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Review Article

NANOSTRUCTURED POROUS SILICON – A NOVEL BIOMATERIAL FOR DRUG DELIVERY

D.SATHIS KUMAR*, DAVID BANJI, BINDU MADHAVI.B, VENKATRAMREDDY BODANAPU, SHIVANJALI DONDAPATI, AND ANUGU PADMA SRI
Nalanda College of Pharmacy, Nalgonda, Andhrapradesh-508 001.
Senior Lecturer, Nalanda College of Pharmacy, Nalgonda, Andhra Pradesh.
Email: satmpdina@yahoo.co.in, Mobile: 09966796051.
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ABSTRACT

Nanostructures may be used to deliver drugs where they are required to avoid the harmful side effects. The recent discovery that following nano structured silicon can be rendered biocompatible and biodegradable has far reaching and profound long-term implications for the pharmaceutical industry and indeed medicine as a whole. Drug particles are structured within nano width pores of silicon particles, membranes or fibres; gives controlled release/ improves solubility of hydrophobic drugs. This review explained the benefits of porous silicon in drug release kinetics, drug loading efficiency and as a part of its localized chemotherapy program, it also demonstrates optical properties that provide the basis for a variety of potential devices for biodegradable and biocompatible diagnostic products. Finally it can be concluded that nano structured porous silicon offer new ways to address hydrophobic and low bioavailable drugs and are being applied in a wide range of healthcare settings.

Key words: Porous silicon, Biodegradability, Biocompatibility, Controlled drug release

INTRODUCTION

Nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization, and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer or one billionth of a meter. During the last decades, pharmaceutical technology has taken the advantage of the advent of nanotechnology and, now days, new pharmaceutical dosage forms are under development to deliver many physicochemically different drug molecules. Nanotechnology is unique in that it represents not just one specific area, but a vast variety of disciplines ranging from basic material science to personal care applications. The importance of nanotechnology in drug delivery is in the recent and ability to manipulate molecules and supramolecular structures for producing devices with programmed functions. Silicon is making a major debut in the therapeutics sector. Silicon has been doing this indirectly for many years through the numerous electronic products and devices that are used every day in hospitals (e.g. pacemakers, anti arrhythmia devices, table top drug infusion devices etc). However, it is the coupling of the electronic properties of silicon with ability to miniaturise that is now paving the way to a new era in the implantable medical products. In the recent discovery it was established that the principle semi conductor, silicon, can be rendered bio compatible and equally importantly bio degradable, following nano structuring opens up important opportunities[1].

Table 1 : Nanodrives leading medicine

Tissue engineering	artificial nano scale building blocks may one day be employed to repair tissues such as cartilage, bone and skin
Drug delivery	nano structure may be used to deliver drugs where they are required avoiding harmful side effects.
Diagnostics	Nanotags or labels may make diagnostics quicker and more Specific.
Drug screening	nanotechnology may find use in research systems to Accelerate screening and detection.

Development of nanostructural materials

Nano structured materials are defined as solid with nano scale or poorly nano scale structuring within. Nano structured materials have the ability to impart nano scale 'order' and nano scale 'control', which are providing a versatile template for building of biological structures to support the drivers in medicine. There are two fundamental driving forces which involve in nano structure are as follows:

1. Enhanced performance improves hardness, strength or toughness of ultra fine-grained metallic materials.
2. Radically novel performance brings novel optoelectronic and bio chemical assembly. Eg: Silicon[2].

There are two approaches to realize a nanostructure.

- Self-assembly of molecules (bottom up approach): Bottom up approaches begin by designing and synthesizing custom made molecules that have the ability to self assemble or self organize into higher order mesoscale and macroscale structures[3,4].
- Breaking up of bulk structure into nano size units (top down approach): Top down technique begins with a macro scopic material or group of materials and incorporate smaller scale details into them. The best known example of a top down approach is the photo lithography technique used by the semi conductor industry to create integrated circuits by etching patterns in silicon wafers[5].

