface. Although illumination is not needed for the anodization of p-type Si substrates, the illumination during anodization has an effect on the formation of p-type PSi also, and illumination can be utilized to produce smaller structures (enlargement of the pores) even after anodization (post-anodization) [9–11].

Although PSi can be fabricated with the very simple setup described above, the disadvantage of this system is the non-optimal uniformity in both the porosity and the thickness of the PSi layer. This is especially true if highly resistive Si substrates are used. The potential laterally drops along the substrate the deeper the substrate is located in the electrolyte, and the current flow gradient increases as the resistivity of Si increases. This induces porosity and thickness gradients into the PSi layer. If the substrate is highly doped (low resistivity) and the lateral dip length is comparatively short, the porosity and thickness gradients are reasonable small.

These gradients can be avoided by using a sophisticated anodization system. In the system, the anodized Si substrate is etched on the one side only and the other side of substrate is in contact with a conductive anode material, which produces a more homogeneous PSi layer. In this setup, a good electri-

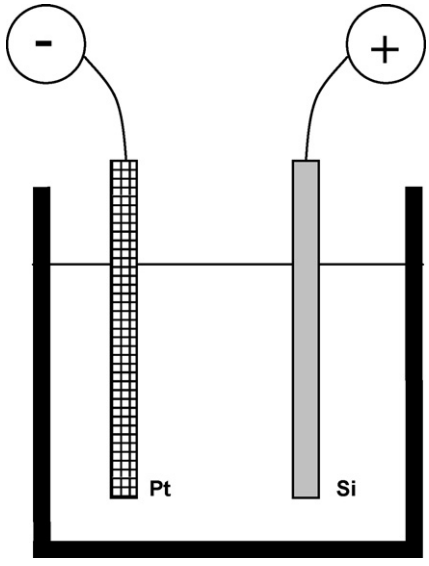

Fig. 2. Simple etching setup for PSi anodization.

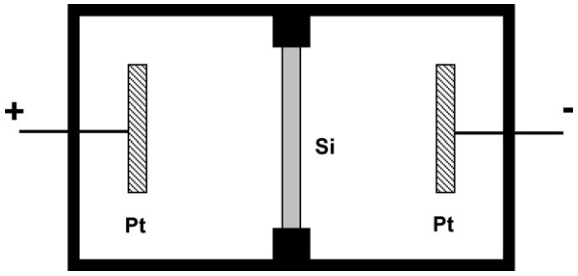

Fig. 3. Double tank setup for PSi anodization.

cal contact is important and commonly this is obtained using a metal deposit on the backside of the Si wafer. The more resistive the wafer, the more complicated it is to obtain good electrical contacts on the backside.

To ensure good backside contact without any additional metal deposits, a so-called double-tank cell construction can be used (Fig. 3). In this construction, the Si wafer is placed between two electrolyte cells, in which platinum electrodes are placed on either side of the Si-wafer. The front side of the Si substrate acts like an ordinary anode where the PSi layer is formed. The back side of the substrate is a cathode where proton reduction takes place leading to hydrogen evacuation. This ensures uniform backside contacts, which is quite complicated to obtain using alternative methods. On the other hand, a very homogeneous PSi is required only in a few applications, for example, in optical multilayer structures.

The dissolution chemistry of Si is still unclear, but in most of the studies two different types of dissolution reaction have been observed. The dissolution could be a direct production of H_2SiF_6 and molecular hydrogen H_2 (Fig. 4) or indirect, in which the dissolution takes place through the oxidation of the Si surface producing H_2SiF_6 and H_2O. The former is related to the formation of PSi in aqueous based solutions and the dissolution valence is close to two. The latter is associated either with the electropolishing or with etching in aqueous solution. In these cases, the dissolution valence is four and hydrogen is not produced at the anode.

Despite the uncertain chemical dissolution mechanism, two conclusions could be drawn on the dissolution. Firstly, the dissolution of Si needs both HF and holes, and secondly, during the dissolution, there is hydrogen evolution taking place at the surface of PSi. For safety reasons, the latter should be taken into account, when the etching setup is planned.

2.2. Other fabrication methods

Although the electrochemical anodization is unambiguously the most commonly used method to fabricate PSi, stain etching is a simpler alternative, which is based purely on the chemical reactions and no additional current is needed. Stain etched PSi layers have been studied for over 30 years [13]. Archer discovered that the rate of PSi layer growth was proportional to the concentration of nitric acid and independent of the substrate resistivity. Like in the anodization, the hole generation is important in stain etching and for this purpose HNO_3 is most commonly used. In aqueous HF and HNO_3 solution, cathodic reactions produces NO, which serves as a hole injector enabling Si dissolution. The problem in the stain etching is the non-uniform etching profiles, which is associated with the fact that both cathodic and anodic sites are randomly but constantly present in the Si surface during the etching. In addition, the possible thickness of the PSi layer formed with the stain etching is quite limited and reproducibility is inefficient compared to the samples produced by anodization.

