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Mesoporous silicon: a platform for the delivery of therapeutics

Clive A Prestidge, Timothy J Barnes, Chi-Hian Lau, Christian Barnett†, Armando Loni & Leigh Canham
†*pSiMedica Ltd, Malvern Hills Science Park, Geraldine Rd, Malvern, WR14 3SZ, UK*

Nanostructuring materials can radically change their properties. Two interesting examples highlighted here are nanoscale porosity inducing biodegradability, and nanoscale confinement affecting the physical form of an entrapped drug. Mesoporous silicon is under increasing study for drug-delivery applications, and is the topic of this review. The authors focus on those properties of most relevance to this application, as well as those recent studies published on small molecule and peptide/protein delivery.

Keywords: drug delivery, nanostructuring, porous silicon

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1. Introduction

Improving drug efficacy and as a result, patient safety and quality of life, are the key clinical goals of novel drug delivery systems. A key commercial benefit to large pharmaceutical companies is the extension of the industrial life of approved proprietary drugs. Drug delivery is already a multibillion market and is predicted to grow rapidly over the next decade. Therefore, it is not surprising that there are in excess of 200 drug-delivery companies and dozens of materials and technologies already available for this purpose. However, from a large pharmaceutical company perspective, drug delivery is yet to fulfil its potential. This is reflected in its fairly low percentage (< 20%) of the total pharmaceutical market of > $500 billion. There remain significant opportunities in achieving radically improved efficacy in a cost-effective way.

Nanotechnology has received much attention in recent years with regard to its medical potential in various areas, especially in the continuing battle against cancer [1]. Mesoporous silicon is a nanostructured material with closely spaced 2 – 50 nm wide pores throughout its volume. The material was first made in the 1950s [2] and, thus, is not a new nanomaterial, but one whose nanostructure and remarkable properties remained undiscovered for decades.

Since the striking luminescent properties of porous silicon were published in 1990, the nanostructural, optical and electronic properties of the material have been subjected to in-depth scrutiny by physicists and electronic engineers, in thousands of academic papers. However, other properties are of prime importance for biomedical applications, and only recently have the biochemical and mechanical properties started to receive substantial scrutiny by pharmaceutical scientists, biochemists, biologists and biomedical engineers. The first *in vitro* study of nanostructured silicon in 1995 demonstrated significant dissolution in physiological fluids and hence potential *in vivo* biodegradability [3]. Subsequent studies initially focussed on *in vitro* applications, such as biosensing [4] and bioreactor technology [5], but have subsequently evolved to include *in vivo* use and drug delivery, driven in part by interest in biomedical applications of microelectromechanical systems [6].

Porous silicon microparticles, with the phosphorus-32 radiosisotope incorporated into the silicon lattice, have been shown to induce tumour necrosis in preclinical studies [7], and are now being evaluated in the clinic for the treatment of both primary liver cancer [8] and, more recently, pancreatic cancer. These constituted the

first-in-man trials of this new biomaterial. Drug delivery using mesoporous silicon is at the preclinical evaluation phase.

2. Fabrication

There are a number of electrochemical techniques for rendering semiconducting silicon highly porous, but the most widely used for electronic or optoelectronic purposes is anodisation (versatile and ideally suited to processing standard wafers). In this process, silicon is present as the anode of electrochemical cells containing hydrofluoric acid based electrolytes (Figure 1A). The passage of current densities of 10 – 200 mA/cm^2 are typically required for an array of mesopores to spontaneously nucleate on the surface and propagate at speeds of microns per minute into the bulk of the wafer. For a detailed review of silicon electrochemistry and pore formation, the reader is referred to the book by Lehmann [9]. Silicon is preferentially removed at the pore tips according to the coupled equations:

$$Si(s) + 2H_2O(l) + 4h^+ \rightarrow SiO_2(s) + 4H^+$$
$$SiO_2(s) + 6HF(l) \rightarrow H_2SiF_6(l) + 2H_2O(l)$$

The h^+ refers to electronic carrier (hole) injection into the valence band of the semiconductor, as a result of current flow across the silicon–electrolyte interface. Semiconductors, as a result of doping with specific impurities, are either p-type, with conductivity due to the flow of positive holes or n-type, with negative electrons. Common dopants are boron and phosphorus, for p-type and n-type semiconductors, respectively.

With the anodisation technique, electrical bias promotes etching, so layer morphology is highly dependent on the uniform current flow and electrical properties of the wafer, but also electrolyte composition. A surfactant such as ethanol is often added to suppress the effects of hydrogen gas evolution within the growing layer, which can adversely affect uniformity.

In the 1990s, this technique was developed into high volume manufacture (e.g., 10,000 wafers per month) [10]. A second technique, stain etching [11], has now also received industrial attention (Figure 1B), producing microparticles of low porosity to GMP standard at the tens of kilograms level. Here, a chemical oxidising agent is added to the hydrofluoric, acid-based electrolyte, removing the need to apply electrical bias.

Other electrochemical techniques, such as galvanic etching [12] are in their infancy, but have significant potential for specific uses. This review focuses on the two techniques that have been utilised to make the submicron or micron-size biodegradable particles that are needed for delivery of therapeutic agents.

Figure 2 shows how both techniques can be used to generate porosified particles for drug delivery. With anodisation, thick (> 100 µm), fully porous films are electrochemically lifted off wafers by applying a high current pulse, and large batches of these membranes are then mechanically milled and classified into microparticle form. With stain etching, silicon feedstock, already in the required microparticle form, is subjected to porosification in batch processing.