Carrier systems for drug delivery

Many drug's potencies and therapeutic effects are limited or otherwise reduced because of partial degradation that occurs before they reach a desired target in the body. Indeed, many drugs can be delivered by several routes each with their own advantage and disadvantages. In an ideal drug delivery system, the drug profile in the desired tissue will be maintained at optimum therapeutic concentrations with minimum fluctuation, predictable and reproducible release rates for extended durations. Currently several approaches are being pursued for improved delivery of therapeutic products like nanocapsules, nanoparticles, vesicles, low density lipo proteins and nanoemulsions.

Conventional approaches to nanoparticulate carriers, including polymeric nanoparticles and liposomes, do however have the following limitations.

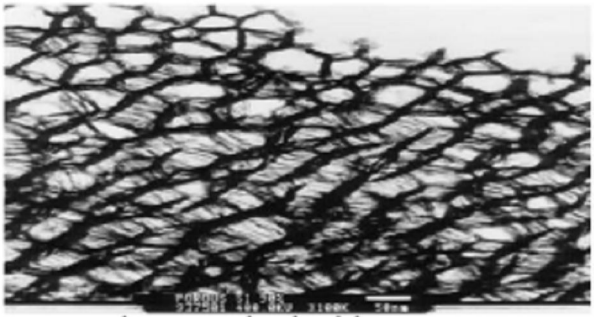
- Relatively high costs of production.
- Physical processing that can be harmful to the drug.
- Low drug encapsulation efficiency.
- Use of toxic solvents/reagents
- Limited ability to realize sub 80nm particle formulations.

Silicon as nanoparticle

Recent research suggests that silicon is not only bio-friendly but also potentially lends to an array of applications based on the novel properties following nano structuring; these include, drug delivery, tissue engineering and diagnostic functions in the body[6]. As a new biomaterial Silicon is a nanostructured form of elemental silicon, one of the most abundant elements on the earth's crust. Silica can offer the properties needed for nanoparticle based

drug delivery, namely nano toxicity, bio compatibility, high stability, and a hydrophilic and porous structure useful for tailoring the encapsulation of drugs[7]. Using hydro fluoric acid-based solutions, nanometer size pores with exceptionally high aspect ratios can be generated in silicon wafers, 'chips' or particles, and with a high degree of control. The resultant material is still pure silicon, but it behaves very differently to nano-porous 'bulk' silicon; one important example is that it becomes strongly fluorescent in the visible, engineered to create a 'honeycomb' structure of pores. This structure allows silicon to biodegrade while allowing the retention of various drugs and vaccines within the honeycomb matrix.

Fig. 1 : TEM image showing highly porous structure of silicon



Silicon- properties and scope

Researchers have now discovered a method to make composite photonic crystals of porous silicon and polymer, on a micron scale, and with a high degree of particle size regularity. The resultant crystals have greatly improved mechanical and chemical stability and are of a more uniform geometry than that obtained previously. The properties and scope of silicon are mentioned in Table 2.

Table 2 : Silicon properties and scope

Silicon Property	Potential scope
Semi conductivity	Microelectronics and oscillator based timing accuracy
Crystal stability	Thermally and mechanically robust structures
Micromachinability	Micro sensors and micro actuators
Purity	Electronics- grade silicon has purity that wouldbe the envy of most pharmaceuticals (99.9999%)
Luminescence	visibly fluorescent particles through nanostructuring
Biocompatibility	a relatively bioinert material for tissue interfacing
Biodegradability	nanostructured silicon will degrade without apparent

Biocompatible and biodegradable property of porous silicon

Porous Silicon retains the key semiconductor properties of silicon and is machineable at a micro level. Porous Silicon also demonstrates optical properties that provide the basis for a variety of potential devices for biodegradable and biocompatible diagnostic products. It has created a unique biomaterial that has the potential not only to serve as a biomedical device but also as a novel drug delivery carrier for a wide range of drug entities. During such studies thin layers of highly porous silicon or poly crystalline silicon of nano meter size grains could actually dissolve completely away in simulated human plasma.