In the photochemical etching, the hole generation is made with intense illumination [14,15]. The electrolyte composition similar to the electrochemical anodization could be used and any additional agents to generate holes are not required. Unfortunately, this method also suffers from similar drawbacks as stain etching. The absorption of the formed PSi layer limits the light intensity at the PSi/Si interface leading to gradients in porosity, pore size and etching rate as a function of thickness. However, the photochemical etching is a very useful method when fabricating small PSi structures without any lithographical tools [16,17].

Although the galvanic etching is not a zero-current method, an external current source is not required. The method is based on the internal current generating between Si and Pt or Au. The current could be obtained, for example, using Si-wafers with a backside deposited Pt/Au layer, which is immersed in an HF based electrolyte. The internal current leads to a similar etching process as in electrochemical anodization, and quite thick (>10 μm) PSi layers could be produced with the method [18,19].

In addition to the methods described above, there are also other methods to produce PSi. Some of these methods are modifications of other existing methods, like hydrothermal etching, which is basically a thermally induced stain etching method [20,21]. A completely different approach to PSi production is used in spark-processing [22–24]. In this liquid-free technique,

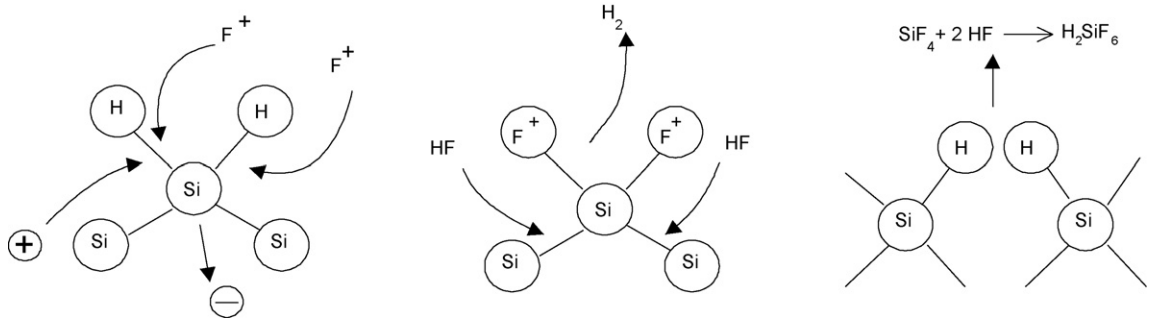

Fig. 4. Silicon chemical dissolution mechanism in HF solution [12].

high voltage unidirectional electric pulses with high frequency and low average current are applied between the Si substrate and the counter electrode (usually W) which are typically separated by a 1 mm gap. Since the spark-processing does not involve HF or other sources for the surface stabilization, and as it is usually done in air atmosphere, the produced surface is mainly terminated with oxides. Like almost all of the methods described already, also the spark-processing suffers from several problems when producing homogenous PSi, especially a thick PSi layer.

After the fabrication of PSi with processes, in which liquids are required, the next step considered is the drying of the etched PSi. If the electrolyte in the pores is allowed to evaporate at atmospheric temperature and pressure, drying may induce cracking and shrinkage. Especially the brittle, structures with high porosity (>80%) do not usually have the mechanical strength to survive the electrolyte evaporation without significant damages to the structure. This is due to the formation of a liquid vapor interface that can generate very high capillary stresses. In the cases of porosity below 80%, drying of PSi in laboratory air or under nitrogen flush is feasible. More information about the different types of drying can be found in [25] and references therein.

Generally, the fabrication of PSi should not form the stumbling block for biomedical applications. Already today, Si is produced with high purity levels, which are more than adequate for biomedical applications of PSi. The high purity levels currently used in the microelectronics industry are not even required for most of the applications. The problems related to large scale production of PSi have already been solved years ago. For example, Takao Yonehara in Canon Inc. anodizes 10,000 Si wafers per month [26].

2.3. The pore morphology

The properties of PSi, such as porosity, porous layer thickness, pore size and shape have strong dependences on the fabrication conditions. In the case of anodization, these conditions include HF concentration, chemical composition of electrolyte, current density, wafer type and resistivity, its crystallographic orientation, temperature, time, electrolyte stirring, illumination intensity and wavelength, etc. The complete control of the fabrication is complicated and all the possible parameters should be taken into account. Fortunately, some of these parameters also depend on one another and most of them are to be kept constant to ensure reproducibility. The effects of some of these parameters are discussed below.

