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molecular pharmaceutics

Sustained Antibacterial Activity from Triclosan-Loaded Nanostructured Mesoporous Silicon

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Received July 7, 2010; Revised Manuscript Received October 5, 2010; Accepted October 25, 2010

Abstract: In this work, nanostructured particles of porous silicon are demonstrated to act as an effective carrier for the sustained delivery of antibacterial agents with an enhanced inhibitory activity. Methods are described for the incorporation of significant amounts of the established antibacterial compound triclosan (Irgasan) into mesoporous silicon of varying porosities. Such materials were characterized by a combination of scanning electron microscopy (SEM), energy dispersive X-ray analysis (EDX), X-ray diffraction (XRD), thermal gravimetric analysis (TGA), and antimicrobial assays. Assessment of antibacterial activity was carried out versus the bacterium *Staphylococcus aureus* as a function of time with concomitant assessment of triclosan release; significant, sustained inhibition of bacterial growth is demonstrated in the triclosan-containing porous Si for time intervals greater than 100 days. Significantly, enhanced dissolution (relative to room temperature equilibrium solubility) of the triclosan was observed for the initial 15 days of drug release, inferring some amorphization or nanostructuring by the porous Si matrix.

Keywords: Porous silicon; nanomaterials; antibacterial

1. Introduction

Controlled delivery of antibacterial agents remains a topic of widespread significance, given the need for sustained release of therapeutically relevant concentrations of the active agent.[1] Improvement of aqueous solubility of these compounds (with an associated enhanced bioavailability, if relevant) is another goal, often improved using porous carrier materials,[2] macromolecular complexation,[3] or amorphization protocols.[4] Using a new carrier matrix, this work describes procedures developed for the incorporation of antibacterial agents into a mesoporous form of the elemental semiconduc-

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10.1021/mp100227m
Published on Web 10/25/2010

tor silicon (Si) and an evaluation of its efficacy in killing the known pathogenic bacterium *Staphylococcus aureus.* Porous Si (PSi), and the mesoporous form in particular, is a diverse material. It possesses several useful properties relevant to its possible use in medical therapies such as drug delivery[5,6] and tissue engineering.[7−9] For drug delivery, both the biodegradability of mesoporous Si and its ability to nanostructure a given encapsulated substance present marked advantages; while initial drug delivery studies have focused on chemotherapeutic cancer agents,[10−12] other significant disease targets exist, including those of a bacterial origin. The ability of mesoporous silicon to stimulate calcification *in vitro* upon degradation adds further value to its use as a drug delivery platform for oral medicine.[13] The motivation for this work is to promote sustained delivery of such compounds that would, either as a stand-alone agent or as a component of a more complex formulation, inhibit bacterial growth for sustained periods.

Staphylococcus aureus is commonly found on nasal passages and mucous membranes of humans (as well as skin) and causes a variety of well-known infections and toxinoses in humans.[14] *S. aureus* is a major cause of hospital acquired infection of surgical wounds and infections associated with indwelling medical devices. In particular, methicillin-resistant *Staphylococcus aureus* (MRSA) constitutes a growing public health concern. *S. aureus* also causes food poisoning by releasing enterotoxins into food, and toxic shock syndrome by the release of superantigens into the bloodstream. Practical examples relevant to oral health are also significant targets. Specifically, inflammation resulting from bacterial infection at sites of teeth prone to decay destroys the attachment fibers and supporting bone that hold the teeth in the mouth, culminating in loss of teeth.[15]

The results described herein focus on incorporation of the known antibacterial compound triclosan into mesoporous Si. Triclosan, also known as Irgasan, has been used as effective oral antiseptic since the 1960s. It inhibits bacterial growth by blocking the synthesis of lipids, and it has recently been suggested that Irgasan does this by specifically inhibiting the enzyme enoyl−acyl carrier protein reductase.[16] While some long-term environmental concerns regarding the use of this compound in large segments of the population have been indentified,[17] it nevertheless serves as a useful initial candidate for an evaluation of loading, release, and associated antibacterial activity when released from porous Si. Here it is demonstrated that not only is prolonged sustained delivery of the antibacterial agent possible from porous Si but also enhanced concentrations of the triclosan can be released in the first fifteen days. Moreover, the surface chemistry of the porous Si carrier can be adjusted to modify the release kinetics of the triclosan in this time period.