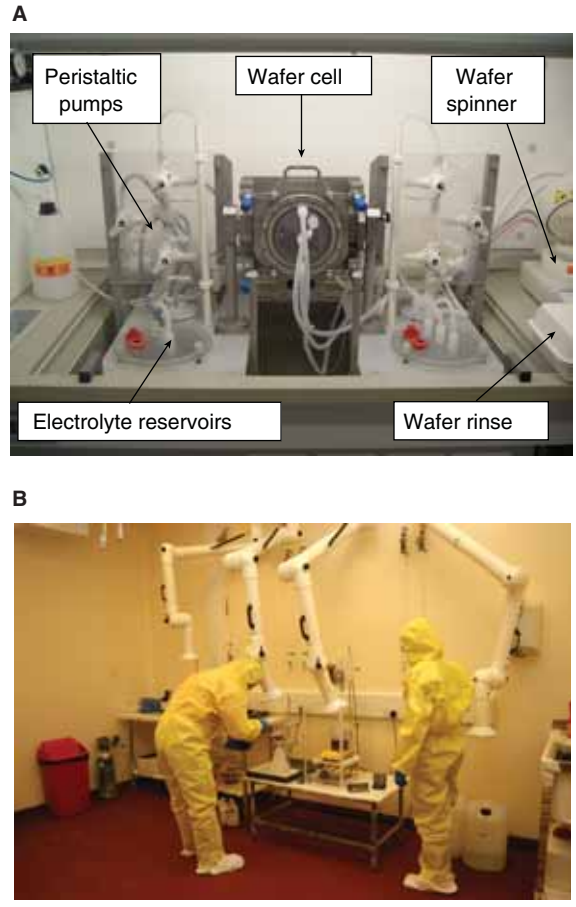

Figure 1. A. Anodisation cell for porosification of silicon wafers B. stain etch apparatus for porosification of silicon powders.

3. Structure and surface chemistry

A wide range of techniques have been used to characterise the nanostructured forms of this material. For detailed information the authors refer the reader to the reviews of Cullis *et al.* and Bisi *et al.* [13,14]. Electron microscopy has been particularly useful in revealing the diverse morphologies that can result from electrochemical etching. Figure 3A illustrates how high-porosity material from anodisation retains the crystallinity of the original wafer, even after milling into microparticle form. Figures 3B and 3C shows typical mesopore size distributions and the directionality of porosity in heavily doped, p-type silicon films on wafers.

The surfaces of freshly etched mesoporous silicon are terminated with a monolayer of covalently bonded hydrogen atoms, in the form of SiH, SiH_2 and SiH_3 surface groups. This type of surface is similar to that manipulated by the semiconductor industry, where highly planar wafers are exposed to hydrofluoric acid during chemical cleaning. This

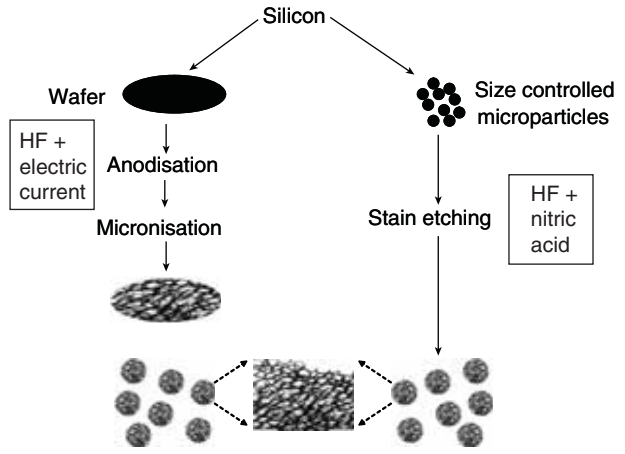

Figure 2. Fabrication of mesoporous silicon particles by anodisation or stain etching.

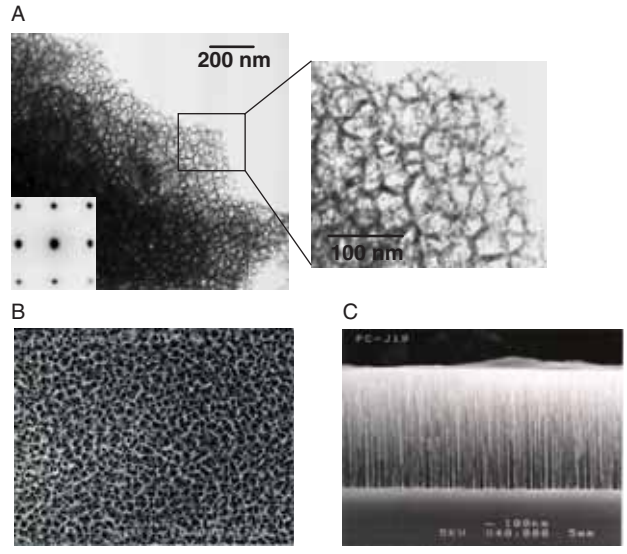

Figure 3. Nanostructure of A. mesoporous microparticles after jet milling B. mesoporous silicon film plan view C. mesoporous silicon film cross-sectional view.

imparts electronic passivation (there are very few surface defects, referred to as dangling bonds), hydrophobicity, and makes it metastable in air, undergoing gradual oxidation at room temperature. Fourier transform infrared analysis is one of the most versatile techniques for monitoring chemical bonding of the internal surface during storage and subsequent processing of mesoporous silicon. Other surface analysis techniques, such as X-ray photoelectron spectroscopy or auger electron spectroscopy, are of lesser value in revealing inner pore wall chemical bonding. Thermoporometry [15] and NMR spectroscopy [16] are examples of techniques that, with further application, could provide detailed structural information.

4. Properties

Table 1 summarises some properties of the mesoporous and microporous forms of silicon, and emphasises their tunability. Of most relevance to drug delivery are specific structural, chemical and mechanical properties. Examples of structural parameters that influence drug payloads include pore diameters, porosity and the internal surface areas achievable. The mechanical strength of the nanostructure can be important for physical methods of particle size reduction and classification. Drug-loading techniques and biodegradation are strongly influenced by wetting and, thus, hydrophobicity.

5. Biodegradability

Biodegradable or bioerodible polymers are increasingly being used in medical therapy, for controlled drug delivery and tissue engineering. The primary advantage of a biodegradable implant over a permanent one is that it can help the body to heal itself, but avoids the potential for chronic foreign body responses. It also does not need eventual surgical removal or revision.

Nanostructuring of silicon can raise its dissolution kinetics dramatically, thereby making the material biodegradable and of interest for human therapeutic use. Initial *in vitro* studies [3] demonstrated remarkable solubility in simulated human plasma, which has relevance to soft tissue implantation. Subsequent *in vitro* work [17,18] has encompassed a range of other body fluids, relevant to mesoporous silicon solubility in the stomach, intestine, lung and urinary tract.