The effects of the dopant type and the concentration on the pore morphology of the particles are well documented and the morphologies are usually grouped into four categories based on the doping levels of substrates: n, p, n+, p+. As the dopant concentration increases and the resistivity decreases, the pore diameters and inter-pore matter lengths also increase. Hence, finer mesoporous structures could be obtained with low-doped Si substrates, but the type of dopant affects the pore diameters also. In the n-type PSi, the pore diameters are usually larger than in the p-type PSi, and the pores seem to form straight cylinders in <1 0 0> directions [9]. However, this formation depends on the current density, and in the n-Si, remarkable variations have been observed due to the illumination parameters, such as the wavelength of illumination and its intensity [11,27–29].

The pore structure also changes as a function of resistivity. In the low-doped n- and p-type PSi, the pores are quite randomly orientated in <1 0 0> directions and form 3D sponge-like network. The typical pore size of the sponge-like PSi produced on the low doped substrates is in the range of 1–6 nm leading to a large specific surface area 400–800 m^2/cm^3. However, macropores from 100 nm to several micrometers could be produced on the low-doped samples also. In the present review, we will mainly concentrate on the mesoporous Si and the detailed information on the fabrication of macroporous Si can be found elsewhere [30].

As the resistivity of the substrates decrease the average pore size increases and the specific surface area decreases. In the highly doped substrates, like in n+- and p+-type PSi, the average pore size is 6–20 nm and the specific surface area only 100–300 m^2/cm^3. The pores are already well-orientated perpendicular to the initial surface of the substrate and in many cases, the pores are cylindrical with smooth pore walls and they are not interconnected. However, depending on the current density and the composition of the electrolyte, very branched, fir tree-type pore structures can be produced on the highly doped substrates. In the case of the fir tree structure, the branching pores are not orientated in <1 0 0> directions anymore, but in <1 1 3> and similar directions (Fig. 5).

Decreasing the HF concentration usually increases the diameters of the forming pores [32,33], and the pores become smoother and straighter. Also, the use of diluting agents other than water (e.g., ethanol) leads to the formation of smoother and larger pores. The pore shape is frequently observed to be cylindrical (or spherical), but also rectangular pores are present at least in n-type PSi [34,35], and sometimes even an X shape, has been reported [36]. Independent on the type of PSi, fir tree- or sponge-like structures are formed, when a low current density is used. Generally, an increase in the current density or the anodization potential also leads to an increase in the pore diameter and straighter pores, and the increasing of the pore sizes decreases the interpore connections and the degree of branching [33].

3. Chemical surface modifications

The as-anodized PSi is hydrogen terminated consisting of Si-H, $Si-H_2$ and $Si-H_3$ hydrides. The main impurity observed in the PSi surface is oxygen, but some other minor impurities are also commonly detected shortly after the fabrication. The detected impurities are mainly adsorbed during the storage in ambient or laboratory air and the only commonly observed impurity resulting from the anodization process is fluorine [37]. For various applications, the non-reactivity of the material is an important property and the unstable hydrogen termination of the as-anodized PSi has to be replaced.

Already in 1965, Beckmann found out that PSi films were substantually aged when they were stored in ambient air for a long period of time [38]. This aging is mainly due to the native oxidation of PSi, similar to observations with Si wafers. PSi films