2. Materials and Methods

2.1. Materials. Four distinct types of porous silicon structures were utilized in these experiments (Table 1): high porosity mesoporous Si (81%), midporosity mesoporous Si (65−75%) (both as-prepared and surface oxidized), and macroporous Si. Mesoporous silicon particles were prepared by a three-stage process of silicon wafer anodization, mesoporous membrane detachment and mesoporous microparticle classification. Heavily boron doped (0.01 Ω cm) 150 mm diameter wafers were anodized in methanoic HF electrolyte in custom-built equipment to create 150 μm thick membranes of either 81% or 65% porosity. These were then mechanically milled and classified into porous microparticles of specific size distributions. For the macroporous Si films, high resistivity n^- wafers are used in the etch process, producing films of approximately 48 μm thickness that remain attached to the Si wafer substrate. For selected

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Table 1. Triclosan-Loaded Porous Si Samples: Loading and Release Data

Sample ID/Original Porosity	Particle Size (μm)	Triclosan Loading % (TGA)	Total Triclosan Loaded (mg)	Triclosan Released in First 15 Days (μg)	Av Concn in First 15 Days (μg/mL)	% Released	Max. Daily Release Concn in First 15 Days (μg/mL)
Mesoporous 81% (Melt A)	150−250	72.9	3.645	119.97	8.0	3.29	11.53
Mesoporous 65−75% (Nonblended)	<100	44.08	2.216	176.41	12.6	7.96	17.78
Mesoporous 65−75% (Blended)	<50	47.92	2.270	132.57	10.2	5.84	14.48
Mesoporous 81% Surface Oxidized	<75	37.52	1.876	12.83	0.86	0.68	1.92
Mesoporous 81% Surface Oxidized	150−250	69.64	3.482	20.76	1.38	0.6	3.32
Macroporous 13%	Film Size: 39.59 mm^2	1.1	0.42	33.82	2.25	7.87	3.96

experiments, mesoporous Si particles of 65−75% porosity were surface oxidized by a 60 min annealing in air at 600 °C.

Triclosan (Irgasan), with a formal chemical name of 5-chloro-2-(2,4-dichlorophenoxy)phenol, was obtained from Sigma-Aldrich, Inc.

2.2. Drug Loading Methodology. For drugs with an intrinsically low solubility, simple melt loading processes are suitable options for loading if the drug possesses good thermal stability to its melting point. This is certainly true for triclosan, with a relatively low melting point of 55−57 °C. For the PSi samples described above, some slight differences between the loading processes were employed. For the high-porosity mesoporous sample (81%, referred to as melt A), a preweighed quantity of PSi powder was immersed in a known weight of molten triclosan at 90 °C for 35 min, with masses selected based on a target loading capacity of 72% by weight. For the midporosity PSi powders, the impact of drug/carrier premixing was evaluated as follows. So-called nonblended samples were loaded by the same process as described above at temperatures under 100 °C. As an alternative, preblended samples were fabricated whereby the PSi powder and triclosan (with masses selected based on a theoretical loading capacity of 70%) were homogeneously mixed first, and then heated together at 100 °C.For the oxidized mesoporous powders, two different average particle size types (75 μm and 150−250 μm) were loaded by the blended technique described above.

For triclosan loading into macroporous silicon, a given film (still attached to the underlying Si substrate) was cut into small pieces (0.5 × 0.7 cm^2), which were subsequently characterized by SEM. Then depending on the size and porosity, the volume of pores and the theoretical loading were calculated. Films were initially soaked in a 1:1 water/ethanol mixture overnight to remove any surface impurities. A small glass slide with molten triclosan was placed face down onto a given macroporous silicon film heated at 80 °C for 10 min to complete the loading process. After completion, any surface liquid was removed when the sample was sandwiched between filter paper and rubbed with light manual pressure. When dry, the extra triclosan on the surface of the macroporous Si was removed by swabbing with ethanol under microscopic observation.

2.3. Antibacterial Assays. To reflect a dynamic physiological environment, a protocol was used which analyzes the aqueous supernatant into which the triclosan diffuses from the loaded mesoporous Si powder. This supernatant was monitored continuously in 24 h intervals by soaking onto filter disks and testing for its antibacterial activity. This activity was specifically evaluated by measuring the inhibition zone of bacterial growth of *S. aureus* and the overall duration of inhibition activity for triclosan released from PSi carriers.

For the triclosan-loaded mesoporous Si samples, 5 mg of loaded PSi powder was soaked in 1.0 mL of sterile water in a 1.5 mL microcentrifuge tube for each type of material. Then the tubes were continuously rotated using a LabQuake agitating apparatus at 37 °C. After a time interval of 24 h, the supernatant was drawn to a new microcentrifuge tube. A 20 μL fraction was spotted onto a paper disk already placed on the top of a LB-agar plate containing 10^6 bacteria of *S. aureus* for 24 h incubation at 37 °C. Another fresh 1.0 mL aliquot of sterile DI water was added again into the microcentrifuge tube containing the PSi, with active agitation of the sample in the LabQuake instrument for 24 h. The above procedure was repeated until no inhibition activity was detected from the supernatant exposed to the porous Si powder.