In other words, nanostructured silicon was shown to be biodegradable *invitro*[8].

Porous silicon dissolves in body fluids into silicic acid, commonly found in everyday foods. The ubiquity of silicon in microelectronic applications is the result of the properties of silicon in crystalline form. Crystalline silicon is very resistant chemically, requiring very aggressive processing conditions for the fabrication of electronic devices.

Suitability of porous silicon

The porous "honeycomb" structure provides a large surface area, which is an ideal matrix for high capacity and efficient drug loading and release. Controlled drug release over days, weeks or months - drug release kinetics are controlled by altering the physical properties of the Porous Silicon matrix, eg: By adjusting the level of porosity, altering the pore size or particle size. Porous Silicon is an attractive candidate because the porosity and average pore size can be readily tuned by adjustment of the electrochemical processing conditions. Utilizes micron-sized particles of silicon have been etched and then chemically modified that each individual particle has its own addressable identity. This feature allows one to use thousands of the particles together, each with its own "tag", for high-sensitivity chemical or biological sensing, diagnostics, and low and high throughput screening of biomolecular compounds.

Drug loading

Porous silicon has been shown to be amenable to derivitisation, replacing the unstable silicon hydride bonds by Si-C bonding with a broad range of functional group attachments[9]. This means that drugs can be covalently attached to the Si- skeleton of a microparticle or nanoparticle via an enzyme sensitive bond for example. It also means that linked antibodies on the porous particle exterior could act as targeting agents in a similar manner to Targesome particles. Nano particles are easier candidates for surface or inter-face reconstructions which may help to reduce local stress and detrimental effects caused by the mismatch of mechanical properties between the ceramic and metal phases. These properties make nano particles particularly desirable as dispersion materials, especially high temperature alloys such as those in the molybdenum-silicon (Mo-si) system[10].

Drug loading properties

- It is Applicable to a wide range of therapeutic entities from small molecules to peptides and proteins including hydrophobic and hydrophilic entities.
- Efficiency of drug loading is up to 95% of starting material - typical formulations with 60% porosity have drug loadings of 35-40% w/w.
- Drug loading can be further enhanced by increasing the level of porosity of the matrix.
- Drug loading does not require chemical modification of the molecule – there are no changes in drug structure or activity after loading and subsequent release.
- Particularly well suited for solving the formulation problems associated with hydrophobic drugs.

Enhancement of hydrophobic drug solubility

Many of these methods rely on reducing drug size to nanoparticles, thereby greatly increasing the surface area and leading to enhanced dissolution. As with conventional methods, however, stabilizers are often

required to prevent recrystallisation and reagglomeration, while mechanical size-reduction processes can damage delicate molecules. Porous Silicon avoids these problems related to physical stress, as the drug is retained within a biocompatible nanoporous matrix and is released through pores in a controlled manner as the matrix biodegrades[11,12].

The nanostructured silicon crystal-lattice scaffold of porous Silicon provides a huge surface matrix for hydrophobic drugs and can be produced in diverse forms to suit a variety of drug delivery requirements. This technology exemplifies the critical difference in the scientific concept of the nanostructuring approach compared with nanoparticle-based technologies. Porous Silicon has been found to be particularly well suited for improving the solubility and bioavailability of poorly water-soluble drugs. This results from the nanostructuring of the drug within the nanosized pores of the Porous Silicon matrix so that drug surface area is increased thereby aiding dissolution and absorption. The kinetics of drug release from the majority of controlled-release formulations are less than ideal, often comprising an initial burst of enhanced solubility but failing to ensure complete delivery and absorption of the drug dose. This is a common problem for oral Biopharmaceutics Classification System class II drugs[13,14] (with low solubility but high permeability) formulated with surfactants, as the surfactant that aids on-site drug dissolution or dispersion at one level will suppress it at a higher concentration. Novel methods of reducing this reliance on release-accelerating agents, and prolonging controlled delivery of oral drugs[13]. Many poorly water-soluble drugs (both class II and IV compounds) have been successfully formulated and their solubility improved using Porous Silicon. Preclinical in vivo studies have demonstrated that Porous Silicon can not only significantly improve the solubility of poorly water soluble drugs but also enhances the absorption and bioavailability of such compounds.

