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Tailoring the biodegradability of porous silicon nanoparticles

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Abstract: Porous silicon nanoparticles (PSiNPs) are attractive carriers for targeted drug delivery in nanomedicine. For *in vivo* applications, the biodegradation property of PSiNPs provides a pathway for their safe clearance from the body. Particles sizes of 80–120 nm are of particular interest as they are important for cellular applications, such as drug delivery for cancer therapy, because these nanoparticles can take advantage of the enhanced permeability and retention effect to deliver drug preferentially to tumors with leaky vasculature, yet large enough to avoid renal clearance. However, the biodegradability rate of such particles is often too fast, which limits particle half-life and potentially reduces their *in vivo* delivery efficiency. In this work, we focus on the degradation of nanoscale particles and study the effect of both thermal oxidation and silica coating on the stability of PSiNPs in phosphate buffered saline solution (a close mimic of a basic biological fluid). Using thermal oxidation, the half-life of PSiNPs can be varied from 10 min up to 3 h. Using silica coating, the half-life can be extended further to 8 h. The particles produced using both these techniques can be functionalized using standard silica surface chemistries developed for applications in drug delivery. © 2012 Wiley Periodicals, Inc. J Biomed Mater Res Part A: 100A: 3416–3421, 2012.

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INTRODUCTION

Recently, there has been a great deal of attention focused on nanoparticles for use as drug delivery vehicles. The ability of functionalized nanocarriers to target cells for controlled drug release potentially improves delivery efficiency and specificity by orders of magnitude. A number of nanocarriers including liposomes,[1] polymeric nanoparticles,[2] iron oxide nanoparticles,[3] and mesoporous silica nanoparticles,[4,5] have been studied for this purpose. Porous silicon (PSi), with its attractive physical, chemical, and optical properties,[6,7] has been investigated for use in biomedical applications, such as optical sensors,[8] implantable devices,[9] orthopedic tissue engineering,[10] and recently for an autonomously functioning delivery platform.[11] Fabricated from PSi wafers, PSi nanoparticles (PSiNPs) are comprised of a nanocrystalline network, which provides a large surface-to-volume ratio for functionalization, as well as nanosize pores for drug loading. Additionally, PSiNPs are inherently fluorescent, biocompatible, biodegradable, and nontoxic. These attractive physical and chemical characteristics have enabled research on PSiNPs to result in their preliminary use as *in vivo* drug carriers.[12,13]

Among their various properties, the biodegradability of PSiNPs is of particular interest. PSiNPs degrade readily in biological environments to form silicic acid, which is a natural trace compound in humans.[14] PSiNPs with sizes in the range of 80–120 nm are desirable for drug delivery applications, as they are the right size to take advantage of the enhanced permeability and retention (EPR) effect and enhance tumor uptake while still being large enough to avoid renal clearance.[12] However, the *in vivo* degradation rate of such particles is often too fast for optimum drug delivery efficiency. To achieve efficient *in vivo* targeting of cells with high specificity, it is ideal for particles to exhibit blood circulation times of at least 12 h.[15] In previous work, on drug delivery using PSiNPs,[13] the fabricated PSiNPs had a half-life (i.e., the time it takes for dissolved silicon content to reach 50% of the initial content) of approximately 10 min. The half-life is too short for *in vivo* usages and thus they reported the use of water to oxidize the particles and increase the half-life up to approximately 30 min for their *in vivo* demonstration. Thus, there is a need to study and control particle stability in biological fluids and to significantly increase particle half-life up to 10 h to facilitate effective *in vivo* drug delivery.

