Nanostructured Silicon – Applications in Drug Delivery

A nanoengineered form of silicon – BioSilicon™ – has many properties that make it an ideal drug delivery platform.

By Gavin Rezos, Managing Director, pSivida Limited

Gavin Rezos is Managing Director of pSivida Limited. He is qualified in law and has extensive international investment banking experience as a former Investment Banking Director of the HSBC Group, with roles based in London, Sydney and Dubai.

Silicon is a ubiquitous element found in many everyday items, notably computers, mobile phones – in fact almost every electronic device. Now, a new nanostructured form of silicon, BioSilicon™, is finding application in several areas of medicine – notably controlled slow-release drug delivery. The key to the potential of BioSilicon in medical applications lies in the finding that, by nanoengineering silicon into a honeycomb structure with an increased surface area, the material can be made to dissolve in the body at a predetermined rate. This article reviews the various properties of BioSilicon and how it is being developed by pSivida as a drug delivery vehicle.

BIOSILICON

BioSilicon™ is a porous form of silicon that is both biocompatible and biodegradable; it dissolves in the body to become silicic acid, a non-toxic compound that is harmlessly excreted by the kidneys. BioSilicon retains the key semiconductor and other properties of silicon, and is created through a physical change in silicon at the nano-level (in essence, the silicon is filled with holes through the application of acid via an etching process), as opposed to a chemical change. BioSilicon is an element – not a compound – and the resultant porous honeycomb structure from physical nanostructuring mimics the porous membrane structures found in nature.

As a true platform ‘nanotechnology’, BioSilicon has multiple potential applications across many sectors of health care. BioSilicon is an example of top-down nanostructuring, whereby elemental silicon is nanostructured to create nanopores within the material; these are typically about 10 atoms across and can be loaded with drugs, peptides, genes, proteins, radionuclides and other therapeutics or vaccines. Bottom-up nanostructuring, on the other hand, involves building a material or structure piece by piece or atom by atom.

In health care applications, BioSilicon has a number of competitive advantages:

◆ It is biodegradable, biocompatible and a semiconductor
◆ It is abundant and low-cost (silicon makes up approximately 28% of the earth’s crust and is freely available)
◆ Scale-up and manufacture of silicon is proven (with more than 40 years’ experience in the electronics industry)

DRUG DELIVERY

BioSilicon has many properties that make it an ideal drug delivery platform:

◆ High drug-loading rates (up to 95% – typical polymer average is 50%)
◆ Excellent control over change in release-timing (hours, days, weeks, months)
◆ Structural protection from dose-dumping,
◆ Biodegradable, biocompatible and non-toxic (safety of silicon by-products – silicic acid – following biodegradation)
◆ Micro-machining can create a variety of structures at the micro-level (cubes, darts and scaffolds) all of which are themselves made porous at the nano-level
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- Conduction of charge – charge can be altered to regulate drug delivery
- Intelligence – potential incorporation into microchips and diagnostic products
- Range of delivery formulations – oral, injectable, transdermal, patch, implant and coatings

The use of novel drug delivery systems is a growing strategy for major pharmaceutical companies to extend the commercial life of their currently marketed drugs, and drug delivery is a core application for BioSilicon in what is a rapidly growing market. The specialised drug delivery market is in excess of US$50 billion, with an estimated US$80 billion worth of pharmaceutical products expected to have come off patent by 2005, including many of the top 20 drugs by revenue. By using an alternative delivery system such as BioSilicon to show better efficacy, safety or compliance, a new generic-plus patent can be granted extending the life of the investment by pharmaceutical companies in patented drugs.

pSivida’s core focus is on controlled release formulations to deliver small molecule, protein and peptide drugs that require release over periods of days, weeks or months. In the longer term, the company is also seeking to utilise the semiconductor properties of BioSilicon to create ‘smart’ drug delivery devices. The development of a partnering strategy is currently being advanced in this area, with leading electronics and chip technology companies expressing strong interest in the development of such devices.

ORAL ADMINISTRATION

Oral administration remains the most favoured route of treatment for medicines, being painless and enabling the patient to self-administer. One of the key issues associated with oral delivery is the stability of pharmaceutical compounds in the digestive system; many current tableted products have enteric coatings to protect the active material in the highly acidic environment of the stomach. BioSilicon addresses many of the current issues associated with oral drug delivery:

- As it does not dissolve in acidic solutions, it protects a drug in the acid environment of the stomach
- It is designed to ‘slow-release’ drugs through controllable biodegradation, providing the opportunity to optimise delivery and absorption
- It offers the opportunity to develop chip-based devices that would provide processor-based delivery targeted to different parts of the gut

BioSilicon allows drug molecules to be held in nano-sized pockets that release drug as it dissolves. pSivida is currently focusing on biodegradable tablets that deliver over optimised periods; this will be followed by focusing on ‘smart’ tablets that release drug electronically. Electronically controlled drug delivery offers the opportunity for a nearby sensor within the pill to automatically deliver the right amount of drug at the right location. pSivida has also recently been granted a further patent in Singapore for the use of BioSilicon as an information carrier, having a form and composition whereby information is recorded by the carrier.

BRACHYTHERAPY

Brachytherapy is a relatively new form of cancer treatment that involves the delivery of active agents directly into the tumour. The brachytherapy market is valued at over US$600 million and is expected to exceed US$1 billion by 2005. The market is currently dominated by the use of radioactive ‘seeds’, mainly for the treatment of hormone non-responsive prostate cancer. These products are both expensive and cause significant trauma on application.