The dissolution of porous silicon via hydrolysis is of fundamental importance to its *in vivo* applications. Dissolution of unoxidised silicon can be described as a simplified two-step process:

$$Si\ (s) + 2H_2O(l) \rightarrow SiO_2(s) + 2H_2(g)$$
$$SiO_2(s) + 2H_2O(l) \rightarrow Si(OH)_4\ (l)$$

The oxidative step generates hydrogen gas and is dependent on both electronic bandgap (controlled by nanostructuring) and doping. The degradation product is orthosilicic acid, which is the bioavailable form of dietary silicon that is readily excreted via the kidneys [19].

Figure 4 illustrates how the dissolution kinetics of this nanostructured material can be tunable by a physical parameter (void fraction porosity), rather than chemical changes. Table 2 lists other material parameters and the many environmental factors that will also influence dissolution.

6. Biocompatibility and toxicology

Just because a material is biodegradable, it does not necessarily mean that it will be useful for medical applications, unless it is also biocompatible for its intended purpose. Key issues include

Table 1. Properties of as-anodised mesoporous and microporous silicon compared with non-porous silicon (Properties of Porous Silicon, IEE 1997).

	Property	Silicon	Micro/mesoporous silicon
Structural	Pore diameter	NA	1.5 nm-50 nm
	Porosity	NA	20 – 95%
	Surface area	NA	100 – 700 m^2g^{-1}
	Lattice symmetry	Diamond	Diamond
	Lattice constant	0.543 nm	0.543 nm
	Density	2.33 gcm^{-3}	0.12 –1.9 gcm^{-3}
Optical	Optical Bandgap	1.1 eV	1.1 – 3.2 eV
	Infrared refractive index	3.5	1.1 – 3.0
	Photoluminescence efficiency (visible)	10^{-6}	< 0.05
Electrical	Electrical resisitivity	10^{-2}-10^3 ohm cm	10^3 – 10^{12} ohm cm
	Electron mobility	1350 $cm^2V^{-1}s^{-1}$	0.1 – 30 cm^2V^{-1} s^{-1}‡
	Hole mobility	480 $cm^2V^{-1}s^{-1}$	2 – 6 $cm^2V^{-1}s^{-1}$ ‡
	Static dielectric constant	11.5	2 – 8
Thermal	Thermal conductivity	150 $Wm^{-1}K^{-1}$	1-100 $Wm^{-1}K^{-1}$
	Melting point	1414 ˚C	< 1414 ˚C*
	Specific heat	0.7 $Jg^{-1}K^{-1}$	0.7 $Jg^{-1}K^{-1}$§
Mechanical	Young's Modulus	160 GPa	1-100 GPa
	Hardness	11.5 GPa	1.5 –10 GPa
	Yield strength	7 GPa	< 7 GPa*
	Fracture toughness	2 – 3 Jm^{-2}	< 2 Jm^{-2}*
Chemical	Hydrophobicity (contact angle)	80˚	116˚ –122˚

IEE: Institute of Electronic Engineers; NA: Not applicable.

* Range yet to be quantified.

‡ Considerable uncertainty over range.

§ Theoretical estimate.

the systemic pathways for removal and toxicity of degradation products, the mechanical integrity of the material as it degrades, and the local response of surrounding tissues. The degradation product of mesoporous silicon can be monitored using the molybdate blue assay (specific to the monomeric form [20]) tracer techniques [21], atomic absorption spectrophotometry [22] or inductively coupled plasma-optical emission spectroscopy [23]. Elemental concentrations in body fluids, such as blood, in normal healthy individuals are typically 10 µmol/l [24,25].

Rosengren *et al.* have studied the *in vivo* tissue compatibility of as-anodised, mesoporous silicon discs [26]. They compared bulk and mesoporous silicon with control titanium structures in the rat abdominal wall after periods of 1, 6 and 12 weeks. Both porous and planar silicon implants elicited a foreign body response of comparable magnitude to that observed for corresponding titanium surfaces.

Table 3 compares the pKa values for the monomer degradation products of the most important biodegradable polymers with that of mesoporous silicon. Therefore, it provides an indication of the extent to which the pH of surrounding body fluids may change as a result of different monomer release. It implies that pH changes might be significantly less of a problem for biodegradable silicon, provided only the monomer is involved. In body fluids of ~ pH 7, a very small fraction of silicic acid is deprotonated. This could be of particular relevance for protein delivery, as large pH changes, both widespread and localised, are known to induce loss of biological activity.

7. Surface modifications

The hydride surface of hydrofluoric acid-etched porous silicon slowly oxidises in air at room temperature [27]. Interest in porous silicon for biochemical sensing has led to considerable development of alternative chemistries, many of which have potential uses in medical implants and drug delivery [28-31]. Of particular interest in this regard are surface

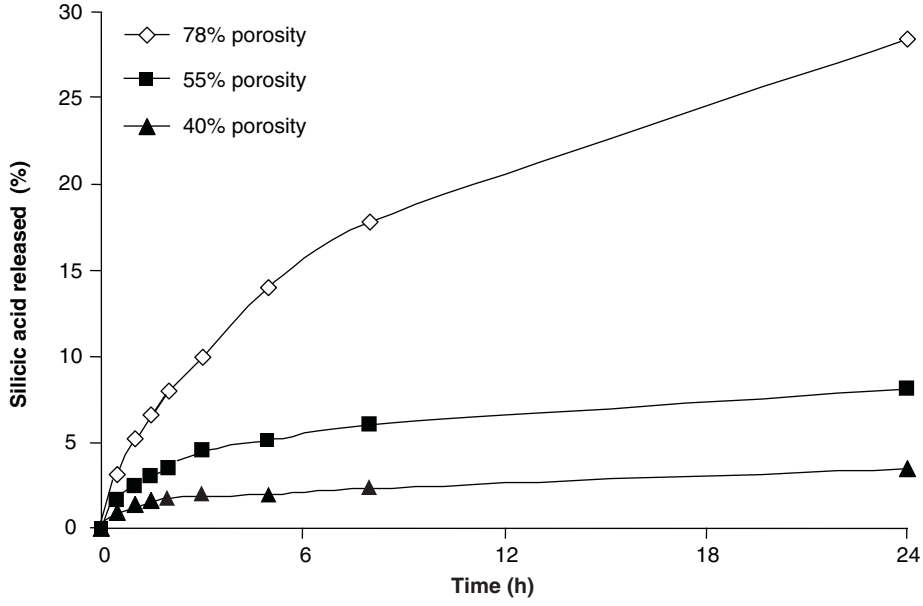

Figure 4. *In vitro* dissolution of anodised mesoporous silicon wafers as a function of varying porosity in Trizma buffer (pH 7.4) at 37°C.

chemistries that, for example, impart molecular recognition, modify biodegradability kinetics, or allow covalent attachment of drug molecules. For detailed information, the reader is referred to recent reviews [32,33].