2.4. Drug Release Assays. Quantitative evaluation of triclosan concentration released from a given porous Si matrix was achieved by spectrophotometric determination of the triclosan-containing supernatant (described in the above antibacterial assay procedure) using absorbance values at 280 nm; such values were converted to triclosan concentrations via use of a standard curve generated independently from solutions of known concentration.

3. Results and Discussion

3.1. Characterization of the Trisclosan-Loaded Porous Si Samples. The relatively low melting point (55−57 °C) of the active antibacterial agent triclosan makes loading into the porous Si network a relatively straightforward process. Variations in the loading process can be evaluated readily, then, as a consequence of porosity of the silicon, the relative ratios of triclosan to PSi, and details of how the

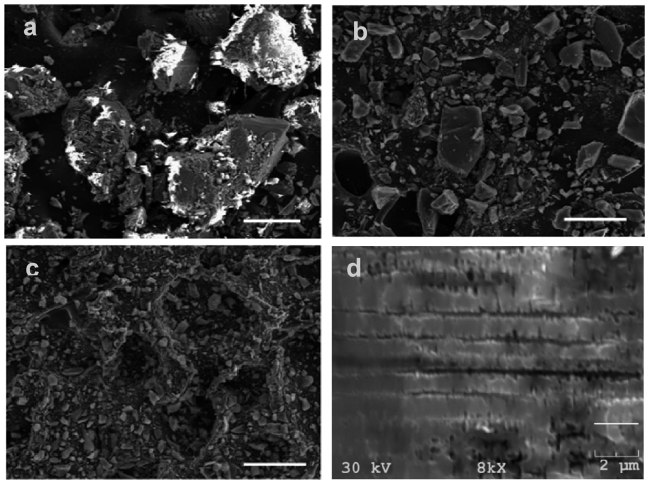

Figure 1. The morphologies of PSi samples loaded with triclosan. (a−c) Plan view images (SEM) for melt A, nonblended and blended samples, respectively. (d) Cross sectional image of a typical macroporous Si film. Scale bars: 200 μm for a−c, 2 μm for d.

active agent is mixed with the porous Si component before or during the heating process. A summary of selected properties of samples prepared for this study is shown in Table 1.

Initial experiments were performed involving the exposure of molten triclosan to relatively high porosity (81%) Si powder for an extended period, followed by cooling, thereby permitting facile uptake of the active antibacterial compound. A comparison of this protocol with the alternative process of mixing the dry components prior to heating was evaluated for moderate porosity silicon (65−75%) samples. In all of the mesoporous samples, the amount of triclosan exposed to the PSi powder was of a quantity targeted to achieve an ideal loading of 70% by mass. A very low porosity (13%) macroporous Si film was also exposed to molten triclosan for purposes of evaluating a radically different porous microstructure.

We begin with a presentation of loaded porous Si particle morphology. Figure 1 shows the SEM images of selected samples noted in Table 1. Note that, for mesoporous silicon powder, the individual pores are too small to be detected by SEM, but the characteristic pore widths on the order of several nanometers can be observed by high resolution TEM (Supporting Information). In the SEM images shown, the larger particle size of the loaded high porosity sample (81% porous; referred to as melt A) is readily apparent; some individual PSi particle agglomeration is also possible for this type of sample due to the presence of excess triclosan during the cooling process. For the macroporous Si films, however, macropores on the order of $\sim 10^2$ nm in the low porosity material are observed in cross sectional images at this level of magnification (Figure 1d).

In terms of composition, detection of triclosan loaded into these porous Si structures is possible by energy-dispersive X-ray (EDX) spectroscopy (Figure 2). Because of the limited sampling volume, it can only provide a selected distribution

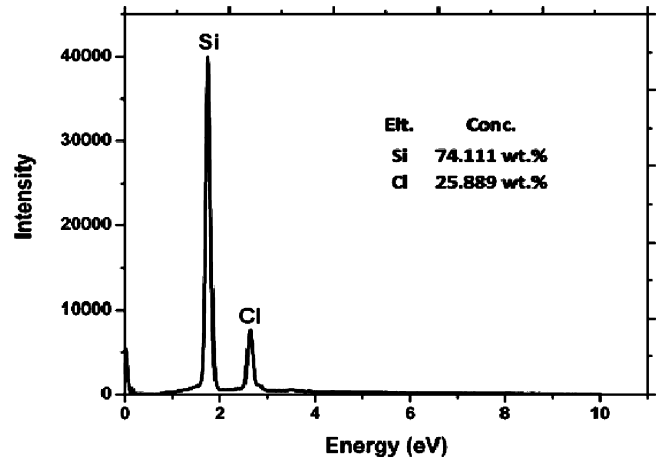

Figure 2. EDX spectrum for a melt A loaded sample.