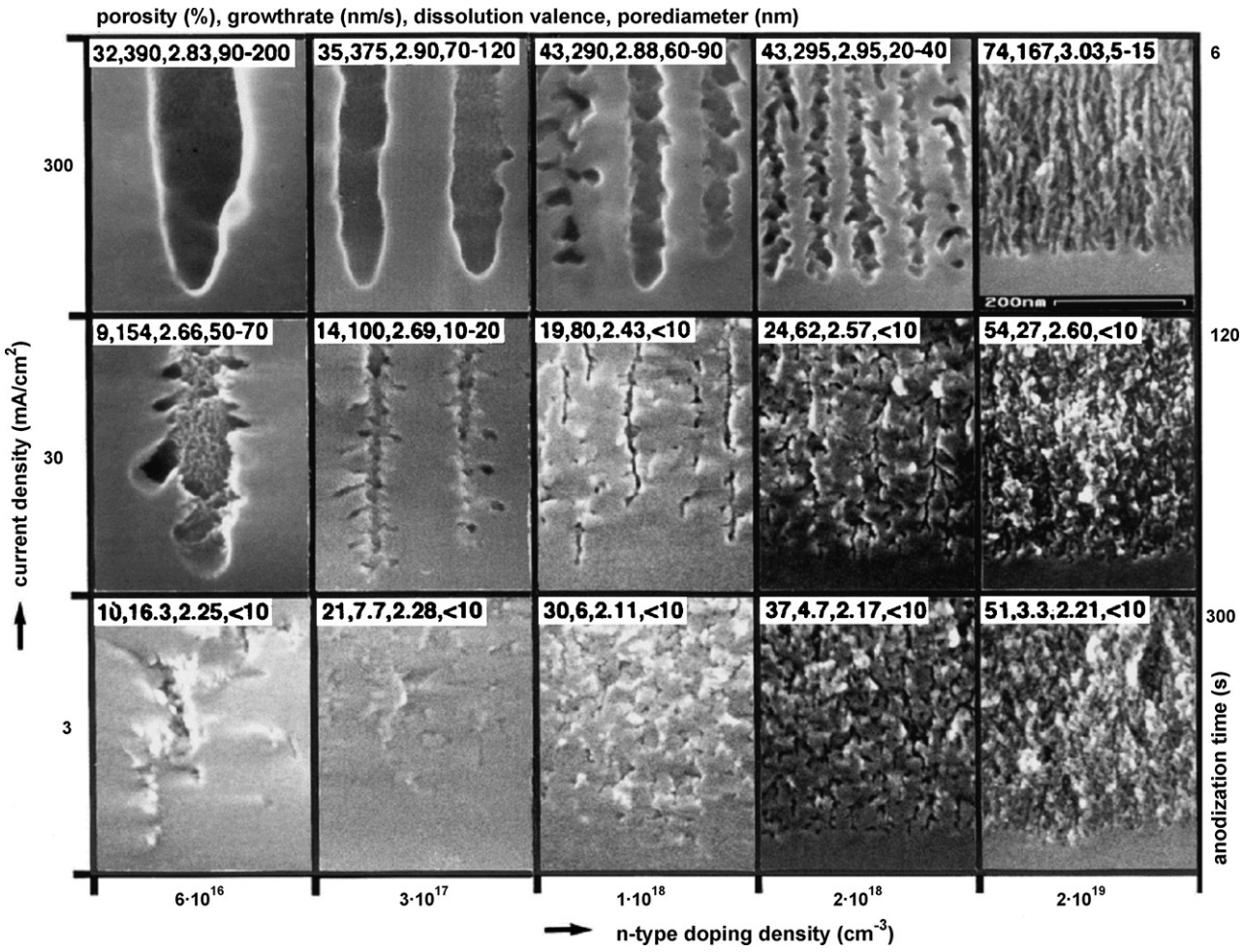

Fig. 5. Scanning electron microscopy pictures of differently doped n-type PSi etched with three different current densities [31].

slowly oxidized in ambient air depending on the environmental conditions, for example, humidity, temperature, composition of air, etc. Consequently, both the structural and optical properties were continuously changed during the storage. Although the aging has been known for a long time, its effects on the properties of PSi have been continuously studied and reported. Unfortunately, some authors do not specify the age of their samples and this complicates the comparison of the results reported. The differences in the properties may not be intrinsic, but could be associated with the various aging durations. The rate of oxidation and its extent depend on many factors, but typically the change from the hydrophobic hydrogen termination to the hydrophilic oxidized surface takes a few months. Complete native oxidation takes a much longer time, depending on the storage conditions and, especially, on the relative humidity and temperature.

The surface treatments of PSi can be divided in three categories: oxidation, stabilization with Si–C bonds and biofunctionalization. In addition to these, many other treatments have also been reported, but they are not discussed here. During the first years after the report of photoluminescence by Canham in 1990 [3], the research of stabilizing methods was focused on the stabilization of luminescence properties. Different kinds of oxidations were studied, like thermal, anodic, photo and chemical oxidations [39–43]. Also, thermal annealing of the PSi in nitrogen atmosphere and nitridation of the surface with NH_3 were frequently studied [44–47]. The results of the thermal annealing were not significant with regards to stabilization, but coarsening of the PSi structure during the annealing in inert ambient conditions was an interesting observation. This enables the modification of the pore size distribution after the anodization, which was an exploitable finding regarding drug delivery applications [48–50]. While some results of the chemical derivations of the PSi surface with organic compounds and formation of Si–C bonds were already reported previously [51–55], the reports by the group of Buriak finally confirmed the advantages of Si–C bond in the stabilization [55–57]. After the Lewis acid catalyzed hydrosilylation, the PSi surface was stable even in boiling aqueous KOH [55].

3.1. Oxidation of PSi

The simplest way to stabilize PSi is obviously a partial oxidation. A few hours even at quite mild conditions, around 300 °C, causes so called back-bond oxidation of PSi [58,59]. The oxygen atoms selectively attack the back-bonds of the surface Si atoms instead of replacing hydrogen atoms. The oxygen bridges

formed between the surface Si atoms and the second atomic Si layer expand the local atomic structure by 30%, causing a slight decrease in the pore diameter. In addition to the increased stability, the oxidation at 300 °C also changes the surface from hydrophobic to hydrophilic, which is important in many drug delivery applications under physiological conditions. Increased temperature also increases the extent of oxidation leading to completely oxidized PSi at around 900–1000 °C [43]. Due to the structural expansion, the pore diameter and porosity are dependent on the extent of oxidation, and a drastic drop in the specific surface area has been observed in PSi oxidized above 600 °C. This could be partly avoided by pre-oxidizing PSi first around 300 °C prior to high temperature oxidation [60].