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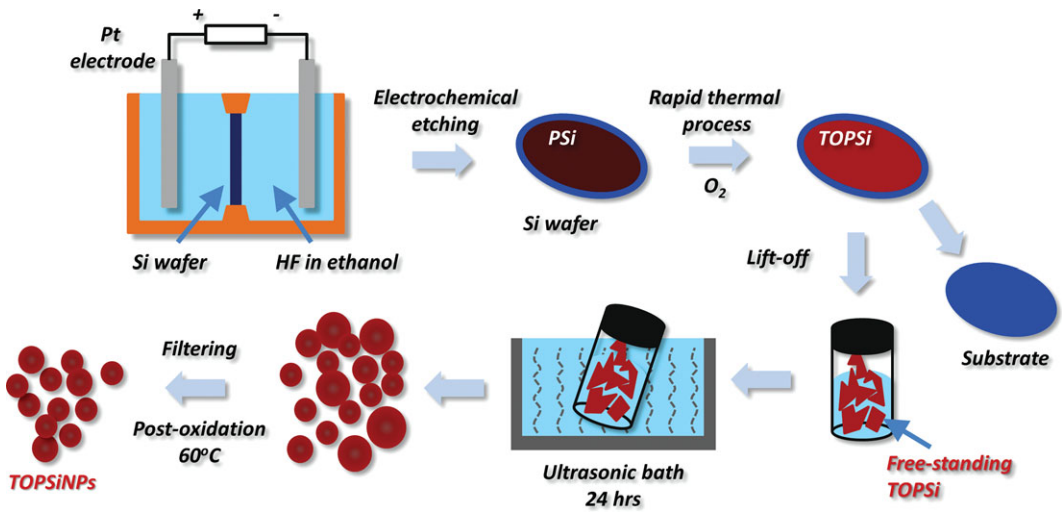

FIGURE 1. Fabrication process of the thermal oxidized porous silicon nanoparticles (TOPSiNPs). Pt, platinum and HF, hydrofluoric acid. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Two conventional physical approaches to improve PSi stability have been applied to PSiNPs: thermal oxidization and thermal hydrocarbonization.[16,17] Thermal hydrocarbonization completely halts the *in vivo* PSi degradation process, whereas thermal oxidation slows the degradation kinetics.[16] Chemical-based stabilizing methods include functionalization using polymers (e.g., polyethylene glycol),[18] and drug loading.[13] All these techniques have been employed to stabilize PSi microparticles, but only limited systematic studies of these approaches exist.[18] Furthermore, PSiNPs, which have a much greater surface-to-volume ratio than PSi microparticles, exhibit much faster degradation rates than their larger counterparts. Due to the increased degradation rate of nanoparticles when compared with microparticles, lifetime study dedicated to nanoparticles is essential and prolonging their lifetime is critical to the successful use of them for *in vivo* applications. As we mentioned in the second paragraph, Park et al.[13] have reported oxidized PSiNPs with half-life up to 30 min. Their particles are stabilized by incubating in water for oxidation. De Angelis et al.[12] also performed thermal oxidation on PSi wafer to stabilize the photoluminescence and thus possibly prolong the particle half-life. Although half-life values are reported, there is no systematic study on the effect of these stabilizing processes.

Here, we demonstrate two techniques to increase the lifetime of PSiNPs over the range of time from minutes to nearly 10 h, which is comparable to that of both PSi microparticles[18] and sol–gel silica microparticles[19] in phosphate buffered saline (PBS) solution which is a close mimic of a basic biological fluid. In this study, we investigate two thermal oxidation processes in details: preoxidation using rapid thermal processing (RTP) and postoxidation using hot aqueous bath which are inspired by the work done by Part et al. and Angelis et al., respectively. These methods enable engineering of the degradation lifetime of PSiNPs with dimensions of 80–120 nm. We also propose and study silica coating as an alternate method to prolong the lifetime of PSiNPs. This method retains the properties of PSiNPs that are pore-dimension sensitive, such as photoluminescence. The silica surface coverage technique is also attractive for incorporating other fluorescent labels into the PSiNPs, as fluorescent proteins or rare-earth flurophores embedded in silica exhibit enhanced photostability within an aqueous environment.[20] Although each technique has distinct merits, both thermal oxidation and silica coating of PSiNPs result in a nanoparticle with a silica surface, which is convenient for bioconjungation.[4,5]

In the "Introduction" section of this article, we investigate two techniques to thermally oxidize PSiNPs. The effects of both processes are discussed and an optimized combination of these two procedures is adopted to provide stable particles. In the "Fabrication and characterization of PSiNPS" section, we study direct silica coating of PSiNPs as an alternative method to prolong the lifetime of PSiNPs.

