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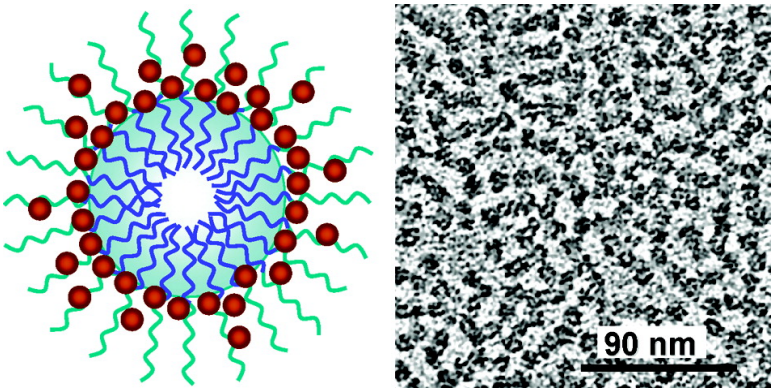

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A New Class of Silica Cross-Linked Micellar Core−Shell Nanoparticles

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Abstract: Micellar nanoparticles made of surfactants and polymers have attracted wide attention in the materials and biomedical community for controlled drug delivery, molecular imaging, and sensing; however, their long-term stability remains a topic of intense study. Here we report a new class of robust, ultrafine silica core−shell nanoparticles formed from silica cross-linked, individual block copolymer micelles. Compared with pure polymeric micelles, the main advantage of the new core−shell nanoparticles is that they have significantly improved stability and do not break down during dilution. We also studied the drug loading and release properties of the silica cross-linked micellar particles, and we found that the new core−shell nanoparticles have a slower release rate which allows the entrapped molecules to be slowly released over a much longer period of time under the same experimental conditions. A range of functional groups can be easily incorporated through co-condensation with the silica matrix. The potential to deliver hydrophobic agents into cancer cells has been demonstrated. Because of their unique structures and properties, these novel core−shell nanoparticles could potentially provide a new nanomedicine platform for imaging, detection, and treatment, as well as novel colloidal particles and building blocks for mutlifunctional materials.

1. Introduction

Nanoparticles (or nanovectors) have attracted great attention for biomedical applications including disease diagnosis and treatment. Various organic and inorganic materials have been studied in drug delivery systems, such as liposomes,[1] microparticles,[2] nanoparticles,[3] and polymeric micelles.[4] Recently, Ferrari summarized[5] a few important desirable properties of multifunctional nanoparticles (Figure 1a): the ability to deliver large amounts of therapeutic or imaging agents, co-encapsulation of one or more drugs and agents, multifunctionalization for bimolecular targeting, biobarrier avoidance, and antifouling.

Solid nanoparticles are widely studied, but the drug can only be attached to the particle surface, thus limiting the loading capacity and the flexibility to protect and release the drug. On the other hand, surfactant and polymer micelles have the potential to meet many of the requirements and have been extensively investigated for drug delivery, for gene delivery, and for carrying various contrast agents for diagnostic imaging.[6] Surfactants and polymeric surfactants contain both hydrophilic and hydrophobic segments. In an aqueous environment, these molecules can aggregate into spherical, core−shell-like particles above their critical micelle concentrations (CMCs) (Figure 1b). The core is formed by the hydrophobic segments and is separated from the aqueous environment by the hydrophilic shell containing the hydrophilic segments. As a result, micelles can be used to effectively solubilize and carry compounds that have poor solubility, low stability, or undesirable pharmaceutical properties in the core structure. Micelles as drug carriers are inexpensive to make and are available in large quantities. Their small sizes also allow them to circulate in the body and accumulate in the affected area with leaky, pathological vasculature.[6]

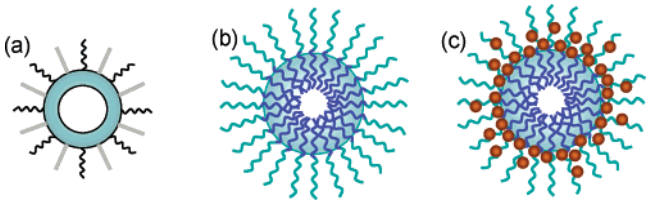

Figure 1. Schematics of nanoparticles for nanomedicine. (a) Idealized nanoparticles for carrying drugs, imaging agents, and other contents. The hollow particle is surrounded by antifouling PEG and functional groups for targeting. (b) Polymeric micelles. (c) Silica cross-linked, micellar core−shell nanoparticles. The micelle core is covered by PEO and silica. The figures were not drawn to scale.