8. Drug delivery

The use of porous silicon to deliver therapeutic agents, including both drugs and peptides/proteins, has received increasing interest. The large internal surface area and nanostructuring capability of porous silicon provide unique opportunities for the delivery of therapeutic agents. Applications of the technology range from improving the solubility/bioavailability of drug molecules, to controlled delivery via a range of delivery routes.

The process of drug loading into porous silicon occurs via two main mechanisms. First, the mesoporous structure of porous silicon provides a large internal surface area for drug adsorption. The extent of drug loading is a function of the degree of surface area available and the specific affinity between the matrix and drug. Matrices such as activated charcoal, with a surface area of up to 1000 m^2/g, have been shown to be able to adsorb compounds to levels of ~ 30% (w/w) [34]. Second, in simple terms, the porous matrix can be considered to be a sponge-like structure. The introduction of a drug via either direct melting or from a solution-phase allows the drugs to be deposited within the internal structure of the pores, rather than just at the pore surface. In this case, the extent of drug loading is a function of the internal pore volume and the concentration of drug in the loading solution. In practice, drug loading will most likely result from a combination of the two mechanisms.

Oral drug delivery still remains the major route of choice for the pharmaceutical industry. However, recent studies have reported that up to 40% of active pharmaceutical ingredients (API) being discovered are classified as having low aqueous solubility and bioavailability [35]. As a result, there is a significant opportunity for enabling technologies to facilitate the development of problematic compounds into a viable therapy. A number of technologies have been developed to address the problem of reduced solubility, including amorphous formulations (e.g., solid solutions), particle size reduction (e.g., nanocrystals), formulation strategies (e.g., cyclodextrins and lipid formulations), cryogenic techniques (e.g., spray freeze drying) and supercritical fluid processing [36-41]. Porous silicon offers the potential to improve the solubility/bioavailability of poorly water soluble drugs through a combined effect of nanostructuring and solid-state modification.

The incorporation of drugs into porous silicon has been shown to affect the solid-state properties of loaded compounds. The loading of ibuprofen and antipyrine into thermally carbonised porous silicon has been shown to reduce the melting point of the compounds, as a result of nanostructuring [42]. The formulation of indomethacin and itraconazole with porous silicon was found to render the drugs amorphous [43]. The API were loaded into the porous

Table 2. Potential parameters affecting dissolution of mesoporous silicon in physiological environments.

Porous Silicon parameters	Biological & environmental parameters
Skeleton size distribution	Body fluid composition & pH
Pore morphology	Body fluid flow rate and wettability
Surface chemistry	Protein adsorption & mineral deposition
Particle size distribution	Extracellular enzymatic activity
Crystallinity and doping	Phagocytosis and intracellular activity

matrix by immersing the porous silicon particles into a concentrated API solvent solution. The particles were removed by filtration and vacuum dried. The specific effect of incorporation of molecules into porous silicon is likely to depend on the size of the pores, the physiochemical properties of the drug molecule and the specific interactions between the drug and porous matrix. Dissolution analysis of the itraconazole formulation in 0.1M HCl was found to result in a 25-fold increase in API solubility compared with the unprocessed crystalline control (Figure 5).

As a result of this nanostructuring and physiochemical modification, Shabir *et al.* demonstrated how the *in vitro* solubility of a range of APIs was improved following incorporation into porous silicon particles [44]. Cyclosporin A, dexamethasone, tamoxifen and paclitaxel were loaded using a rotary evaporation method, and the extent of dissolution enhancement was determined in pH 7.4 phosphate buffer. The results showed that formulation with porous silicon facilitated an increase in solubility of between 1.5- to 5-times that of the unprocessed control.

The potential for modifying the surface of porous silicon through chemical or thermal treatments provides a range of possible matrices for different drug delivery applications. Salonen *et al.* demonstrated how the surface modification of porous silicon by either thermal carbonisation (TCPSi) or oxidation can modulate drug dissolution in a range of physiologically relevant media [45]. The TCPSi particles were found to provide controlled release when the dissolution rate of the unloaded compound was high, and increase the rate of dissolution for poorly dissolving compounds. The extent of drug loading was dependent not only on the surface chemistry of the matrix, but also on the chemical properties of the drug and loading solvent used.

The ability of porous silicon to improve the bioavailability of cyclosporin A following subcutaneous administration to rats was demonstrated by Bulpitt and Conner [46]. The study showed that the porous silicon/cyclosporin A formulations resulted in a 3.8-fold increase in the C_{max} of cyclosporin A and a 4.6-fold increase in the total bioavailability, compared with the unprocessed drug control.

Table 3. Monomer degradation products of bioerodible polymers and silicon.

Biomaterial	Associated monomer	pKa
Polylactic acid	Lactic acid	3.9
Polylacticglycolicacid	Glycolic acid	3.8
Polycapralactone	Lactic acid	3.9
Polyhydroxybutyrate	Hydroxybutyric acid	4.7
Mesoporous silicon	Orthosilicic acid	9.5

As well as improving the solubility of poorly water soluble drugs, porous silicon can also be used for controlled delivery applications. One specific area of interest where the controlled delivery of a drug is important is the area of chemotherapy. The use of a controlled-release technology for anticancer agents is advantageous in terms of both drug toxicity and efficacy [47]. The ability of porous silicon wafers to control the release of doxorubicin was demonstrated by Vaccari *et al.* [48]. The release of the cytotoxic agent was controlled over a 5-h period, and resulted in the inhibition of adenocarcinoma cells *in vitro*.

