Applied Surface Science 330 (2015) 358–365

Contents lists available at ScienceDirect

Applied Surface Science

journal homepage: www.elsevier.com/locate/apsusc

Controlled delivery of acyclovir from porous silicon micro- and nanoparticles

Nalin H. Maniya, Sanjaykumar R. Patel, Z.V.P. Murthy*

Department of Chemical Engineering, Sardar Vallabhbhai National Institute of Technology, Surat 395 007, Gujarat, India

ARTICLE INFO

Article history:
Received 21 November 2014
Received in revised form 6 January 2015
Accepted 9 January 2015
Available online 15 January 2015

Keywords:
Acyclovir
Porous silicon
Microparticles
Nanoparticles
Controlled delivery
In vitro release

ABSTRACT

In this work, micro- and nanoparticles of porous silicon (PSi) are demonstrated to act as effective carrier for the controlled delivery of acyclovir (ACV). PSi films prepared by electrochemical etching were fractured by ultrasonication to prepare micro- and nanoparticles. PSi native particles were thermally oxidized (TOPSi) and thermally hydrosilylated using undecylenic acid (UnPSi). PSi particles with three different surface chemistries were then loaded with ACV by physical adsorption and covalent attachment. Such particles were characterized by scanning electron microscopy, dynamic light scattering, and Fourier transform infrared spectroscopy. In vitro ACV release experiments in phosphate buffered saline showed sustained release behaviour from both micro- and nanoparticles and order of release was found to be native PSi > TOPSi > UnPSi. Drug release kinetics study using Korsmeyer-Peppas model suggested a combination of both drug diffusion and Si scaffold erosion based drug release mechanisms.

1. Introduction

Porous silicon (PSi) has been extensively studied for various biomedical applications including biosensing, bioimaging, biomolecular screening, tissue engineering, and drug delivery [1–5]. PSi is an excellent biomaterial for controlled drug delivery applications owing to its very high surface area, controllable pore size and volume, and easy surface modification and functionalization procedure [6,7]. The high surface area of PSi provides a high drug loading capacity, and different surface modifications allow controlled release behaviour. It is biocompatible and biodegradable material with very low toxicity [8,9]. PSi is prepared by electrochemical etching of single crystalline silicon wafers in hydrofluoric acid based solutions [10]. PSi with desired physical and optical properties such as pore size, porosity, thickness, and reflectance can be easily tuned by varying current density and etching time. The prepared PSi layer can be removed from the Si substrate by electropolishing and subsequently fractured by ultrasonication or wet milling process to prepare micro- and nanoparticles [11–13]. The surface chemistry of PSi has a strong influence on the drug loading and its release behaviour in the biological systems. The as prepared native PSi has hydride terminated (Si—H) surface which observes oxidation in ambient air. Furthermore, native surface is found to be reactive with several drugs. However, this native surface provides a versatile starting point for various reactions that determine attachment and slow release of drugs [14]. The two important treatments of native PSi for drug loading and delivery are; thermal oxidation and thermal hydrosilylation. Thermally oxidized PSi (TOPSi) is prepared by heating at quite mild conditions around 300 °C while thermally hydrosilylated PSi is prepared by reaction of an alkenes or alkynes with a Si—H surface. Microwave assisted thermal hydrosilylation of PSi using undecylenic acid (UnPSi) provides more stable Si-C surface in comparison to Si-O surface of TOPSi and allows controlled release of drug molecules attached via this surface [15].

Drug delivery system using PSi carriers involves loading of the drug in the pores of the porous matrix and then release of the drug in the body using drug diffusion and matrix erosion. PSi films and micro- and nanoparticles have already been studied for loading and release of anti-cancer agents (doxorubicin, daunorubicin, cis-platin), small drug molecules (ibuprofen, dexamethasone), peptides, proteins (peptide YY3-36, Melanotan II, ghrelin antagonist, insulin, human serum albumin, papain), and small interfering RNA [8,16–26].

Acyclovir (ACV) is one of the most widely used antiviral agents against herpes simplex virus (HSV) type 1 and type 2, and varicella-zoster virus infections (Fig. 1). ACV has also shown anti-cancer and anti-hepatitis B activity in recent studies [27–29]. It is a synthetic purine nucleoside analogue of guanosine that inhibits viral DNA synthesis by acting as a chain terminator. ACV

* Corresponding author. Tel.: +91 261 2201648, 2201642; fax: +91 261 2227334.
E-mail addresses: zvpm2000@yahoo.com, zvpm@ched.svnit.ac.in (Z.V.P. Murthy).

http://dx.doi.org/10.1016/j.apsusc.2015.01.053
0169-4332/

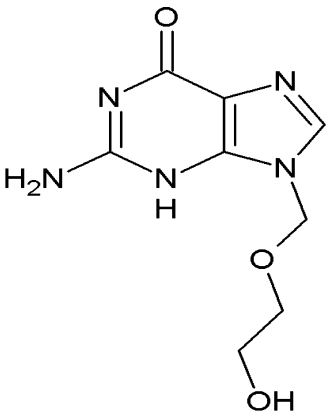

Fig. 1. Chemical structure of ACV.

is currently marketed in the form of capsules (200 mg), tablets (200 mg, 400 mg, and 800 mg), suspensions, intravenous injections, and topical ointments. The conventional therapy using ACV has many drawbacks such as low bioavailability (10–20%), variable and incomplete absorption in the gastrointestinal tract. Furthermore, five times a day drug administration is required owing to short plasma elimination half-life of 2.5 h which is associated with systemic toxicity. In order to combat these drawbacks especially low bioavailability, micro- and nanoparticulate drug delivery system of ACV using microemulsion, liposome, niosome, and cyclodextrin has been studied [30–33].