There are also many other techniques to oxidize PSi, such as anodic oxidation [39,40,61–63], photo-oxidation [64,65], and chemical oxidation. Like the thermal oxidation, the chemical oxidation is quite simple, in which PSi is oxidized with inorganic or organic agents [66–71]. For example, oxidation in pyridine solution or the presence of pyridine vapor oxidized PSi ten times faster than in humid air [72,73].

3.2. Stabilization with Si–C bonds

Interesting results on the chemical derivatization of PSi were reported before 1998. Many groups studied the possibilities to modify the PSi surfaces with Si–C bonds. Their work finally led to the derivatized PSi surface, in which the Si–H_x bonds were replaced with the Si–C bonds using hydrosilylation of alkenes or alkynes on the PSi surface.

The group of Buriak introduced three different approaches to obtain the chemically derivatized PSi surface: Lewis acid mediated hydrosilylation, white light-promoted hydrosilylation and cathodic electrografting [56,57,74–79]. The highest treatment efficiency (the proportion of replaced Si–H_x) of 28% was obtained with one-pentene using Lewis acid mediated hydrosilylation [80]. Boukherroub et al. extended the usable techniques for hydrosilylation by introducing a simple thermally promoted approach for hydrosilylation [81,82]. Later on, they have used microwaves to improve the treatment efficiency [83], and also produced a hydrophilic derivatized PSi surface with undecylenic acid [84]. Due to the simplicity, thermal hydrosilylation is an interesting choice considering the biomedical applications. At the beginning, the treatment efficiency remained quite low (20–30%), but further improvements in the treatments have uplifted the efficiency to 80% [85]. The hydrosilylation, its chemical and biological applications, and also some other approaches to PSi stabilization have been reviewed in detail elsewhere [66,86,87].

Instead of the organic liquids used in hydrosilylation, the use of gaseous hydrocarbons could be considered due to their small size and rapid diffusion into the pores. Indeed, the poor treatment efficiency due to the low substitution levels generally obtained with the long organic molecules used in hydrosilylation may be avoided by using small gas molecules, such as acetylene or acetone vapor [88–93].

Thermal carbonization of PSi has been studied since the year 2000 [91–93]. The technique uses an interesting property of acetylene molecules. Adsorbed acetylene molecules stick so strongly on the Si surface at room temperature that they remain on the surface although the temperature is increased and undergo dissociation at temperatures above 400 °C. At the same time, hydrogen from the surface termination of the as-anodized PSi desorbs and the carbon atoms bind to the silicon atoms resulting in the carbonized PSi surface. Due to the rapid and easy diffusion of the relatively small acetylene molecules, complete carbonization of the surface can be achieved.

Two different surface terminations can be obtained. Using a treatment temperature below 700 °C, a continuous acetylene flow (mixed with nitrogen) can be used. The formed surface termination contains hydrocarbons, which have similar properties as the hydrosilylated PSi [92]. The hydrocarbon-terminated surface is hydrophobic, but the contact angle can be varied by changing the treatment parameters [94], such as the duration of acetylene flow and the treatment temperature. If the treatment temperature is above 700 °C, continuous acetylene flow cannot be used. Instead, the acetylene flow has to be stopped immediately before the temperature treatment. Due to the high treatment temperatures, the formed surface contains non-stoichiometric Si–C species but it is completely hydrogen free and thus, hydrophilic [49]. The thermally carbonized surface has been found to be very stable in chemically harsh environments and even in HF and KOH solutions [95].

3.3. Biofunctionalization of PSi surface

Most of the functionalization methods reported so far attach aliphatic or aromatic hydrocarbons to the PSi surface via routes as hydrosilylation of alkenes or alkynes. Such methods rarely provide opportunity to further modifications of the PSi for biomedical applications using standard organic chemistry strategies. In this chapter, we will focus on some methods that are favorable for further functionalization by means of standard chemistry.

In some cases, even with a very simple and straightforward strategy a suitable surface chemistry with good stability could be obtained, like in hydrosilylation of undecylenic acid [84], after which the carboxyl groups attached on the PSi surface are already functional or could be easily modified further. For example, Schwartz et al. have used undecylenic acid treated photonic crystal of PSi to monitor physiological changes in living cells *in situ* [96] and Wei et al. have used carboxyl groups as the precursors which were converted to an amine-reactive crosslinker species and finally to a Bovine Serum Albumin monolayer on the PSi surface [97]. A number of similar approaches to attach functional carboxyl groups on PSi have been reported so far [53,86,98,99].