The application of porous silicon for the delivery of cytotoxic agents was reported by Saffie-Siebert *et al.* [49]. Both paclitaxel and chlorambucil were loaded into porous silicon particles and administered into xenograft mice by intratumoural injection. The porous silicon formulations were found to significantly retard the rate of tumour growth and improve the survival rate when compared with controls.

The loading and release of the hydrophobic steroid, dexamethasone, from Fabry-Pérot films of porous silicon has also been reported [50]. Drug release into phosphate buffered saline (pH 7.4) from freshly etched films was rapid, and coincided with matrix degradation. Chemical modification of the porous silicon films by thermal hydrosilylation with dodecene improved both the stability of the matrix and reduced the drug release rate by a factor of 20, compared with the fresh, porous silicon film. The reduction in drug dissolution rate was attributed to the predominance of a drug diffusion mechanism over matrix dissolution.

Due to their large size, complex structure and stability issues, the delivery of therapeutic proteins and peptides creates a specific challenge. Parenteral delivery is still the most widely used route of delivery for proteins and peptides, but achieving a therapeutic effect can require a strict regimen of daily injections. As a result, there has been a significant amount of interest in the development of novel technologies to improve and control the delivery of biologics. So far, the main technologies available are biodegradable, polymer microparticles/implants (e.g., polylacticglycolicacid, polylactic acid) and PEGylation [51].

A recent study by Shabir *et al.* demonstrated how porous silicon could control the release of a hydrophilic peptide [52]. A range of formulation options were investigated, including particles, compressed pellets and implants. A fabricated

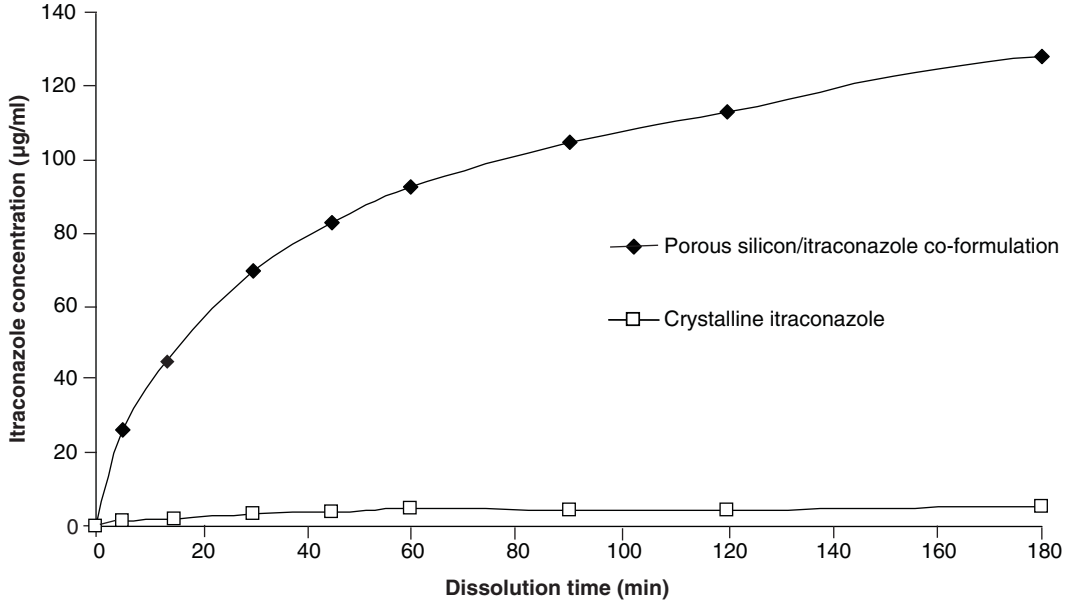

Figure 5. Dissolution performance of itraconazole before and after co-formulation with porous silicon. Porous silicon particles were loaded by immersion into a concentrated solution of itraconazole dissolved in a mixture of dichloromethane:methanol (1:1), followed by vacuum drying. Dissolution was performed in 0.1M HCl at 37°C and 100 rpm [43].

implant of porous silicon membranes provided a zero order release profile, with 40% of the peptide released over 12 days. A study into the release of insulin from porous silicon microparticles and subsequent transport across a model caco-2 cell monolayer has been reported [53]. Freeze drying was used to load the insulin into the porous silicon particles, and sodium laurate was used as a permeation enhancer. A 10- to 50-fold increase in insulin transport efficiency across the caco-2 cell monolayer was achieved from the porous silicon particles, compared with a liquid formulation controls.

The size of biological molecules and the lack of organic solvent solubility poses a particular problem when formulating with mesoporous structures. The penetration of human serum albumin (HSA) into porous silicon layers with different pore size and layer thickness has been investigated using ellipsometry [54], with particular interest in the depth of penetration. Loading was achieved by incubating porous silicon in phosphate-citrate buffer (pH 4.8, 21°C) for 3 h. It was concluded that HSA could not penetrate pores with a diameter of < 5.5 nm which was almost double the hydrodynamic radius of HSA (~ 3 nm) [55]. Increasing the initial loading concentration was observed to increase the amount of HSA loaded into the pores; ~ 70-times more HSA could be loaded into the porous silicon layers compared with a nonporous silicon surface.

Prestidge *et al.* investigated the application of atomic force microscopy and time-of-flight secondary ion mass spectroscopy to gain a better understanding into the effect that protein/peptide size and hydrophobicity had on loading into porous silicon wafers [56]. The results showed that the smaller, hydrophobic peptide gramicidin A was more readily loaded within the pores than the larger, hydrophilic protein papain. However, a significant level of sustained papain release was observed from loaded porous silicon microparticles [57]. Further work is required to better understand the effect that protein size, structure and chemistry has on both loading and release, in order to further develop the technology.

The observation that co-formulation of drug compounds with porous silicon renders the compounds amorphous, raises questions regarding long-term stability. Amorphous compounds have long been known to be physically and chemically unstable, hence their lack of widespread application within the pharmaceutical industry. It has been shown for porous silica that amorphisation through nanostructuring results in a formulation that was physical stable, presumably as a combined effect of surface interactions and confined mobility [58]. Future studies are required to investigate the implication of both nanostructuring and amorphisation on molecule chemical stability.