of drug loading in different microscopic areas instead of an entire sample, but nevertheless confirms the presence of the drug in these materials. In this study, chlorine (Cl) is the characteristic element for triclosan, for which it contains 25.9% by weight. For mesoporous silicon samples, the distribution of triclosan is relatively uniform (measured in ten different areas on each sample under the same magnification). The Cl concentrations are all above 10%. For the macroporous silicon film, there is an uneven distribution of Cl level within a given pore.

For a more representative evaluation of the macroscopic drug loading in the entire sample, thermogravimetric analysis (TGA) is employed (Figure 3). TGA is an established, effective technique for quantification of drug loading in PSi.[18] For the mesoporous silicon samples analyzed here, significant mass loss begins around 125 °C, slightly above the boiling point of triclosan (120 °C). If a large excess of triclosan is present on the surface of a given sample, then there should be two stages of weight loss observed. The first stage is for the surface component, followed by the second stage for loss of triclosan in the pores. In our case of mesoporous Si, the triclosan is eliminated from the carrier in a single extended period ranging from 125 to 225 °C, reflecting diffusion from the porous matrix. For the macroporous silicon film, the lower triclosan loading in large parallel pores is reflected in the small mass loss that is complete by 150 °C required for thermal desorption of the loaded active species.

In order to look for additional evidence of triclosan present on the outer PSi surface and/or drug nanostructuring through intensity loss or broadening of signature X-ray reflections, pure triclosan, triclosan-loaded porous silicon samples, and nonloaded PSi were examined by X-ray diffraction (Figure 4). While scans of the 25−60° area contain prominent Si peaks {28.4 (111), 47.3 (220), and 56.1 (311)} and some smaller peaks for triclosan, further investigations show the 20−30° region a better selection as several strong triclosan

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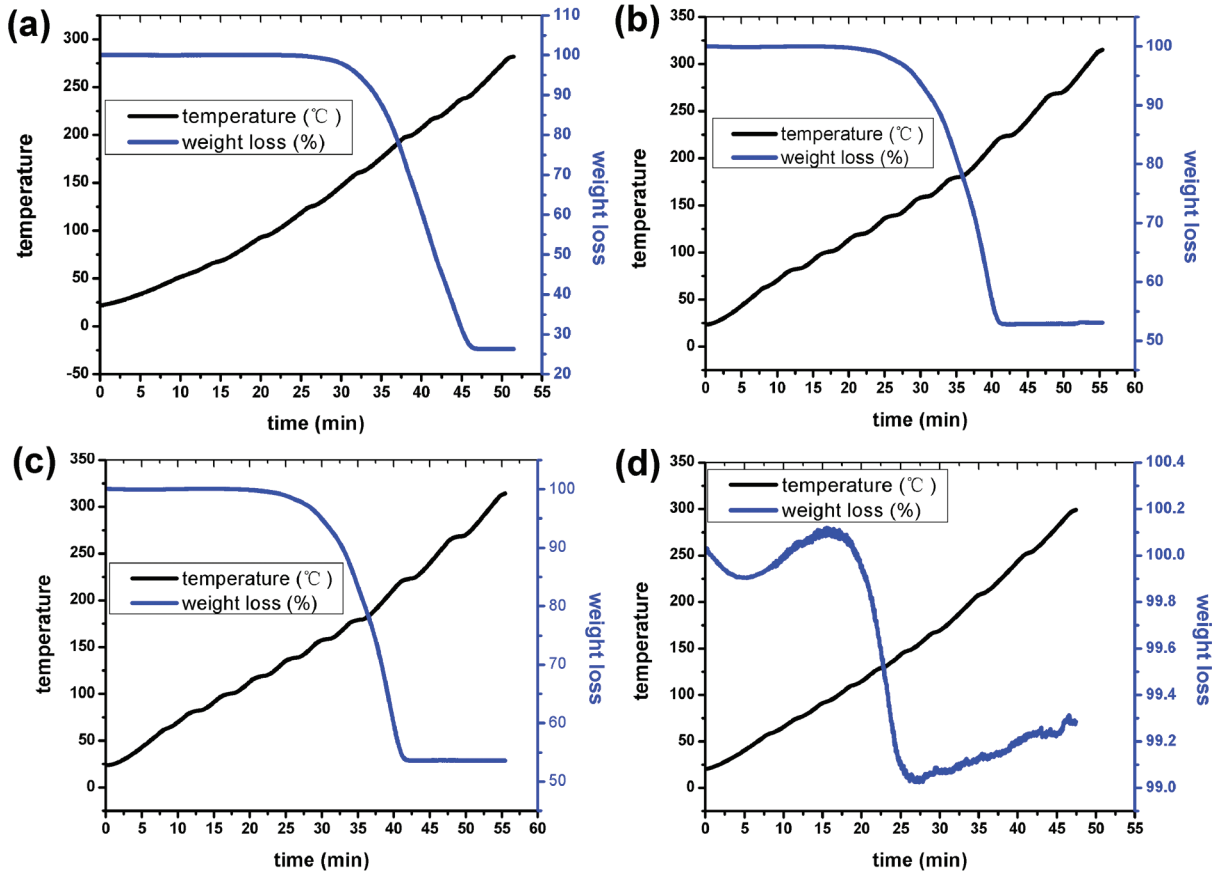