A number of techniques and methods to graft amines, oligonucleotides or related species on the PSi surface have been reported [86,100–106]. The PSi surface could be thermally treated in ammonia containing atmosphere to obtain partial amine termination (∼8%) [107,108] or by wet chemical approaches [85,86,106]. Arroyo-Hernandez et al. have used a different type technique to obtain amine functionalized PSi surface [107]. They used 3-aminopropyltriethoxysilane (APTS)

as organometallic precursor which was deposited on PSi with thermal activated chemical vapor deposition. They demonstrated the feasibility of the APTS treated surface for the further functionalization with fluorescein isothiocyanate labeling and with mouse antibodies successfully.

Due to the great importance of silicon to electronic industry, the chemistry of silicon has been studied intensively for decades and extensive knowledge of it has been obtained. This is advantageous aspect for PSi biomedical applications. Many of those functionalization strategies developed for flat silicon surfaces [86,109,110] can be and have been adapted to PSi already.

4. Biomedical applications

Only few papers on Si biocompatibility and none on PSi biocompatibility were published [26] before the first biocompatibility report by Canham in 1995 [4]. After this paper, a lot of work on PSi biocompatibility and bioapplications has been conducted. Most of these papers deal with *in vitro* studies, including calcification [111–115], cell adhesion and culturing [116–118], protein adsorption [119–121], and biodegradability studies [122–124], but also some *in vivo* assessments of tissue compatibility have been carried out [115,125]. In addition, some interesting studies relating to biomedical applications of PSi, such as autoclaving of PSi [126] and other techniques for sterilizing PSi [127], and health and safety issues of PSi fabrication [128], have been published.

4.1. PSi biocompatibility

One of the most fascinating properties of PSi is its biocompatibility. While the highly porous Si ($p > 70\%$) dissolves in all the simulated body fluids, except in the simulated gastric fluid, PSi with medium porosity ($p < 70\%$) is bioactive, i.e., hydroxyapatite grows on the PSi surface both *in vitro* and *vivo*. Interestingly, the medium porous PSi is also slowly biodegradable, which means that PSi acts as a substrate for the hydroxyapatite growth, but it slowly dissolves as the hydroxyapatite growth proceeds. The very low porous Si and macroporous Si are both quite bioinert materials similar to the non-porous Si. The bioactivity of PSi depends also on the pore size, and the growth of hydroxyapatite can be accelerated with cathodic biased DC current [112].

One important issue for biomedical applications is the toxicity of the dissolved Si. Fortunately, PSi degrades mainly into monomeric silicic acid ($Si(OH)_4$), which is the most natural form of Si in the environment. In a test using radio-labeled silicic acid, drinks were given to human volunteers resulting in the concentrations of the acid in the bloodstream rising only very briefly above the typical values of about 1 mg/l [129]. Urine excretion of silicic acid is also very efficient and expels all the ingested silicon. In addition, silicon may be important in human physiology hindering the toxic effects of aluminum. The *in vitro* dissolution studies of PSi confirm the fact that the silicic acid concentrations remain quite low and can be controlled with the porosity of PSi [124].

In vivo tests of tissue compatibility of PSi have provided evidence for PSi promoting calcification [125]. The tissue compatibility of both bulk Si and PSi were found to be comparable to that of pure titanium. However, only few reports on this topic have been published and a more general view is difficult to summarize.

Beyond the simulated environments and *in vivo* tests, PSi has been found to support living cultures of mammalian cells. Successful adhesion of Chinese hamster ovary cells and rat hippocampal neurons (B50) [118] on PSi has been carried out by Bayliss et al. in a simulated environment, which also contained human serum albumin. Low et al. studied the adhesion of rat pheochromocytoma (PC12) and human lens epithelial cells to the surface modificated PSi [130]. They reported some interesting results about PSi being capable of acting as a reducing agent, and when redox based assays are used together with PSi care should be taken into consideration. They also observed that the hydrophilic surface (oxidized PSi) did not promote attachment of the cells, which is in accordance with previous reports [131].