9. Conclusions

Mesoporous silicon is the first semiconducting material to be evaluated for drug delivery applications. Encouraging *in vitro*

and *in vivo* data has been published regarding its potential to improve the dissolution and bioavailability of hydrophobic small molecules. More work is required to evaluate the capabilities of this open, nanoscale, matrix technology for protein and hydrophilic molecule delivery. Manipulation of surface chemistry and its semiconducting nature offer short- and long-term opportunities, respectively, in targeted delivery and electrically controlled delivery.

10. Expert opinion

Biodegradable polymers have been developed over many decades for a wide range of medical applications, including drug delivery. More data on mesoporous silicon is required to comprehensively assess and compare its performance as a drug delivery vehicle for specific applications. Nonetheless, there is already evidence that nanostructured silicon could be particularly useful for poorly soluble/low bioavailability drugs, of which there are increasing numbers coming through the drug-discovery pipeline. There are a range of porous silica-based matrices that have found application within the pharmaceutical industry, in particular as thickening agents and tableting excipients [59]. More recently, there has been a renewed interest in mesoporous forms of silica for various drug-delivery applications [58-62].

From a materials science perspective, it is useful at this stage to identify differentiating aspects of silicon, and where these might lead to in future research and product development. The most obvious of these relate to its semiconducting nature, micromachinability and potential for integration with sensors and electronics. To what extent could such microelectronic systems impact drug delivery? Two quite different approaches have been under investigation. One is a pacemaker-style implant offering microprocessor-controlled pulsatile drug release [63]. At the other end of the scale, in terms of complexity and cost, is a disposable 'ticking tablet' for oral delivery [64]. Here, the challenge is to integrate a microbattery, a means of drug expulsion and a silicon 'clock' (microcontroller) in a very cost-effective pill format. Both systems benefit from the clinical need for controlled, pulsatile release of particular drugs, and in particular chronopharmacology [65]. It seems likely that over the next decade, smart chip-based delivery systems will emerge from what is presently being learnt from passive formulations with the semiconductor. Transdermal delivery could be the first area to benefit from a microelectronic extension of microneedle patch technology [66].

Conflict of interest

CA Prestidge and TJ Barnes are presently involved in a project funded by the Australian Research Council Linkage program and pSivida Ltd.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. FERRARI M: Cancer nanotechnology: opportunities and challenges. *Nat. Rev. Cancer* (2005) 5:161-171.
2. UHLIR A: Electrolytic shaping of germanium and silicon. *Bell Syst. Tech J.* (1956) 35:333-347.
3. CANHAM LT: Bioactive silicon structure fabrication through nanoetching techniques. *Adv. Mater.* (1995) 7:1033-1035.

• First evidence for biodegradability of mesoporous silicon.

4. JANSHOFF A, DANCIL KPS, STEINEM C *et al.*: Macroporous p-type silicon fabry-perot layers. Fabrication,characterization and applications in biosensing. *J. Am. Chem. Soc.* (1998) 120:12108-12116
5. DROTT J, ROSENGREN L, LINDSTRÖM K, LAURELL T: Pore morphology influence on catalytic turn-over for enzyme activated porous silicon matrices. *Thin Solid Films* (1998) 330:161-166.
6. KOTZAR G, FREAS M, ABEL P *et al.*: Evaluation of MEMS materials of construction for implantable medical devices. *Biomaterials* (2002) 23:2737-2750.
7. ZHANG K, LOONG SL, CONNOR S *et al.*: Complete tumor response following intratumoral 32P BioSilicon on human hepatocellular and pancreatic carcinoma xenografts in nude mice. *Clin. Cancer Res.* (2005) 11(20):7532-7537.
8. GOH AS, CHUNG AY, LO RH *et al.*: A novel approach to brachytherapy in hepatocellular carcinoma using a phosphorus 32 brachytherapy delivery device – a first-in-man study. *Int. J. Radiat. Oncol. Biol. Phys.* (2006) 67(3):786-792

• First-in-man study for silicon.

9. LEHMANN V: Electrochemistry of Silicon. Wiley-VCH (2002):51-75

• Good textbook on silicon electrochemistry.

10. YONEHARA T: Epitaxial layer transfer by bond and etch back of porous silicon *Appl. Phys. Lett.* (1994) 64(16):2108-2110.
11. KOLASINSKI K: Silicon nanostructures from electroless electrochemical etching. *Current Opinion in Solid State and Materials Science* (2005) 9:73-83.
12. ASHRUF CMA, FRENCH PJ BRESSERS PMMC , KELLY JJ: Galvanic porous silicon formation without external contacts. *Sens. Actuators A Phys.* (1999) 74:118-122.
13. CULLIS AG, CANHAM LT, CALCOTT PDJ: The structural and luminescence properties of porous silicon. *J. Appl. Phys* (1997) 82(3):909-965.
14. BISI O, OSSICINI S, PAVESI L: Porous silicon: a quantum sponge for silicon based optoelectronics. *Surf. Sci. Reports* (2000) 38(1-3):1-126.
15. YAMAMOTO T, ENDO A, INAGI Y, OHMORI T, NAKAIWA M: Evaluation of thermoporometry for characterisation of mesoporous materials. *J.Colloid Interface Sci.* (2005) 284(2):614-620.
16. TSUBOI T, SAKKA T, OGATA YH: Structural study of porous silicon and its oxidized states by solid state high resolution

29Si NMR spectroscopy. *Phys. Rev. B* (1998) 58(20):13863-13869.