Figure 3. TGA measurements for (a) melt A sample, (b) nonblended sample, (c) blended sample, and (d) macroporous Si film.

peaks appear with only one strong Si feature in this range (at 28.4°). For the high porosity triclosan-loaded (melt A) sample, some triclosan features are observed, most notably for the peaks near 24° and 25°; the most significant differences between the sample and pure triclosan include substantial line broadening in the 25° peak (6 times broader for melt A), and unlike pure triclosan, the feature at 25° is more intense than the peak at 24°. For the nonblended and blended samples, no significant characteristic peaks of triclosan were found. This suggests that some crystalline triclosan is present in the high porosity (81%) samples but not in the 65−75% porosity samples.

3.2. Assessment of Antibacterial Activity. Figure 5 illustrates the typical antibacterial activity as a function of time for a 5 mg mesoporous Si sample (65−75% porosity) loaded with triclosan (by the blended method) at ∼47.9% by mass. Also shown in this plot are the corresponding concentrations of active drug released (measured spectrophotometrically) per 24 h period. For the mesoporous materials, the extended release of triclosan over the period measured is quite remarkable; by the 15th day, only 5.84% of the loaded drug has been released to the surroundings (and ∼10% in 70 days), and the release and associated activity continues beyond a period of 100 days. Similar behavior is observed in the other mesoporous samples; the sample of originally 65−75% porosity loaded by the nonblended technique (at an average level of 44.08%) released approximately 7.96% of the total triclosan payload in the same time frame, with the high porosity (81%) loaded with 72.9% triclosan releasing 3.29% in 15 days (7.87% in 70 days). The macroporous sample serves as a useful benchmark for diminished loading and activity, at 13% porosity and a lower triclosan loading percentage (1%), can only release a maximum of 560 μg (in contrast to the 2−3 mg maximum release capacity of the mesoporous samples); its antibacterial activity is complete within 18 days of release.

A relevant associated question that bears on the therapeutic promise of porous Si lies in terms of drug concentrations released to the surroundings in a given 24 period and differences with triclosan dissolution in water during the equivalent time window. To probe this difference, exposure of comparable amounts of triclosan (3 mg) and triclosan (2.3 mg) loaded into mesoporous Si (5 mg total) to water were individually evaluated at hour intervals at 37 °C up to a total of 24 h (Figure 6); at a given time interval the concentration of triclosan released from the mesoporous silicon is effectively 3−4 times greater than the value extracted for the aqueous solution exposed to solid triclosan. For example, at 7 h exposure, the nonblended sample has released triclosan at a concentration of approximately 15 μg/mL, while the amount of triclosan extracted into water from the solid antibacterial compound is 5 μg/mL.

The possibility that this specific loading process generates some type of amorphization or nanostructuring by the porous