A very important class of polymeric surfactants is amphiphilic block copolymers.[7] For example, Pluronic block copolymer surfactants consist of hydrophilic ethylene oxide (EO)

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and hydrophobic propylene oxide (PO) arranged in an EO_x-PO_y-EO_x triblock structure.[8] The poly(ethylene oxide) (PEO) segments form a tight hydrophilic shell protecting the drugs in the core from hydrolysis and other biodegradation processes. The PEO shell is also effective in preventing the adsorption of proteins, adhesion to tissues, and recognition by the reticuloendothelial system.[9]

The physical stability of the drug carrier is a critical issue.[10] For many applications it is desirable to have good stability and keep the pharmaceuticals and contrast agents in the blood pool over a sustained period of time. Recent studies have shown that the in vivo antitumor activity of a drug incorporated into the polymer micelles is positively correlated with the stability of micelles.[11]

However, micelles may be intrinsically unstable in a natural, biological environment, even though some polymeric micelles are significantly better in terms of having a higher CMC and a more rigid structure. The micellar stability is particularly important for applications involving changes in temperature, solution concentrations, aggressive physical forces (mechanical shearing for example), or competing interactions in in vivo conditions. For example, Pluronic block copolymer micelles dissociate readily upon dilution.[12] This could be a serious problem because when delivered into body fluids, the surfactant concentration will be diluted by many orders of magnitude, possibly to below the CMC. Under these conditions, the micelles would disintegrate, and the drug would precipitate. In addition to dilution, the micelles will encounter many biomolecules and chemicals. Most of these polar molecules will have a large effect on the ability to form stable micelles. Small polar molecules may significantly increase the CMC and make it more difficult to form stable micelles.[13] Finally, many nonionic surfactant micelle systems are temperature dependent.[7] The micelles could disintegrate and release solubilized drug if they are stored or used at different temperatures.

The most widely studied method to improve micellar stability is to cross-link and lock in the micellar structures,[14,15] either in the hydrophobic core region, in the hydrophilic shell region, or on the micelle surface. In order for this method to work, the polymers or surfactants must contain reactive, polymerizable groups, or they need to be specifically modified to contain such groups,[16,17] affecting the choices of polymers and polymer chemistry. In addition, shell or surface polymerization may need to be performed at high dilution levels to avoid interparticle cross-linking,[16] and core polymerization may reduce the loading capacity.[12]

In this study, we report a new class of robust, silica cross-linked micellar core−shell nanoparticles to maintain the long-term stability of polymer micelles with slow release rates. This study develops a very simple method to strengthen individual polymer micelles with polymerized silicate in the hydrophilic shell region, characterizes the structure and stability of the new core−shell nanoparticles, and compares the drug loading capacity and in vitro release properties from such composite particles. The nanoparticles described here could potentially provide a new platform for diagnostic probes and effective drug delivery.

2. Experimental Section

Experimental details are included in the Supporting Information.

3. Results and Discussion

3.1. Formation of Silica Cross-Linked Micellar Core−Shell Nanoparticles. The basic idea in our approach is to allow the polymeric surfactant to self-assemble into micellar structures, polymerize the silicate in the hydrophilic shell (PEO) region, and at the same time, encapsulate the active compounds in the core or shell regions (Figure 1c). The silicate polymerization needs to be controlled so that it serves to strengthen the micellar structures but does not cover all the PEO segments or cause agglomeration through interparticulate polymerization.