17. ANDERSON SHC, ELLIOTT H, WALLIS DJ, CANHAM LT, POWELL JJ: Dissolution of different forms of partially porous silicon wafers under simulated physiological conditions. *Physica Status Solidi (A): Applied Research* (2003) 197(2):331-335.
18. CANHAM L: Predicted biodegradability of mesoporous silicon in various sites of the human body. In: *Porous Semiconductors - Science and Technology.* Cullera-Valencia, Spain (2004) O44:102-103.
19. REFITT DM, JUGDAOHSINGH R, THOMPSON RP, POWELL JJ: Silicic acid: its gastrointestinal uptake and urinary excretion in man and effects on aluminium excretion. *J. Inorg. Biochem.* (1999) 76:141-147.
20. ILER RK: In: *The chemistry of silica : solubility, polymerization, colloid and surface properties and biochemistry.* J.Wiley & Sons (1979):195-202.
21. POPPLEWELL JF, KING SJ, DAY JP *et al.*: Kinetics of uptake and elimination of silicic acid by a human subject: a novel application of ^{32}Si and accelerator mass spectrometry. *J. Inorg. Biochem.* (1998) 69(3):177-180.
22. SRIPANYAKORN S, JUGADAOSHSING R, ELLIOTT H *et al.*: The silicon content of beer and its bioavailability in healthy volunteers. *Br. J. Nutr.* (2004) 91:403-409.
23. WROBEL K, BLANCO GONZALEZ E, SANZ-MEDEL A: Progress with the speciation of aluminium and silicon in serum of chronic renal patients using atomic spectroscopic techniques *J. Anal. Atom. Spectrom.* (1994) 9:281-284.
24. DOBBIE JW, SMITH MJB: In: *Silicon Biochemistry* Evered D, O'Connor M (Eds) Wiley & Sons (1986) 26:194-213.
25. BISSI E, EPTING T, BEIL A, LINDINGER G, LANG H, WIELAND H: Reference values for serum silicon in adults. *Anal. Biochem.* (2005) 337:130-135.
26. ROSENGREN A, WALLMAN L, BENGTSSON M, LAURELL TH, DANIELSEN N, BJURTSEN LM: Tissue reactions to porous silicon: a comparative biomaterial study. *Physica Status Solidi (A): Applied Research* (2000) 182:527-531.
27. PETROVA EA, BOGOSLOVSKAYA KN, BALAGUROV LA, KOCHORADZE GI *et al.*: Room temperature oxidation of porous silicon in air. *Materials Science and Engineering* (2000) B69/B70:152-156.
28. BURIAK JM, STEWART MP, GEDERS TW *et al.*: Lewis acid mediated hydrosilylation on porous silicon surfaces *J. Am. Chem. Soc.* (1999) 121:11491-11502.
29. BOUKHERROUB R, WAYNER DDM, LOCKWOOD DJ, CANHAM LT: Passivated luminescent porous silicon. *J. Electrochem. Soc.* (2001) 148(9):H91-H97.
30. MATTEI G, VALENTINI V: In Situ Functionalization of Porous Silicon during the Electrochemical Formation Process in Ethanoic Hydrofluoric Acid Solution. *J. Electrochem. Soc.* (2003) 125:9608-9609.
31. LOW SP, WILLIAMS KA, CANHAM LT, VOELCKER NH: Evaluation of mammalian cell adhesion on surface-modified porous silicon. *Biomaterials* (2006) 27:4538-4546.
32. SONG JH, SAILOR MJ: Chemical modifications of Crystalline Porous Silicon Surfaces. *Comments on Inorganic Chemistry* (1999) 21(1-3):69-84.
- Useful introductory review to silicon surface chemistry.
33. BURIAK JM: Organometallic chemistry on silicon and germanium surfaces. *Chem.Rev.* (2002) 102:1271-1308.
34. VASANTH KUMAR K, SIVANESAN S: Equilibrium data, isotherm parameters and process design for partial and complete isotherm of methylene blue onto activated carbon. *J. Hazard. Mater.* (2006) 134:237-244.
35. LIPINSKI C: Poor aqueous solubility – an industry wide problem in drug discovery. *Am. Pharm Rev.* (2002) 5:82-85.
36. LEUNER C, DRESSMAN J: Improving drug solubility for oral drug delivery using solid dispersions. *Eur. J. Pharm. Biopharm.* (2000) 50:47-60.
37. MERISKO-LIVERSAGE E, LIVERSAGE GG, COOPER ER: Nanosizing a formulation approach for poorly water soluble compounds. *Eur. J. Pharm. Biopharm.* (2003) 18:113-120.
38. SINGH M, SHARMA R, BANDERJEE UC: Biotechnological applications of cyclodextrins. *Biotechnol. Adv.* (2002) 20:341-359.
39. HU J, JOHNSTON KP, WILLIAMS III RO: Spray freeze drying into liquid (SFL) particle engineering technology to enhance dissolution of poorly water soluble drugs: organic solvent versus organic/ aqueous co-solvent systems. *Eur. J. Pharm. Sci.* (2003) 20:295-303.
40. GINTY PJ, WHITAKER MJ, SHAKESHEFF KM, HOWDLE SM: Drug delivery goes supercritical. *Materials Today* (2005) 8(1):42-48.
41. POUTON CW: Formulation of poorly water-soluble drugs for oral administration: Physiochemical and physiological issues and the lipid formulation classification system. *Eur. J. Pharm. Sci.* (2006) 29(3-4):278-287.
42. LEHTO V-P, VÄHÄ-HEIKKILÄ K, PASKI J, SALONEN J: Use of thermoanalytical methods in quantification of drug load in mesoporous silicon microparticles. *Journal of Thermal Analysis and Calorimetry* (2005) 80(2):393-397.
- Interesting study into the quantification of drugs loaded porous matrices.
43. LAU CH, TOTOLICI M, BARNETT C: Enhanced dissolution of poorly soluble drugs using mesoporous silicon. *AAPS PharmSci.* (2006) W4143.
- Definitive solid state data on API in porous silicon.
44. SHABIR QA, LAU CH, YANG HL, SAFFIE RS, CANHAM LT: Enhanced dissolution kinetics of poorly soluble drugs using mesoporous silicon. In: *Porous Semiconductors - Science and Technology.* Stiges, Spain (2006): 2-58.
45. SALONEN J, LAITINEN L, KAUKONEN AM *et al.*: Mesoporous silicon microparticles for oral drug delivery: loading and release of five model drugs. *J. Control. Release.* (2005) 108:362-374.
- •• Good study into the loading and release of API in porous silicon.
46. BULPITT P, CONNOR SE: Improved bioavailability of cyclosporine A using porous silicon: single dose pharmacokinetic study in the rat. *Proceedings of the 33rd Annual Meeting and Exposition of the Controlled Release Society.* Vienna, Austria (2006) 849.
- *In vivo* data demonstrating the potential for bioavailability enhancement.
47. BIRNBAUM DT, BRANNON-PEPPAS L: Microparticle drug delivery systems. In: *Drug Delivery Systems in Cancer Therapy.* Brown DM (Ed.) Humana Press inc., Totowa, NJ (2003):117-136.