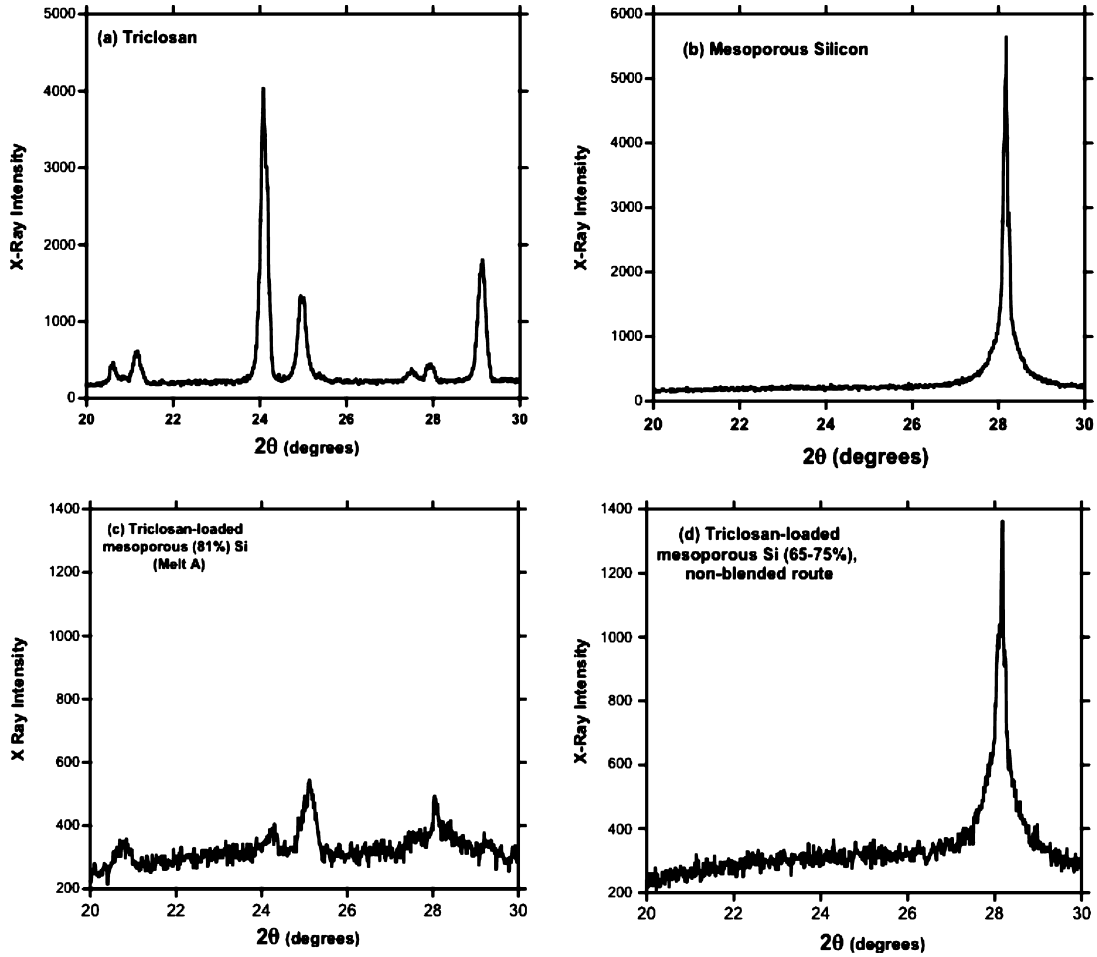

Figure 4. X-ray diffraction spectra for (a) crystalline triclosan, (b) nonloaded mesoporous Si (65−75% porosity), (c) triclosan-loaded mesoporous Si (melt A), and (d) triclosan-loaded mesoporous Si, nonblended sample.