Controlled release of hydrophobic compound

Sustained drug action may be achieved in various ways, including enhanced circulatory persistence of the drug and cellular targeting, as well as by controlled-release methodologies. Effective controlled-release drug technologies focus on solid dose formulations of hydrophobic compounds rather than lipid-based systems. The structuring of biocompatible nanomatrices for controlled drug release is an important application of nanotechnology as it avoids the dependence on chemical modifications of the matrix to suit individual drugs, which is typical for polymer based systems. This immediately simplifies the drug delivery system as well as reducing the toxicity potential. Nanostructured silicon also has the benefit of being made biodegradable where the kinetics of drug release depends on the rate of biodegradation of the matrix. The rate of degradation can be customized and depends on matrix porosity and pore width. Also, in this case, the porous structure presents a massive surface area, which has the effect not only of increasing the solubility of hydrophobic drugs loaded into the nanopores, but also allowing a very high drug-loading potential compared with other drug carriers.

Silicon based technology used in treatment of disease

Cancer therapy

The nanostructuring of silicon has also permitted the targeted heat ablation of experimental tumors in mice (eg: Nanospectra Biosciences' nanoshell-assisted photo thermal therapy [NAPT] [15]). Intravenously injected nanoshells, having a silicon core sealed into an outer shell of gold and 'tuned' to near infrared optical absorption, accumulate in tumors via the abnormal vasculature, enabling selective ablation of the tumor by the conversion of directed laser light into heat. In addition, non-biodegradable nanoporous silicon membranes are being used in implanted devices to control the prolonged release of drugs (for up to six months) from enclosed polymer reservoirs (iMEDD's NanoGate; DebioTECH's DebioSTAR), also to screen implanted islet cells from the host's immune defences: letting out insulin produced by the pancreatic cells and letting in nutrients and glucose but not the relatively large antibodies (University of Boston Department of Medical Engineering[16]). In particular, the production of 'nano-holes' to incorporate drug molecules simply avoids the safety issues associated with nanoparticles. The primary application for Porous silicon has been in controlled and localized delivery of drugs and other therapeutic agents. The high porosity of the nanostructured silicon confers a high capacity for loading with a therapeutic agent (up to 95%). On entering the site of treatment, the porous silicon slowly dissolves, releasing the therapeutic agent at a controlled rate. The Porous silicon can be very conveniently produced as micro-particles, which are loaded with the therapeutic agent. These can be injected using a fine needle. In this way drug is administered via a minimally invasive route, directly to the site of interest for treatment. The resulting treatment thus becomes very efficient in both the use of potentially expensive therapies and addressing the exact location of the disease. The porous nano-structure of porous silicon, presenting an internal pore volume of ~0.9cm3/gram, is available for drug loading[16]. It is possible to introduce drugs with poor aqueous solubility into the porous structure, thus increasing the dissolution/ solubility of the drug in the aqueous, physiological environment up to approximately 10–fold. Finally it can be concluded that controlled release porous Silicon formulations of chemotherapeutic drugs injected directly into tumors in mouse models show significantly improved efficacy in reducing tumor growth, in addition to an enhanced survival advantage compared to free drugs.