In brachytherapy treatment, BioSilicon has many significant advantages:

- Versatility – application in both radiotherapy and chemotherapy
- A short range – a 32-P isotope is used which has a shorter tumour-kill range (8mm) than other competing products resulting in less damage to healthy tissue

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Figure 1: The Structure of BioSilicon™:
- a) Nanostructure
- b) Cross-section
- c) Nanospheres
- d) Nanoparticles
Direct delivery via fine-gauge needle – accurate, controllable, convenient and not requiring surgery or any special protective measures for physician or patient

A variety of tumours – potential application to all solid tumours, unlike current products which are restricted to a single indication, such as liver or prostate cancer only

Inexpensive – low cost, abundant availability of silicon, with proven scale-up

Distribution – 32-P half-life of 14 days (versus 64 hours for Y-90, for example) allows for more convenient distribution to hospitals and application to the patient

Immobilisation – the 32-P device is immobilised in the tumour, significantly reducing the risk of leakage or systemic side-effects

BioSilicon brachytherapy products are being developed through pSivida's Singapore operating subsidiary, pSiOncology, with clinical trials at Singapore General Hospital. The company's lead brachytherapy product, BrachySil\textsuperscript{TM}, will offer clinicians a short-range, longer-life 32-P isotope that can be delivered through a fine-gauge needle, making it more user-friendly for both patient and physician. By being applied intra-tumourally, the product has shown tumour regression with minimal damage to healthy liver tissue.

Interim results from the first four patients of the current Phase IIa clinical trial, announced in mid-October 2004, demonstrated the safety and efficacy of BrachySil, with tumour regression of up to 60% and validation of the fine-gauge needle administration route. The Phase IIa trials commenced in Singapore in May 2004 in eight patients with inoperable liver cancer; the primary objective of the trial is to assess the safety profile of BrachySil, with a secondary objective to provide important efficacy data on tumour regression in patients with inoperable tumours of the liver.

The next steps are dose-ranging studies to determine the optimum dosage and then commencement of a multicentre Phase IIb trial, in 2005. The targeted launch date for BrachySil is 2007, following registration in 2006 as a device, although some sales may be made after Phase IIb trials in 2005.

A manufacturing route for BrachySil, compliant with regulatory requirements worldwide, has been established. Partners in this process include Micron Group and Atomising Services Ltd (size definition), HighForce Ltd (nanostructuring and stain-etching) and AEA Technology Ltd, Auriga Medical (neutron bombardment, final formulation and packaging, logistics and distribution).

pSiOncology is now looking to apply the BrachySil product to other tumours, such as pancreatic, bladder, and head and neck cancers, for example.

**LOCALISED CHEMOTHERAPY**

Further localised cancer products based on chemotherapeutic agents are also in development; pSiOncology is developing localised chemotherapy products using generic cytotoxic drugs in slow-release BioSilicon. A localised intra-tumoural chemotherapy preclinical trial has produced compelling results. Expertise and clinical data gained from pSiOncology will assist in the development of the broader BioSilicon drug delivery platform, and will complement partnerships in this area.

**TRANSDERMAL DELIVERY**

One of the key attributes of BioSilicon is its capacity to be micro-engineered into complex and precise shapes; this property stems from a long history of silicon-based micro-engineering in the electronics industry. pSivida is capitalising on this property to create microstructures suited to the delivery of drugs directly into cells or through barriers, such as the skin. This is achieved through the construction of needle microarrays that are so small that they are invisible to the naked eye.

A key attraction in using BioSilicon for the construction of such drug delivery arrays is the fact that the material is biodegradable – unlike needles constructed out of conventional metals, such as steel. Thus, a needle microarray on a transdermal patch for the delivery of drugs through the skin would enable a drug to cross the skin barrier. Such needle arrays are expected to be virtually pain-free due to the extremely small needle size. Furthermore, any needles lost in the skin would safely biodegrade. The technology also provides a method for transferring drugs through the cell membrane in specific settings. Another transdermal route available using BioSilicon is subcutaneous depot injection.

**COMMERCIALISATION STRATEGY**

pSivida's commercialisation strategy involves a combination of internal product development and
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In the fabrication of new generations of intelligent drug delivery devices, orthopaedic implants and intelligent diagnostic tools, pSivida owns all intellectual property rights royalty-free in relation to BioSilicon for which there are 24 granted patents, 23 patent families and over 80 patent applications. The core patent – which recognises BioSilicon as a biomaterial – was granted in the UK in 2000 and the US in 2001.

QinetiQ, under the initial assignment of the IP, is required to assist in the defence of the first 10 patent families in the event of any challenge.

In July 2004, pSiMedica Limited (the UK operating subsidiary) was granted a further Australian patent for BioSilicon, relating to the invention of orally administrable pharmaceutical products (for example, tablets, capsules, pellets and powders) that comprise porous and/or polycrystalline silicon (BioSilicon). In August 2004, pSiMedica was granted a further US patent for BioSilicon – US Patent Number 6,770,480 – providing protection for the transfer of a substance, such as a drug or genetic material, into a cell utilising resorbable silicon, such as certain biodegradable forms of porous or polycrystalline silicon (BioSilicon). Another important patent recently granted in the US related to the implanting of an electronic device with bioactive silicon for ‘smart’ drug delivery applications, utilising the semi-conductor properties of silicon.

The author can be contacted at gavinrezos@psivida.com.au