Mesoporous Silicon in Drug Delivery Applications

JARNO SALONEN,[1] ANN M. KAUKONEN,[2,3] JOUNI HIRVONEN,[3] VESA-PEKKA LEHTO[1]

[1]Department of Physics, University of Turku, FI-20014 Turku, Finland

[2]Drug Discovery and Development Technology Center, Faculty of Pharmacy, FI-00014 University of Helsinki, Finland

[3]Division of Pharmaceutical Technology, Faculty of Pharmacy, FI-00014 University of Helsinki, Finland

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ABSTRACT: During the last few years, a number of interesting drug delivery applications of mesoporous materials have been demonstrated. Mesoporous silicon has many important properties advantageous to drug delivery applications. The small size of the pores confines the space of a drug and engages the effects of surface interactions of the drug molecules and the pore wall. The size of the pores and the surface chemistry of the pore walls may be easily changed and controlled. Depending on the size and the surface chemistry of the pores, increased or sustained release of the loaded drug can be obtained. Drug loading from a solution at room temperature enables the use of porous silicon (PSi) also with sensitive therapeutic compounds susceptible to degradation, like peptides and proteins. This article reviews the fabrication and chemical modifications of PSi for biomedical applications, and also the potential advantages of PSi in drug delivery. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:632–653, 2008

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INTRODUCTION

The progress of micro- and nanotechnology during the last decades has impacted a tremendous incentive to the current research of biomedical applications. Quantum dots, controlled-release nanoparticles, targeted delivery and cancer nanotechnology are all intensively studied nowadays, and the results of these biomedical applications are very encouraging. However, many of these applications of nanotechnology are still far away from practical use, but the speed of the progress raises hopes of achieving completely new biomedical applications even in the near future.

Mainly these future prospects fall into two categories: improved cancer therapy and more user-friendly administration of active pharmaceutical ingredients (APIs). The latter includes, for example, the continuously emerging problem of noninvasive insulin delivery. Pharmaceutical industry has encountered problems in the development of new drug molecules as commercial products. Many potential yet lipophilic/hydrophobic molecules cannot be delivered in oral form due to their poor pharmacokinetics. This includes the poor solubility and dissolution of the drug in the intestinal lumen, poor permeation properties in the gastrointestinal (GI) tract, as well as high intestinal or hepatic first pass metabolism. It is estimated that more than 95% of new drug candidates suffer from that kind of limited bioavailability.[1]

On the other hand, the duration of therapeutic effect has become an important factor to control the frequency of administration in the cases of

Correspondence to: Jouni Hirvonen (Telephone: 358-9-191-59-139; Fax: 358-9-191-59-144;
E-mail: jouni.hirvonen@helsinki.fi)

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immediate or rapid drug release. Especially, many new protein- and DNA-based compounds suffer from limited therapeutic concentration range, and toxicity is often observed for concentration peaks.[2] Thus, challenges (and efforts) in the research of controlled and sustained drug release have increased during the last few years. In addition to the conventional dosage forms, such as oral drug delivery systems and injectable formulations, new routes for drug administration are continuously studied. Nanotechnology has a lot of potential, for example, in transdermal and pulmonary drug delivery, where promising results have already been reported.[3–5]

Mesoporous materials have many interesting properties considering drug delivery applications. The small size of the pores (2–50 nm) confines the space of a drug and engages the effects of surface interactions of the drug molecules and the pore wall. Depending on the size and the surface chemistry of the pores, increased dissolution rate or sustained release of a drug can be obtained.[6,7] Since the first paper in 2001,[8] in which ibuprofen was loaded into the mesoporous material (MCM-41), a lot of interesting results have been published on the mesoporous materials. The advantages of the mesoporous materials include, for example, the possibility to vary the pore size[6,9] and to "finetune" the material for certain drug molecules by chemical modification of the surface.[10–13] In this review, we will focus on one of these mesoporous materials, porous silicon (PSi). PSi-materials are regarded as "top-down" materials on the contrary to the synthesized mesoporous molecular sieves, which are so called "bottom-up" silica materials that refers to the self-assembly of silicon oxide by means of polymeric templates determining the structure obtained. PSi has some advantages compared to the silica-based materials, but also some disadvantages, like a wider pore size distribution. These will be described and discussed later in this review. In addition, some new data considering stability, drug loading/release, and biocompatibility issues will be presented.

FABRICATION AND CHARACTERIZATION OF POROUS SILICON MATERIALS

The current interest in PSi results primarily from the demonstration of efficient visible photoluminescence of PSi, first reported by Prof. Canham[14] in 1990. However, PSi is not a new material: it was first reported over 40 years ago by Uhlir.[15] During studies of the electropolishing of silicon (Si) in aqueous hydrofluoric acid (HF), he observed that the surface often became black, brown or red. More detailed studies were performed by Turner[16] and Archer,[17] but these films were not recognized as being PSi. It was Watanabe et al.[18] who first reported their porous nature.

The next important step in PSi research was the report of PSi behavior in a simulated body fluid (SBF) in 1995, again by Prof. Canham.[19] Contrary to the perceived poor biocompatibility of Si, PSi was found to be bioactive. Actually, it was observed that depending on the porosity and pore size, PSi could be bioinert, bioactive or biodegradable.[20] Since then, the issues of bioactivity and biocompatibility of PSi have been intensively studied and very interesting results reported.[21–31] For example, the speed of dissolution of PSi depends on the porosity and pore size, and it can be predicted and controlled with fabrication parameters.[20,27] Because of the background as a material used in semiconductors, some unique properties for bioactive material could be found in PSi. For example, the calcification of PSi can be promoted using cathodic DC-current,[22] and the biocompatibility of microelectrodes may be improved with PSi scaffolds.[32]

One of the main research topics in the PSi bioapplication studies, in addition to drug delivery, has been biosensing and, based on this, protein adsorption on the PSi surface. A number of reports on that topic have been published.[33–47]

Fabrication of Porous Silicon

The basic method to fabricate PSi is electrochemical dissolution of Si in HF based solutions. This is obtained by monitoring either the anodic current (galvanostatic) or voltage (potentiostatic). In general, constant current is preferable as it allows better control of the porosity and thickness. It also provides better reproducibility from sample to sample.

In the simplest setup to fabricate PSi, plates of Si and Pt are dipped into HF solution and an etching current is applied between these electrodes. The porous layer is formed on the surfaces of the Si, which is used as a positive anode. Usually a cathode is made of platinum and the fabrication cell has to be made of HF-resistant material, for example Teflon. Dilute aqueous HF or ethanolic HF are generally used as electrolytes. Ethanol is added to reduce formation of hydrogen bubbles