FABRICATION AND CHARACTERIZATION OF PSiNPs

Thermally oxidized PSiNPs

PSi thin layers are formed by electrochemical etching of silicon wafers.[6] A 4-in. diameter p-type silicon wafer (orientation ⟨100⟩, boron-doped, resistivity 1.2–1.9 mΩ cm) is etched in a two half-cell tank filled with 49% HF:ethanol (1:3) electrolyte using a constant current density of 200 mA/cm^2 for 2.5 min, as shown in Figure 1. This results in a 20-μm thick of PSi layer formed on top of the silicon wafer. The wafer is then thermally oxidized at 800°C using RTP in oxygen (O_2 flow rate is 40 sccm). Oxidation times are varied from 0 to 6 min. A free-standing PSi layer is obtained in a 49% HF:ethanol (1:90) electrolyte using a current pulse density of 1 mA/cm^2. After the lift-off process, the hydrophilic PSi surface is used to confirm that oxide formed by RTP still remains. This means that the HF electrolyte used in the lift-off process does not remove the surface oxide totally and thus the effect of RTP is retained. The freestanding PSi layer is collected in ethanol and sonicated using an ultrasonic bath cleaner for 24 h. Sonication is chosen for the sake of simplicity, although ball milling is another option

for creating PSi particles. The particle shape obtained using sonication is less regular compared with ball milling which gives regular ball-shaped particles.[17] It is known that particle shape affects the efficiency of drug delivery[15] but it is not the focus of the study presented here. But the techniques we discuss here for tailoring the biodegradation rate is applicable to PSiNPs prepared by both sonication and ball milling. To obtain particles of diameter smaller than 200 nm, the dispersed particles are filtered using a 0.2-μm membrane filter. To remove particles smaller than 50 nm, the sample is first centrifuged at 14,000 rpm for 20 min, and the supernatant is removed carefully. After the pellet is resuspended in deionized (DI) water, the centrifugation and suspension process is repeated several times to wash the particles. Finally, for postoxidation treatment, the dispersed particles are heated in a 60°C water bath. Postoxidation times range from 0 to 42 h. For 1 g of free standing PSi thin film, 2 mg of PSiNPs can be obtained after final processing. This yield of 0.2% is largely due to the fact that the filtering removes the majority of particles, which have diameters larger than 200 nm. The yield can be further improved by using longer sonication times or using another particle formation method such as ball milling.

Silica-coated PSiNPs

A conventional sol–gel process, traditionally used for synthesizing silica particles, is used for silica coating of the PSiNPs.[19] Because the above-prepared PSiNP seeds are conveniently terminated with hydroxyl groups, no other surface preparation is required. Initially, 2.5 mg of PSiNPs dispersed in 70 μL of DI water are added to 1 mL ethanol (99%) and 20 μL NH_4OH (30%, w/v aqueous solution). To initiate the reaction, 60 μL of 99% tetraethyl orthosilicate (TEOS) is added to the mixture, which is then sonicated for 10–30 min. Centrifugation is performed at 14,000 rpm for 20 min to separate the silica-coated PSiNPs (SCPSiNPs) from small silica particles that spontaneously form during the reaction. The pellet of SCPSiNPs is resuspended in DI water. Finally, the particles are washed with DI water several times and kept in DI water.

Particle characterization

Dynamic light scattering is used to characterize the size distribution and electrophoretic light scattering is used to measure the Zeta potential of the particles in DI water (pH7). Both thermally oxidized PSiNPs (TOPSiNPs) and SCPSiNPs fabricated have a mean size of 100 nm with a standard deviation of 20 nm. For all samples of both TOPSiNPs and SCPSiNPs, the Zeta potential is measured to be −6 mV. The pore size of these particles is estimated using transmission electron microscopy (TEM) image analysis. For TOPSiNPs, the average pore diameter is approximately 5 nm, whereas for SCPSiNPs, the average pore diameter ranges from 0 to 5 nm, depending on the silica coating time. The calibrated silica coating rate is 0.2 nm/min. Longer coating times correspond to smaller pore diameters. Using gravimetric analysis, the porosity of the PSi formed is estimated to be around 70%. Inductively coupled plasma optical emission spectrometry (ICP-OES) is used to evaluate the concentration of PSiNPs in solution. A known concentration of an ICP silicon standard is used to draw a standard curve.