Brachytherapy

This is a radiotherapy treatment of tumors, where the radioisotope is delivered directly to the tumor site. This highly targeted use of isotopes carries lower risks of side effects, since the radioactive material is delivered solely to the tumor. It is also efficient in the use of expensive isotopic materials, because only sufficient treatment for the specific tumor need to be administered at any one treatment. The radiation resistant silicon is an ideal vehicle for the radioisotope and because so little radioactive material is administered at one time, there is no need for highly

specialized facilities to carry out this treatment [16, 17.] 32P is the radioactive isotope, has substantial potential for the treatment of a wider range of solid tumors than current brachytherapy treatments[16, 17].

Orthopaedics and tissue engineering

The biocompatibility of Silicon also lends itself to apply as a matrix for promoting bone re-growth. Polymer composites containing Silicon have been developed that stimulate the growth of osteoblasts, which promote bone mineralisation[16, 17].

Ophthalmology

It has approved products for administering drugs within the eye for instance to treat Uveitis. One of these products is a polymer implant with a lifetime of 30 months that delivers sustained levels of drug directly to the back of the eye. The treatment of eye diseases such as Age-related Macular Degeneration, Diabetic Retinopathy, Uveitis and others, has been very problematic. The largest barrier to effective treatment is the difficulty of delivering an appropriate concentration of drug to the correct location in the eye for a sufficient length of time. Various solutions have been attempted, including repeated intraocular injections of drug, or surgical implantation of drug-permeating material. However, these methods are impractical and present a significant risk to the patient[16, 17].

For type 1 diabetes

Microfabricated porous silicon particles can enhance the delivery of insulin across the permeable barrier in the intestine; the barrier is so difficult for large molecules to cross. The Holy Grail for treating type I Diabetes would be to develop some thing patients can take orally rather than by injection.[21]

Advantages of silicon nanotechnology in ocular drug delivery

Multiple injections are required, each carrying a finite risk of infection, and surgical procedures are cumbersome and not always effective (1). The nanoporous silicon, or a biopolymeric cast of it, can be tailor-made for each type of drug, to control the kinetics of sustained drug release such that the drug can be delivered in the eye with the optimal spatio-temporal profile, and over a long period of time. Further, several drugs can be delivered simultaneously, each with its own release parameters. (2) This customized nanomaterial has optical properties that allow one to monitor drug levels in the implant without invasive procedures to the eye. The optical properties of this material change in a reproducible fashion as the concentration of drug decreases within the implant, so that one can view the implant through the iris to determine the amount of drug remaining. These properties make this an ideal material for drug delivery and non-invasive reporting of drug levels[17].

Benefits

The use of this nano-material minimizes the number of injections required, reducing cost, scarring and the likelihood of infection, and ensures that the patient receives an effective dose throughout the treatment period[17].

Features

Pore size, spacing and layering can be controlled, and the surface chemistry of the nanoporous silicon or its biopolymeric equivalent can be modified to accommodate almost any type of compound. Further, the

optical properties of the material can be customized such that each drug can have its own optical signature, thus allowing one to monitor several drugs simultaneously. Porous silicon is biocompatible and bioresorbable, and has tunable pore volumes and a high surface area, so that its drug loading capacity is high[17].

Development status

Nanoporous silicon has been implanted into the eye and its spectrum visualized through the iris for 4 months or longer, with no obvious toxicity. Nanomaterial has been customized to release dexamethasone into solution[17].

Commercial strategy

In the drug delivery area, the strategy is to work with pharmaceutical and biotechnology companies to develop novel nanostructured porous Silicon based products incorporating the third parties' drugs. These may be the drugs that require a controlled rate of release or those that require enhanced bioavailability and/or are proving problematic in formulation[17].

CONCLUSION

There has been a sharp growth in the pace of discovery and development of targeted nanostructured porous silicon based nanoparticles over the past few years. Current preclinical and clinical data support the hypothesis that targeted nanostructered porous silicon based nanoparticles can provide the means to deliver drugs at a prolonged controlled release to specific targets. Once optimized, these targeted nanoparticles will provide the improved treatment options.

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