4.2. Biosensing with PSi

Although PSi has many interesting properties in the sense of biomaterial applications, it has not been studied for bone tissue engineering. The studies of PSi bioapplications are divided into two main categories: biosensing and therapeutics delivery. In the sensing application, the large specific surface area and easily functionalized surface chemistry are remarkable advantages. In addition, the possibility to fabricate optical multilayer structures enables the use of PSi also in optical sensor applications. Also, other approaches using PSi as a sensing material has been reported and PSi can be used in biomedical sensors detecting changes in electrical, optical and photoluminescence properties. These properties have been utilized; for example, in enzyme immobilization and protein capture studies [132,133], in biomolecular screening [134] and in DNA sensing [102,135–137]. Thust et al. used electrolyte-insulator-semiconductor structures in their potentiometric biosensor to detect penicillinase, which was used as a model enzyme in the study. Archer et al. used macroporous silicon electrical sensor for DNA hybridization detection and Chan et al. used nanoscale optical microcavities. The group of prof. Sailor has developed encoded PSi photonic crystals for different type of biosensing [134], microcarriers [138] and other applications [96].

4.3. Drug delivery using PSi

The research of porous silicon in drug delivery applications became more prevailent after the year 2000, although some reports about silicon based nanopore technology were published prior to that [139]. Two different methods to fabricate nano-scale pores have been commonly used: electrochemical anodization of areas, which are large, compared to the size of pores, and application of microfabrication techniques adopted from microelectronics, which can be used to produce more sophisticated structures like small size implants. While the former is less time-consuming and quite inexpensive, the latter offers versatile

possibilities to produce much more complex microsystems. In some applications, both the methods are used [140].

A number of different types of drug delivery strategies using PSi have been studied and reported. Leoni et al. reported quite extensively on the characterization of diffusion properties and tissue effects of mesoporous silicon membranes produced by the microfabrication methods [141]. They used three different size molecules: glucose, human albumin and immunoglobulin (IgG) in their study. Diffusion of the molecules through membranes was determined for four pore sizes: 7, 13, 20 and 49 nm. It was found out that when the pore size approaches several times the molecular dimensions, the rate of diffusion starts to deviate from the values predicted by Fick's law. Although the membranes did not provide complete immunoisolation, it was observed that IgG diffusion was stalled for all the pore sizes tested. Compared to glucose and albumin, the relative diffusion coefficient of IgG was several orders of magnitude lower.

The idea of using nanoporous membranes to the control of drug delivery was extended by Martin et al. in 2005 [142]. They fabricated a cylindrical titanium encasement, which had a small opening for an affixed nanoporous membrane (Fig. 6). The size of the opening was small compared to the volume of drug reservoir enabling prolonged drug release. The release of ^{125}I-labelled bovine serum albumin (BSA) and human recombinant interferon α2b was studied. In the *in vitro* studies both the compounds showed almost constant release rates (zero-order kinetics). For example, in the case of a capsule with a 13 nm membrane, BSA release rate was constant up to 60 days and again clearly deviating from the Fick's law.

The use of porous silicon particles with permeability enhancers in order to deliver insulin across the intestinal Caco-2 cells has been also studied [143]. A major disadvantage of permeation enhancers is the lack of specificity, which may open up a route for food-borne pathogens and toxins to migrate together with the therapeutic compounds. To minimize this risk,

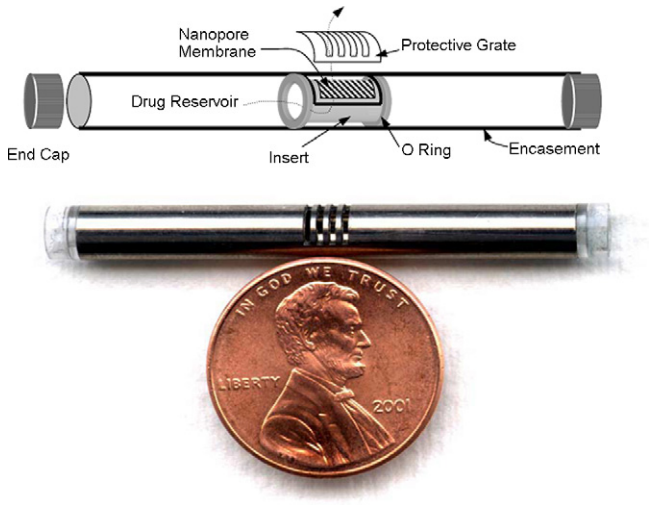

Fig. 6. Implant device fitted with nanopore membrane. (*Top*) Drawing illustrating key features of the device. The dashed arrow represents a possible diffusion path of a drug molecule held within the device reservoir. (*Bottom*) Photograph of prototype implant device illustrating its size in relation to a U.S. 1 cent piece [143].

they developed novel porous silicon particles that can be used as oral drug-delivery vehicles. These particles were designed to target into the intestinal epithelial cells, adhere to the apical cell surface, and deliver the drug formulation containing a co-administered permeation enhancer that will open up the local tight junctions of the paracellular transport pathway. Further targeting and specificity could be obtained by attachment of cytoadhesive lectins specifically binding to the intestinal mucosa, the feasibility of which has previously been demonstrated *in vitro* with similar microdevices [144]