Degradation study in simulated biological conditions

To measure the degradation rate of the various types of PSiNPs, we monitor the dissolved silicon concentration in PBS solution at a constant temperature of 37°C. For each sample, 0.02 mg of PSiNPs is incubated in 2 mL of PBS solution, which corresponds to an initial silicon concentration of 10 ppm. At each time point, 400 μL of the sample solution is removed from the 37°C oven and centrifuged at 14,000 rpm for 20 min. By collecting the supernatant, the dissolved silicon is separated from the solid nanoparticles. 20 μL of 1*M* NaOH is added to the removed supernatant for digestion at 37°C for 12 h. The concentration of dissolved silicon is measured using ICP-OES after dilution to a total volume of 4 mL using 5% HNO_3. The results are normalized with respect to a fully digested sample prepared separately (an additional 4 μg of PSiNPs is taken from each sample and dispersed in 400 μL of PBS, digested by 20 μL of 1*M* NaOH for 12 h at 37°C).

RESULTS AND DISCUSSIONS

Effect of thermal oxidation on the degradation of TOPSiNPs

Here, we investigate thermal oxidation as one avenue to increase the half-life of PSiNPs while avoiding alteration of their chemical properties. Both RTP of the PSi wafer and postoxidation in a hot aqueous bath are expected to improve the stability of PSi particles.[12,13] Without oxide passivation, PSi microparticles are known to be unstable in biological environments, and the degradation rate is believed to depend on pore size.[18] However, for particles with diameters on the order of 100 nm, which commonly have pore sizes ranging from 5 to 20 nm, stability does not strongly depend on pore size.[13] Thus, adjusting the pore size of PSiNPs by altering fabrication parameters is not the best route to improve stability.

Figure 2(a) shows a representative TEM image of PSiNP without any oxidation treatment. The particle diameter is 100 nm with pore diameter of approximately 5 nm. The half-life of the native PSiNPs is 10 min, as shown in Figure 2(c), consistent with the results of Park et al.[13] These unmodified particles are the baseline standard for the following systematic study of thermal oxidation of the PSiNPs.

Effect of RTP. RTP is performed on the PSi wafer before removal from the substrate. The processing time is varied from 0 to 6 min, whereas the process temperature is held constant at 800°C. Using TEM, we imaged particles dried on a Formvar-coated copper grid. Figure 2(b) shows a TEM image of a TOPSiNP after RTP for 90 s. When compared with Figure 2(a), the dot-shaped pore structure changes to line shaped as a result of RTP. Figure 2(c) shows the effect of RTP time on the degradation of TOPSiNPs. No postoxidation was performed prior to obtaining the data shown in Figure 2.

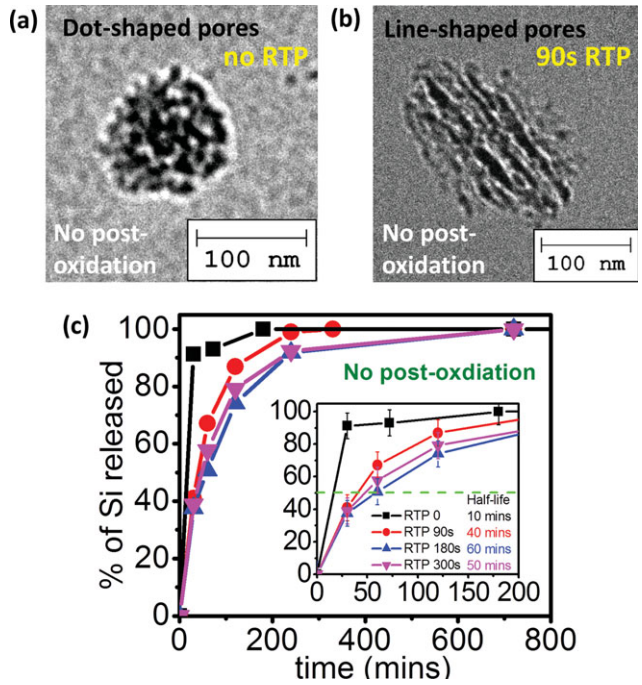

FIGURE 2. Representative TEM images of a PSiNP (a) without any thermal oxidization (b) oxidized using RTP for 90 s but no postoxidation. (c) Degradation kinetics of TOPSiNPs with various RTP times (no postoxidation included) showing that the blood retention time can be extended by increasing RTP duration. The inset shows the magnified plot of degradation kinetics from 0 to 200 min. The percentage of Si contents released into PBS medium at 37°C is measured using ICP-OES. The half-life indicates the amount of time the percentage of Si content of the solvent increases to 50%. TEM, transmission electron microscopy; RTP, rapid thermal processing; PBS, phosphate buffered saline; ICP-OES, inductively coupled plasma optical emission spectrometry. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