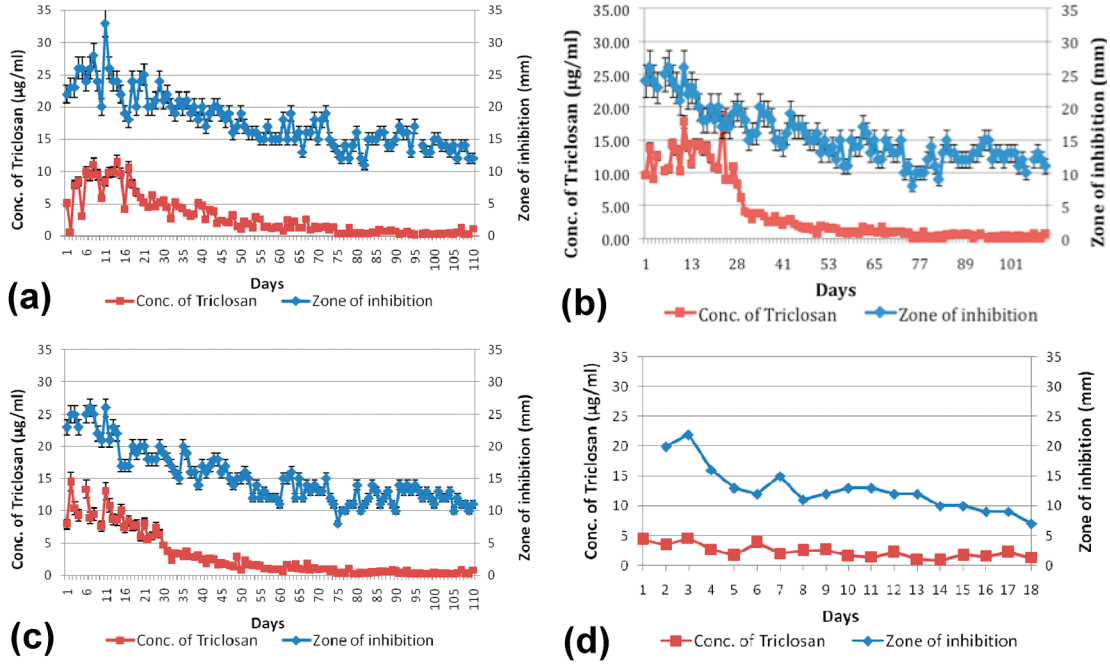

Figure 5. Combined zone inhibition assay/triclosan concentration release assays for (a) melt A, (b) nonblended, (c) blended sample, and (d) macroporous silicon film.

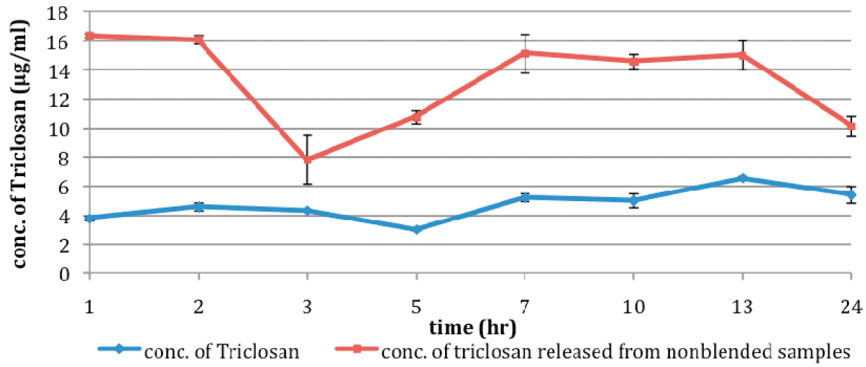

Figure 6. Comparison of triclosan dissolution into water as a function of time for solid triclosan (blue diamonds, bottom line) versus triclosan-loaded mesoporous Si (nonblended sample; red squares, top line).

Table 2. Comparison of Triclosan Concentrations Required To Achieve Selected Inhibition Zone Values for the First 24 h of Activity (Derived from Triclosan-Only Solution Controls) with Actual Experimental Values for a Given Porous Si Sample Type

	Mesoporous			
Macroporous	Melt A	Blended	Nonblended	
4.8μg/mL @ 19mm	11.5μg/mL @ 22mm	13.0μg/mL @ 23mm	20.5μg/mL @ 24mm	Predicted (Based on Solution Controls)
4.1μg/mL @ 19mm	5.0μg/mL @ 22mm	7.9μg/mL @ 23mm	10.0μg/mL @ 24mm	Actual

Si matrix for the triclosan is supported by an examination of release behavior among porous Si samples. For the nonblended mesoporous sample (65−75% porosity loaded with 44.08% triclosan), we are achieving greater than 12 μg/mL on average for this drug loaded into 65−75% porous samples in the first 15 days of release (Table 1). This is a greater than 3-fold increase in the initial concentrations of the macroporous samples, whose initial concentration of released active of 4 μg/mL subsequently drops to 2 μg/mL within a week, a rather significant difference. This possible nanostructuring/amorphization is supported by an analysis of the X-ray powder diffraction results for the 65−75% mesoporous Si samples, where no discernible features for crystalline triclosan can be discerned (data not shown). It should be recalled that the pore dimensions and geometry in the mesoporous materials are radically different from those of the macroporous Si; mesoporous Si consists of pore widths in the 5−50 nm range of a highly interconnected nature, in contrast to the large (~200 nm) parallel cylindrical channels of the macropores.

In terms of antibacterial activity, there is a clear difference between the behavior of the mesoporous Si-containing samples and that of the macroporous materials. While bacterial growth inhibition kinetics are logarithmic, these differences in drug release concentration do correlate overall with antibacterial activity; for the three mesoporous sample types, the average inhibition zone diameter for the *S. aureus* growth lies above 23 mm (Figure 5) for the first 15 days of activity. In contrast, the triclosan-loaded macroporous sample produces an inhibition zone diameter of 19 mm in the first 24 h, but experiences a precipitous drop after this initial release and reaches a value of ~10 mm in 15 days.