We prepared F127 ($EO_{106}PO_{70}EO_{106}$, MW about 12600) micellar solutions in the presence of tetraethoxysilane (TEOS) and then added a small amount (5 wt % with respect to F127 and TEOS) of diethoxydimethylsilane ($Me_2Si(OEt)_2$, DEDMS) to terminate the silicate condensation and prevent intermicellar aggregation and particle growth. We found that, without the addition of DEDMS, a clear solution was obtained first, which would gradually precipitate after more than 1 h of aging due to agglomeration. However, if a very small amount of DEDMS was added, a clear solution was obtained that stayed stable over the entire period of time during which the experiments were conducted (more than eight months). When examined under transmission electron microscopy (TEM), only very uniform, roughly 10 nm spherical particles were observed (Figure 2). More careful examination suggests that most particles have a bright core and a dark contrast region on the edge, typical of core−shell particle morphologies under normal imaging conditions (slightly underfocused). The particle surfaces are not smooth, but appear to be made of subunits 2 nm in sizes. Previous study by cryo-TEM suggested that a 5 wt % pure F127 aqueous solution is made of 6 nm particles (compared to 4−6 wt % surfactant concentration used in our study).[18] This dimension is interpreted to be the core diameter of the micelles.[18] From many studies in the literature for making mesoporous silica using Pluronic surfactants,[19−22] it is agreed that silicate species tend to polymerize in the PEO region of the Pluronic surfactants. Therefore, it is reasonable to suggest here that the silica will deposit on the micelles in a similar fashion. Then based on the size and morphology of the TEM study, we could suggest that

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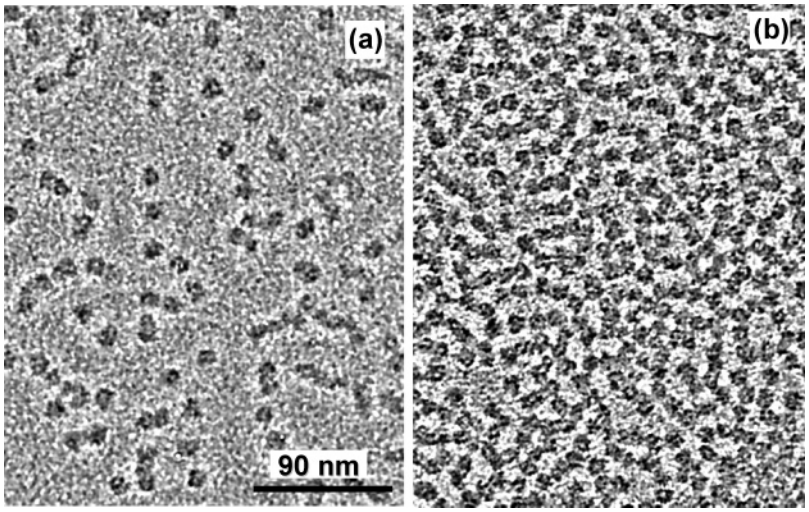

Figure 2. TEM images of silica−micelle core−shell nanoparticles. (a) Particles terminated at 10 min. (b) Particles terminated at 120 min. Both images show typical, uniform core−shell structures, but the particles terminated at a longer time have slightly smaller sizes and are more uniform.

the uniform, core−shell nanoparticles are made of individual micellar particles, with ultrafine, primary silica particles deposited outside the core region of the micelles.

Light scattering measurement provides additional information about the structure of the core−shell nanoparticles. For pure F127 surfactant solutions, the hydrodynamic micelle diameter ranges from 20 to 30 nm as measured by light scattering techniques.[23,24] The hydrodynamic diameter is larger than the diameter measured by TEM[18] because the light scattering measurement includes the contribution of the PEO chains extended in the solution, which showed no contrast in the TEM study.[18] We performed similar light scattering measurement on the core−shell nanoparticles and obtained a size distribution almost identical to the literature result (see Figure 1 in the Supporting Information).[23,24] The *Z*-average particle diameter (cumulants or intensity mean) is 21.4 nm, and the peak position is at 24.4 nm. This result is confirmed by independent measurement using two different instruments. The light scattering experiment shows that the hydrodynamic diameter is not changed by the silica modification as compared to the pure F127 micelles,[23,24] which supports the structure suggested in Figure 1c and implies that the silica is most likely incorporated in the interior of the PEO region, leaving most of the PEO chains extended in the solution. This conclusion is also consistent with the morphology and the particle size observed in the TEM study. No other silica particles were observed either in TEM or light scattering.