In a recent study [145], mesoporous silicon (PSi) microparticles were produced using thermal carbonization (TCPSi) or thermal oxidation (TOPSi) to obtain surfaces suitable for oral drug administration applications. The loadings of five model drugs (antipyrine, ibuprofen, griseofulvin, ranitidine and furosemide) into the microparticles and their subsequent release behavior were studied. The loading of the drugs into TCPSi and TOPSi microparticles showed that, in addition to the effects of stability of the particles in the presence of aqueous or organic solvents, the surface properties of the particles determined the compound affinity towards the mesoporous particles. Besides the surface properties, also the chemical nature of the drug and the loading solution were critical to the loading process. This was reflected in the obtained loading degrees, which varied between 9% and 45% with TCPSi particles. The release rates of the loaded drugs from the TCPSi microparticles were also found to depend on the characteristic dissolution behavior of the drug substance in question. When the dissolution rate of the free/unloaded drug was high, the microparticles caused a delayed release. However, with poorly dissolving drugs, the loading into the mesoporous microparticles clearly improved and accelerated dissolution. Moreover, pH dependency of the dissolution was reduced when the drug substance was loaded into the microparticles.

The effect of the surface chemistry and pore size was more clearly pronounced in the studies of ibuprofen release from microparticles with modified chemical surface properties [146]. While the ibuprofen dissolution rate was clearly increased with TCPSi microparticles, with TOPSi and as-anodized, hydrogen terminated microparticles the increase in dissolution rates was quite minor. On the other hand, when the average pore size was increased from 12 to 47 nm the dissolution rate significantly slowed from TCPSi particles, but with similar pore enlargement, dissolution from TOPSi increased. This indicates the complex role of the surface chemistry in these kinds of applications. In the same study, the prolonged stability study of the ibuprofen loaded microparticles was performed.

The combined release and permeation behavior of furosemide loaded into thermally carbonized mesoporous silicon (TCPSi) microparticles was studied by Kaukonen et al. [147]. Permeation across Caco-2 monolayers at pH-values of 5.5, 6.8 and 7.4, from drug solutions and TCPSi particles was studied and furosemide loaded in the TCPSi exhibited improved dissolution from the microparticles with greatly diminished pH dependence. At pH 5.5 (the lowest furosemide solubility), the flux of TCPSi-loaded furosemide across the Caco-2 mono-

layers was over 5-fold higher compared to the pre-dissolved furosemide. This is quite remarkable since it is the result of the combined effects of the improved dissolution and permeation of a 3.5-fold dose compared to that with the pre-dissolved solution, the concentration of which was restricted by the low solubility of furosemide.

The surface properties form an essential aspect in the design of porous silicon particles to be used in oral drug delivery. Thermal carbonization (TCPSi) and thermal oxidation (TOPSi) showed that in addition to the effects regarding the particle stability, also the surface properties affect significantly the compound affinity towards the particles [145]. This observation presents an important potential to tailor the surface properties.

In addition to the more conventional drug delivery applications above, PSi could also be used in brachytherapy [7]. pSivida Ltd., the leading company in the biomedical applications of porous silicon, has studied their lead product, BrachySil^{TM} for inoperable primary liver cancer, and now also for pancreatic cancer [148,149]. BrachySil^{TM} is a combination of PSi and the isotope 32-phosphorus, a proven anticancer therapeutic. It can be delivered directly to a tumor, and because of size of the particles, they are immobilized within the tissues and deliver a restricted and targeted dose of beta radiation without significant leakages. The porosity increases the dissolution of the particles with time. Interestingly, pSivida has recently also launched pSiNutria for the food industry [150]. The aim of pSiNutria is to develop applications of ingestible BioSilicon^{TM}, for food industry as nutritional food additive [151].

5. Conclusions

The pore shapes and sizes of PSi can be easily adjusted with the fabrication parameters and the initial properties of the used Si wafers. This, together with the versatile possibilities to modify the surface chemistry make PSi an attractive material for biomedical applications. In addition to the common advantages of mesoporous materials, the semiconducting behavior of PSi, highly sophisticated microfabrication technology already existing for bulk silicon (Si) and the possibility to fabricated optical multilayer structures even extend the usability of PSi to many different types of applications. In this review, the aspects of fabrication, morphology and chemical modification of the PSi surface have been presented in the perspective of biomedical applications. Although, a number of biomedical applications of PSi have already been reported and a lot of knowledge about biological behavior of PSi has been obtained, some important questions still remain open. For example, only a few *in vivo* studies have been reported so far on PSi and urgent improvement is required on this topic to facilitate the utilization of PSi in medical treatments and diagnostic.

Acknowledgements

The financial support from the Academy of Finland (project no. 211048 and 118002) is acknowledged.

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