In the present work, PSi based controlled drug delivery system of ACV was prepared and the effect of different surface chemistries of PSi on drug loading and release behaviour was studied. PSi micro- and nanoparticles were prepared by ultrasonic fracture of free-standing PSi films. Native PSi particles were thermally oxidized and thermally hydrosilylated to prepare three different surface chemistries. PSi particles were then loaded with ACV and characterized using scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FTIR). In vitro release of ACV in phosphate buffered saline was examined, and kinetics of drug release was investigated using Korsmeyer-Peppas model.

2. Experimental

2.1. Fabrication of PSi

PSi was fabricated by electrochemical etching of highly boron-doped p^+ type (1 0 0) silicon wafers (resistivity of 0.01–0.02 Ω cm) in a 1:2 (v/v) hydrofluoric acid (40%) and ethanol (99.9%) solution. The wafer was etched in Teflon etching cell by applying constant current density of 50 mA cm^{-2} for 180 s. The resulting porous film was then lifted off by electropolishing with current density of 6 mA cm^{-2} for 120 s using 1:29 solution of hydrofluoric acid in ethanol. The etching and electropolishing procedure was repeated ten times per wafer, and the resulting freestanding films were then placed in ethanol till further use.

2.2. Preparation of PSi micro- and nanoparticles

PSi films in ethanol were ultrasonicated (Elma Transsonic TI-H5 MF2, USA) with frequency of 45 kHz and 100 W power for 10 min and 8 h to prepare PSi micro- and nanoparticles, respectively (Fig. 2) [12]. Thermal oxidation of PSi particles was performed in muffle furnace (Rivotek, Chennai, India) by heating at 300 °C for 2 h. Thermal hydrosilylation of PSi particles was performed in commercial consumer microwave oven (Samsung, ME83HD, India) by heating particles immersed in undecylenic acid (98%, Sigma–Aldrich, India) at 300 W for 4 min. The treated particles were then thoroughly rinsed with hexane and ethanol to remove unreacted undecylenic acid.

2.3. Physicochemical characterization of micro- and nanoparticles

SEM analysis of PSi particles was carried out by using a field emission gun scanning electron microscope (JEOL, JSM-7600F, Japan) with an accelerating voltage of 3 and 10 kV. The average particle size of nanoparticles was measured by using dynamic light scattering (Malvern Zetasizer Nano ZS90, UK). Pore size and particle size of microparticles were measured from the SEM images using ImageJ software [34]. Surface modification and drug loading of PSi particles were characterized by using Vertex 80 FTIR system (Bruker, Germany).

2.4. Drug loading methodology

Approximately 2 mg of native and TOPSi particles were suspended in 1 mL of a 1 mg/mL aqueous solution of ACV (Arochem Industries, Thane, India). For loading of UnPSi particles, 100 μL of 10 mg/mL solution of N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDAC, Sigma–Aldrich, India) and 900 μL of a 1 mg/mL drug loading solution were added. Particles were allowed to load for 5 h with intermittent mixing. The loading solution was then removed by centrifugation and particles were rinsed with phosphate buffered saline (PBS, pH 7.4). Particles were dried in a vacuum oven at 37 °C for 24 h.

In order to determine the amount of drug loaded, PSi particles were dissolved in a solution of 1 M sodium hydroxide, and absorbance was measured using a UV–VIS spectrophotometer (HACH, DR6000, USA). The absorbance maximum at 255 nm was used to determine the amount of ACV loaded via use of a calibration curve generated from solutions of known concentration. Drug loading capacity and encapsulation efficiency of particles were calculated by the following equations:

$$\text{Drug loading capacity (\%)} = \left[\frac{\text{Weight of ACV in PSi particles}}{\text{Weight of PSi particles}}\right] \times 100 \quad (1)$$

$$\text{Encapsulation efficiency (\%)} = \left[\frac{\text{Weight of ACV in PSi particles}}{\text{Weight of ACV in loading solution}}\right] \times 100 \quad (2)$$

2.5. ACV release

ACV loaded PSi micro- and nanoparticles were suspended in 1 mL of phosphate-buffered saline (pH 7.4) in microcentrifuge tubes. The tubes were agitated in orbital shaking incubator (CIS-24 BL, Remi, India) with orbital shaking speed of 100 rpm at 37 °C. At pre-determined time intervals, the supernatant containing released ACV was collected by centrifugation for 5 min (12,000 rpm, C-30 BL, Remi, India). The particles were re-suspended in fresh phosphate buffered saline after the supernatant collection. Concentrations of released ACV in supernatant were determined by measuring the absorbance at 255 nm.

2.6. Drug release kinetics

The drug release profiles obtained from micro- and nanoparticles with different surface chemistries were fitted to Korsmeyer-Peppas model to understand the mechanism and kinetics of drug