The extended PEO groups play an important role in protecting the particles from agglomeration. We performed experiments in which we substituted F127 with a similar surfactant (P123, $EO_{20}PO_{70}EO_{20}$, MW about 5750) with shorter PEO chains. The samples derived eventually precipitated from the solution. This study indicates that the long PEO chains in F127 indeed function as a steric stabilizer to keep the particles from agglomeration even after silica is deposited. These PEO groups also allow the particles to maintain their favorable antifouling properties.

A very interesting observation is that the samples terminated at an earlier stage tended to produce slightly larger, less uniform particles (Figure 2a). We speculated that when the silicate reaction was terminated at an early stage, the silicate did not have time to form condensed particles and might have a less dense structure. We studied the condensation of silicate during the preparation by nuclear magnetic resonance (NMR) techniques (Figure 3). Parts a, b, and c of Figure 3 correspond to the sample terminated at 10 min, the sample terminated at 120 min, and the sample heated at 80 °C overnight (from the sample terminated at 120 min), respectively. In the ^{29}Si NMR spectra, the resonances at approximately −90 ppm, −100 ppm, and −110 ppm are assigned to Q^2, Q^3, and Q^4 species,[25] where the Q^4 species represents the highest degree of polymerization. Relatively broad ^{29}Si NMR peaks observed in Figure 3a suggested the formation of the silicate network in the very early stages of reaction. Semiquantitatively, after 120 min of reaction, the Q^4/Q^3 ratio (integrated area) increased from 0.7 to 0.9, indicating a higher degree of condensation. When the solution was heated, a further increase in Q^4/Q^3 ratio to 1.4 was observed.

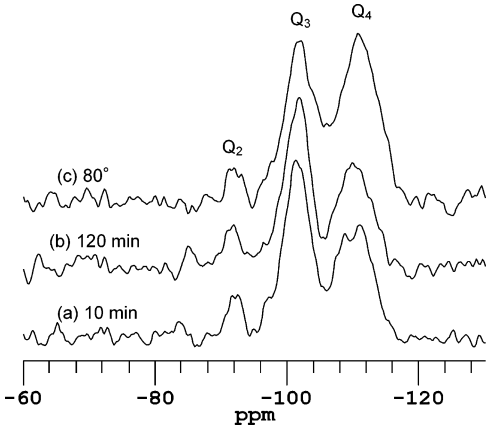

Figure 3. ^{29}Si spectra showing increased condensation with reaction time and heating. (a) A spectrum from the sample terminated at 10 min. (b) A spectrum from the sample terminated at 120 min. (c) A spectrum from a sample heated at 80 °C overnight.

In the literature, Pedroso et al. used a similar terminator to prepare aliphatic hydrocarbon dispersions of silica nanoparticles

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by homopolymerization of TEOS in an alcoholic medium using a base-catalyzed sol−gel process.[26] This work involved particle growth in the first stage, and the introduction of trialkylchlorosilane or trialkylalkoxysilane to stop the particle growth. The silica particles produced by Pedroso et al. were much larger and much less uniform as compared to our micellar based silica core−shell particles.

3.2. Stability against Dilution. The immediate and main benefit of the new core−shell nanoparticles is their greatly enhanced stability. In this study, we used special probe molecules that are sensitive to the chemical environment to track the micelle stability. The fine structure of pyrene monomer emission is known to be dependent on the local polarity (i.e., the Ham effect[27]). The ratio of the intensity of the first (372−374 nm) band to the third (383−384 nm) band in the pyrene fluorescence spectrum, I_1/I_3, is strongly affected by the polarity of the local environment,[28] and has been used to determine the location of the pyrene probe in the micelles. A higher I_1/I_3 ratio (about 1.87) indicates a hydrophilic environment, while a lower I_1/I_3 ratio (about 1.1) indicates a hydrophobic environment.[28,29] The hydrophobic environment suggests that the pyrene molecules are located within the micellar core, while the hydrophilic environment suggests that the micelles have disintegrated and the pyrene molecules are no longer trapped within the micelles.