One means to place these activity results in the proper context is to compare them with the activity of aqueous solutions of triclosan at the first 24 h of release (Table 2). Triclosan solutions range from 4.8 μg/mL required to produce an inhibition zone of 18 mm to a value of 20 μg/mL for a 24 mm zone. It is important to note that the solution control matches well with that observed for the macroporous Si sample (4.1 μg/mL for a 18 mm inhibition zone), but the mesoporous Si samples are consistently more potent for a given observed zone, requiring less active released to the surroundings by a factor of 2. This observation is again consistent with the nanostructuring or amorphization of the triclosan upon loading in the mesporous structures, but conventional crystalline behavior being observed in the macroporous material.

3.3. Effect of Porous Si Surface Oxidation. In order to assess the impact of surface chemistry on drug incorporation and release in this system, a simple surface oxidation treatment (600 °C in air for 1 h) was employed. Given the observation noted above that the maximum impact on drug solubility occurs within the initial 15 day release period, we therefore focused our efforts on the activity and subsequent concentration of triclosan released from this type of treated surface for this specific time window. This was carried out for high porosity (81%) Si at two different average particle sizes (75 μm and 150−250 μm), with a triclosan loading for the smaller sized material (75 μm) of 37.5% (as assessed by TGA; this was intentionally achieved based on a lower mass of exposed triclosan during the melt loading process) and 69.6% for the larger PSi particles in the 150−250 μm range. With surface oxidation treatment some reduction in pore sizes is expected, but significant triclosan loading is readily achieved in any event.

The results of antibacterial (zone inhibition) assays for the first 15 days of activity for these types of materials are shown in Figure 7. Relative to the as-prepared mesoporous samples, a slight reduction in the average *S. aureus* inhibition zone is

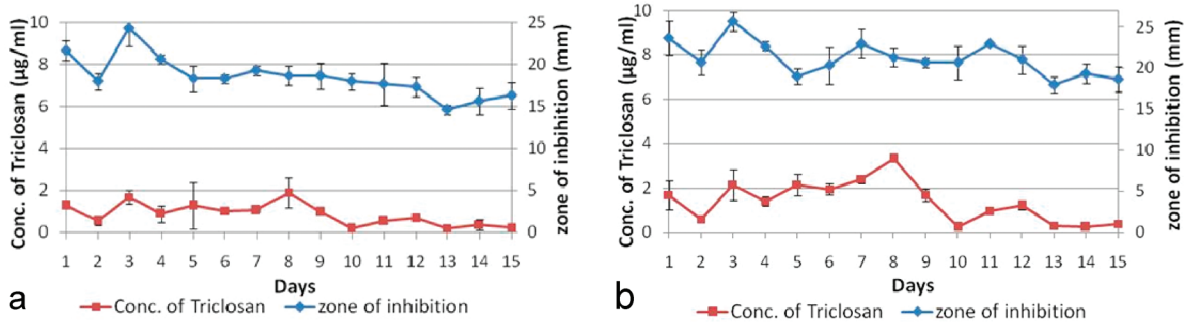

Figure 7. Combined zone inhibition assay/triclosan concentration release assays for oxidized mesoporous silicon sample. Particle size (a) <75 μm and (b) 150−250 μm.

observed for these oxidized samples (over the first 15 days), with aN 18.5 mm value for the 75 μm particles and 21.1 mm for the larger 150−250 μm sized material. It is clear, however, that relative to the active-loaded, as-prepared porous Si samples significantly lower concentrations of triclosan (2−4 μg/mL) are released per 24 h time interval in this initial 15 day time window. This would suggest that the effect of transforming the as-prepared, hydride terminated porous Si surface to a hydrophilic oxidized one (albeit with an associated slight reduction in pore volume) significantly lowers the permissible solubility of the triclosan (as loaded per melting conditions) to a magnitude comparable to the macroporous material.

4. Summary/Conclusions

This study presents, for the first time, the ability of porous silicon to act as an effective carrier for sustained delivery of antibacterial agents such as triclosan for activity versus the bacterium *S. aureus*. Porosity and surface chemistry of the semiconducting carrier clearly impact the maximum loading, average drug solubility, and duration of activity possible with this material. Further investigations exploring the dynamic range of tunable properties achievable with this drug/matrix combination and mechanistic insights into its activity are in progress.

Acknowledgment. Financial support by the Robert A. Welch Foundation (Grant P-1212 to J.L.C.) is gratefully acknowledged.

Supporting Information Available: High resolution TEM images of triclosan-loaded mesoporous Si. This material is available free of charge via the Internet at http://pubs.acs.org.

MP100227M