As mentioned before, the biodegradability of PSiNPs with pore size in the range of 5–20 nm is not highly dependent on the pore dimension. This result suggests that the change in pore morphology and size from dots of 5 nm to line structures of 5–20 nm is not the dominant factor responsible for the prolonged stability in PBS. In this case, the improvement in stability is expected to be a result of the inert silica layer formed during RTP, which protects the silicon core from degradation. However, the fact that the possibility exists to engineer the pore morphology using fabrication process control, which is decoupled from the degradation time, provides control over both the loading and releasing properties of these particles. For RTP times longer than 90 s, the half-life of TOPSiNPs increases to a value of 60 min, for a RTP time of 180 s. The increase in half-life depends on the thickness of the silica surface layer, which increases with oxidation time. However, it is evident that the particle half-life eventually plateaus. Further oxidization beyond 180 s does not improve the stability, and the half-life reaches a constant value. We remark that further oxidization beyond 300 s results in a half-life value in the range of 50–60 min and that the slight decrease in half-life for a RTP time of 300 s is within the experimental error. There are two potential explanations of this effect. First, the silicon oxidation rate is not constant but depends on the thickness of the silica.[21] As time increases, the oxidation rate is reduced as the thicker oxide inhibits the amount of oxygen diffusing to the buried Si/SiO_2 interface. Second, for particles that have half or more of their volume comprised of silica, the core volume fraction of silicon does not influence the half-life measurement. The overall shape of the lifetime curve will be affected by this parameter, but the half-life value is not.

Effect of 60°C postoxidation process. We also study the postoxidation processing of particles in a hot aqueous bath. This simple processing technique employs a heated ultrasonic bath to grow oxide layers on the particle surface. In these experiments, PSiNPs are treated with 90 s of RTP and dispersed in DI water, before being subjected to this additional oxidation process. The particles are kept in a 60°C water bath for times ranging from 0 to 48 h. Figure 3(a) shows a TEM image of the particles before and after postoxidation using this process. Figure 3(b) shows the effects of postheating time on the degradation of TOPSiNPs. Similar to the results obtained using RTP, the stability increases with processing time and reaches a steady-state value after 18 h of treatment. Again, the slight variation in the half-life of

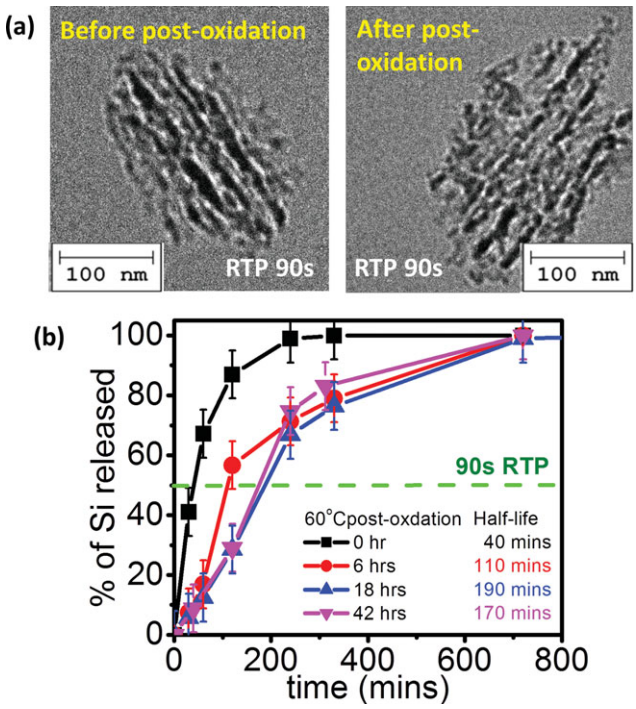

FIGURE 3. (a) Representative TEM images of TOPSiNPs before and after postoxidation in a 60°C water bath for 18 h (PSiNPs are oxidized using RTP for 90 s). (b) Degradation kinetics of TOPSiNPs with various postoxidation times (90 s RTP is included) showing that the blood retention time can be extended by increasing postoxidation duration until the optimized postoxidation treatment of 18 h. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