48. VICCARI L, CANTON D, ZAFFARONI N, VILLA R, TORMEN M, DI FABRIZIO E: Porous silicon as a drug carrier for controlled delivery of doxorubicin anticancer agent. *Microelectronic Engineering* (2006) 83:1598-1601.

49. SAFFIE-SIEBERT RS, DRAGE D, TORABI-POUR N *et al*: Application of BioSilicon in drug delivery and drug targeting: Intratumoral therapy. *AAPS J.* (2004) 6(4) Abstr. W5245.

50. ANGLIN EJ, SCHWARTZ MP, NG VP, PERELMAN LA, SAILOR MJ: Engineering the chemistry and nanostructure of porous silicon Fabry-Pérot films for loading and release of a steroid. *Langmuir* (2004) 20:11264-11269.

51. SINHA VR, TREHAN A: Biodegradable microspheres for protein delivery. *J. Control. Release.* (2003) 90:261-280.

52. SHABIR QA, LAU CH, TOTOLICI M, SAFFIE RS, CANHAM LT: Porous silicon technology for controlled release of highly soluble compounds: Pilot study for a model peptide. In: *Porous Semiconductors - Science and Technology.* Stiges, Spain (2006):2-56.

53. FORAKER AB, WALCZAK RJ, COHEN MH, BOIARSKI TA, GROVE CF, SWAAN PW: Microfabricated Porous Silicon Particles Enhance Paracellular Delivery of Insulin Across Intestinal Caco-2 Cell Monolayers. *Pharm. Res.* (2003) 20(1):110-116.

- Interesting report on potential *in vivo* application.

54. KARLSSON LM, TENGVALL P, LUNDSTROM I, ARWIN H: Penetration and loading of human serum albumin in porous silicon layers with different pore sizes and thicknesses. *J. Colloid Interface Sci.* (2003) 266(1):40-47.

55. RUSO JM, TABOADA P, VARELA LM, ATTWOOD D, MOSQUERA V: Adsorption of an amphiphilic penicillin onto human serum albumin: Characterisation of the complex. *Biophys. Chem.* (2001) 92:141-153.

56. PRESTIDGE CA, BARNES TJ, MIERCZYNSKA-VASILEV A *et al.*: Peptide and protein loading into porous silicon wafers. *Physica Status Solidi (A): Applied Research* (2007) (in press).

- Mechanisms behind protein and peptide loading in porous silicon.

57. PRESTIDGE CA, BARNES TJ, MIERCZYNSKA-VASILEV A, SKINNER W, PEDDIE F, LAU CH, BARNETT C: Loading and release of a model protein from porous silicon powders. *Phys. Stat. Sol A* (2007) (In press).

58. TAKEUCHI H, NAGIRA S, YAMAMOTO H, KAWASHIMA Y: Solid dispersion particles of amorphous indomethacin with fine porous silica particles by using spray-drying method. *Int. J. Pharm.* (2005) 293:155-164.

59. DEGUSSA AG: Technical bulletin Fine Particles (No. 11), Company Publication, Frankfurt, Germany, 4th edition (2006).

60. MONKHOUSE DC, LACK JL: Use of adsorbents in enhancement of drug dissolution I. *J. PharM. Sci.* (1972) 61(9):1430-1435

61. FRIEDRICH H, FUSSNEGGER B, KOLTER K, BODMEIER R: Dissolution rate improvement of poorly water soluble drugs obtained by adsorbing solutions of drugs in hydrophilic solvents onto high surface area carriers. *Eur. J. Pharm. Biopharm.* (2006) 62:171-177.

62. SMIRNOVA I, SUTTIRUENGWONG S, ARLT W: Feasibility study of hydrophilic and hydrophobic silica aerogels as drug delivery systems. *Journal of Non-Crystalline Solids* (2004) 350:54-60.

63. SANTINI J.T, RICHARDS AC, SCHEIDT R, CIMA MJ, LANGER R: Microchips as controlled drug-delivery devices. *Angewandte Chemie* (2000) 39(14):2396-2407.

64. LEONG WY, LONI A, CANHAM LT: Electrically enhanced erosion of porous silicon in electrolyte by pH modulation. *Physica Status Solidi (A): Applied Research* (2007) (In press).

65. REDFERN P: Chapter 11. In: *Chronotherapeutics.* Pharmaceutical Press, UK (2003).

66. PRAUSNITZ MR, MITRAGOTRI S, LANGER R: Current status and future potential of transdermal drug delivery. *Nat. Rev. Drug Discov.* (2004) 3:115-124.

Affiliation

Clive A Prestidge[1] PhD, Timothy J Barnes[2], Chi-Hian Lau[3] PhD, Christian Barnett[†4] PhD, Armando Loni[5] PhD & Leigh Canham[6] PhD

[†]Author for correspondence

[1]Professor, University of South Australia, Ian Wark Research Institute, Australia

[2]PostDoctoral Researcher, University of South Australia, Ian Wark Research Institute, Australia

[3]Senior Scientist, pSiMedica Ltd, Malvern Hills Science Park, Geraldine Rd, Malvern, WR14 3SZ, UK

[4]Pharmaceutical Research Manager, pSiMedica Ltd, Malvern Hills Science Park, Geraldine Rd, Malvern, WR14 3SZ, UK

Tel:+ 44 0 1684 585 304

Fax: + 44 01684 585 357

Email: christianbarnett@psivida.com

[5]Senior Scientist, pSiMedica Ltd, Malvern Hills Science Park, Geraldine Rd, Malvern, WR14 3SZ, UK

[6]CSO, pSiMedica Ltd, Malvern Hills Science Park, Geraldine Rd, Malvern, WR14 3SZ, UK