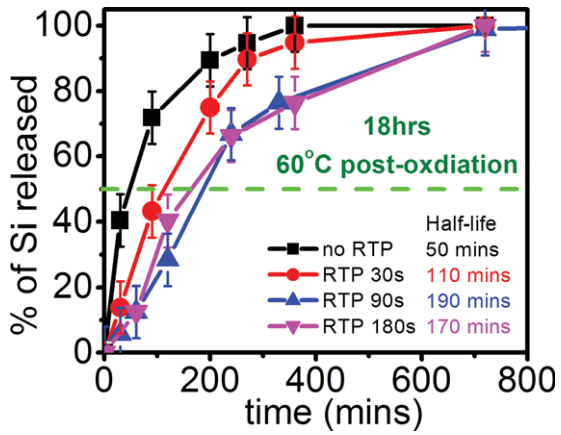

FIGURE 4. Degradation kinetics of TOPSiNPs with various RTP times (postoxidation at 60°C for 18 h is included) showing that the optimized thermal oxidation treatment by varying the RTP duration with optimized postoxidation duration. Using thermal oxidation, the half-life of PSiNPs can be varied from 10 min to 3 h. [Color figure can be viewed in the online issue, which is available at wileyonline library.com.]

TOPSiNPs after 18 h of postoxidation treatment is a result of experimental error.

Optimized process of TOPSiNPs. As shown in Figure 4, the maximum half-life of TOPSiNPs fabricated using aqueous postoxidation without using RTP is 50 min. This value is similar to that of TOPSiNPs fabricated using RTP only, as shown in Figure 2(c). When the porous silicon layer is removed from the substrate and sonicated, the unoxidized silicon surface attaching the particles to the substrate becomes exposed. This exposed surface leads to rapid biodegradation if there is no postoxidation. In contrast, the postoxidation process uniformly oxidizes the silicon surfaces, which should prolong particle stability. Although the use of RTP is expected to result in particles with a shorter half-life than those fabricated using aqueous postoxidation, these two techniques result in similar improvements in particle stability. This suggests that the oxide formed by RTP may yield better protection against degradation than that formed by postoxidation. If the unoxidized region can be protected by postoxidation, the half-life can be further improved. Using 18 h of postoxidation described in "Effect of 60°C post-oxidation process" section (steady-state value), we vary and obtain the RTP time that yields the best particle stability. Figure 4 shows the combination effect of RTP time and 18 h of aqueous postoxidation at 60°C on the degradation of TOPSiNPs. The optimal resulting half-life, obtained using both 90 s and 180 s of RTP, is consistent with the steady-state RTP time obtained in "Effect of rapid thermal processing" section. The optimized TOPSiNPs half-life improves from 10 min to 3 h – a value that is appropriate for PSiNPs intended to be used in *in vivo* drug delivery studies.[13]

Effect of silica coating on the degradation of SCPSiNPs

Rather than oxidizing the silicon particles, which consumes the PSi core, the particle half-life can be improved using silica coating. In this process, a layer of silica is chemically grown on the surface to protect the PSi from degradation, but designed not to fill the pores, which are needed for drug loading. In this case, no oxidization is performed on the particles except when the PSi is exposed to air, and a native oxide forms. Hydroxyl surface termination of the PSiNP surface acts to seed silica formation by the sol–gel process discussed in "Silica-coated PSiNPs" section. Figure 5(a) shows TEM images of SCPSiNPs with various coating times. The particle morphology appears similar to uncoated particles after 10 min of coating, but after 30 min, the particle pores are filled and the shape becomes rounded. Figure 5(b) shows the degradation kinetics of the SCPSiNPs. In this experiment, equal amounts of PSiNPs were used in all trials. Due to the addition of silica from the TEOS, the total silicon content of the SCPSiNP samples increases with longer coating times. Silica coating for 10 min increases particle stability from 10 min to 8 h. However, coating the particles for 30 min reduces the total solubility to 60% of the coated particles. This is due to the fact that a longer coating time results in a thicker silica shell and thus, greater total silicon content per volume. The total concentration of silicon in this case is measured to be 100 ppm, which is greater than the solubility of silica in water at 25°C (70 ppm).[18] In this case, the concentrations of silicic acid and amorphous silica reach equilibrium before the silica protective layer is fully consumed, which halts further dissolution of the particles.

Further improvement

PSiNPs exhibit rapid degradation in biological fluids resulting in limited drug delivery efficiency. The prolonged half-lives of TOPSiNPs and SCPSiNPs are attributed to the

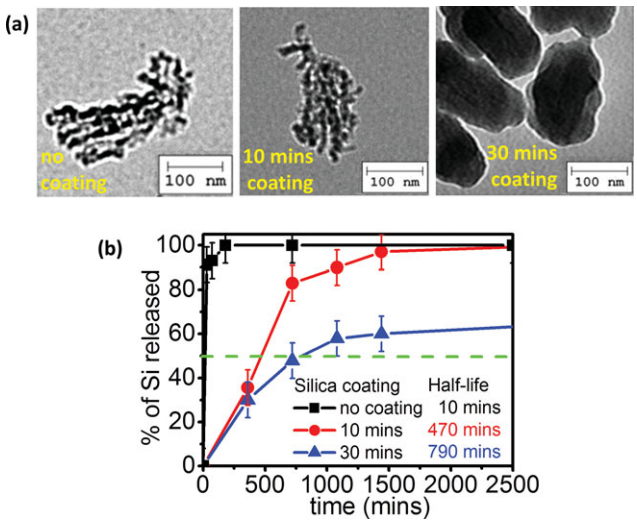

FIGURE 5. (a) Representative TEM images of PSiNPs with no silica coating, 10 min of silica coating, and 30 min of silica coating. (b) Degradation kinetics of silica-coated PSiNPs (SCPSiNPs) with various silica coating times (no thermally oxidation is included) showing that the retention time can be extended by increasing the silica coating time. Using silica coating, we can extend the half-life up to 8 h. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

presence of a silica surface covering the particles. Once the silica surface is dissolved, the PSi core is exposed and degrades readily. As shown in this study, the degradation rate depends on the thickness of silica. The thickness increases with longer oxidation time in the case of TOPSiNPs and longer coating time in the case of SCPSiNPs.

Beside silica thickness, it is known that degradability of silica microparticles depends on the silica quality.[19] The half-life of silica microparticles fabricated using different sol–gel silica precursor solutions ranges from 5 to 20 h. Thus, we can obtain better stability for a given silica thickness by engineering the silica quality through different sol–gel synthesis process.

Aside from simply pushing the stability limit to dictate the usefulness of the particle, there is also a tradeoff between the drug loading capability and stability for both TOPSiNPs and SCPSiNPs. In case of thermal oxidation, 0.46 nm of silicon is consumed to produce 1 nm of silica.[21] Assuming a circular pore, an overall 0.54 nm increase in thickness reduces the pore size by 1.08 nm. In case of silica coating, the coating can be engineered by the reaction time. The thicker the silica coating layer, the less room for drug loading exists. Further analysis of the drug loading and release profile is needed to qualify the *in vivo* performance of the particles.

SUMMARY AND CONCLUSIONS

In conclusion, we have investigated two ways to engineer the stability of PSiNPs. By using RTP and postoxidation, the half-life of TOPSiNPs improved from 10 min to 3 h, which is a reasonable time period for an investigational intravenous drug delivery platform. We have also studied sol–gel based silica coating as a method to extend the half-life of PSiNPs in PBS. This technique was shown to enhance the half-life of SCPSiNPs from 10 min to 8 h. Further improvement can be made to increase the thickness or improve the quality of the silica protective layer, which will further stabilize the PSiNPs. Further analysis of the mechanisms and efficiencies of drug release from stabilized PSiNPs will help determine which method will ultimately be most successful for *in vivo* drug delivery applications.

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