The surfactant and the nanoparticle solutions were diluted in a pH 7.4 buffer solution, and the I_1/I_3 ratios were measured right after the dilution. Figure 4a shows the dependence of the I_1/I_3 ratio on the surfactant concentrations (level of dilutions). For a pure surfactant system, at a low surfactant concentration, the I_1/I_3 ratio is close to the value expected in water (ca. 1.87).[29,30] At a high surfactant concentration, the I_1/I_3 ratio reaches 1.1, suggesting that pyrene is partitioned into the hydrophobic interior of the micelles.[29,30] When the pure surfactant solution was diluted by more than 10 times, the I_1/I_3 ratios increased rapidly to about 1.7. Under these conditions, the pyrene molecules were already in contact with water and the micellar structures mostly collapsed. On the other hand, when the solutions containing the silica cross-linked micellar core−shell nanoparticles were diluted, the I_1/I_3 ratios only increased slightly and then stayed almost constant over many orders of magnitude of dilutions, suggesting that the micelles were stable against dilutions. The slight increase in I_1/I_3 with the silica core−shell particles during dilution is likely due to the diffuse of some pyrene molecules from the micelles into the aqueous environment or due to water penetration into the micelles. As will be discussed later, the silica shell is not a dense layer, which permits the diffusion of molecules from micelles into the solutions when diluted. Alternatively, water molecules could enter nonionic surfactant micelles at a high dilution level and cause a small increase in the I_1/I_3 ratio.[28]

We also studied the micellar stability as a function of time after dilution. Figure 4b gives the time dependence of the I_1/I_3 ratios for the F127 solution (diluted 130 times) and the solution containing core−shell nanoparticles (diluted 130 and 800 times).

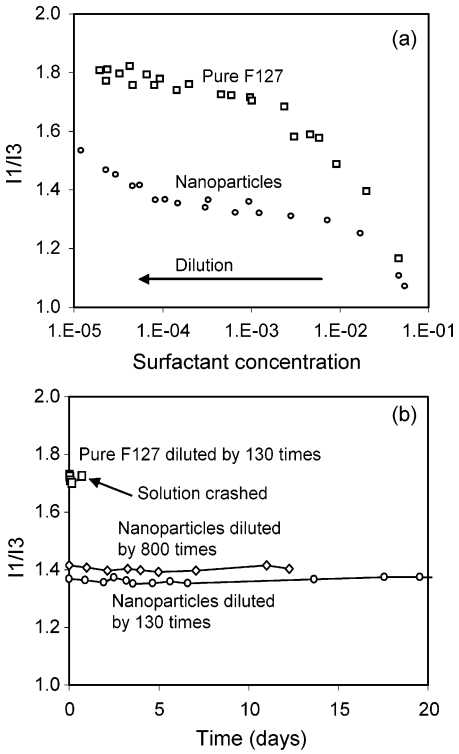

Figure 4. Particle stability studied by dilution. (a) Change of I_1/I_3 ratios during dilution. (b) I_1/I_3 ratios as a function of time after dilution. Both studies showed that F127 micelles disintegrated after dilution, while the nanoparticles maintained the miceller structure.

For the F127 sample, the I_1/I_3 ratio was ∼1.7, which indicates the micelles collapsed and the environment of pyrene was polar (aqueous solution). The whole solution crashed shortly due to precipitation of pyrene in water. For the core−shell nanaoparticles, the I_1/I_3 ratios stayed constant over extended period of time. The I_1/I_3 ratio was ∼1.3 for the low dilution (130 times) and 1.4 for the high dilution (800 times). These results suggest that the environment of most pyrene molecules stayed hydrophobic in the interior of the micelles during dilution and aging. The retention of intact core−shell nanoparticles after dilution and aging was also confirmed by TEM studies.

3.3. Drug Loading and Release Behavior. The solubilizing capacities and release behavior of silica core−shell nanoparticles were compared using different drugs or dyes. A range of agents—hydrophilic, hydrophobic, acidic, basic, and neutral—were studied. Several approaches have been used for studying drug loading, including simple equilibrium and co-solubilizing.[31] The method we used depends on the nature of the drug (see Experimental Section in the Supporting Information). The drug loading capacity was usually carried out using the simple equilibrium method, which is commonly used for moderately hydrophobic surfactants such as F127.[32−35] This method is helpful in our experiments because it is easy to keep the particle concentration the same for comparison, but we should point out that such methods are not designed to optimize the loading capacity. Usually the drug loading capacity depends on the particular drug, the surfactant molecules, and the loading methods. Some new studies showed exceptionally high loading

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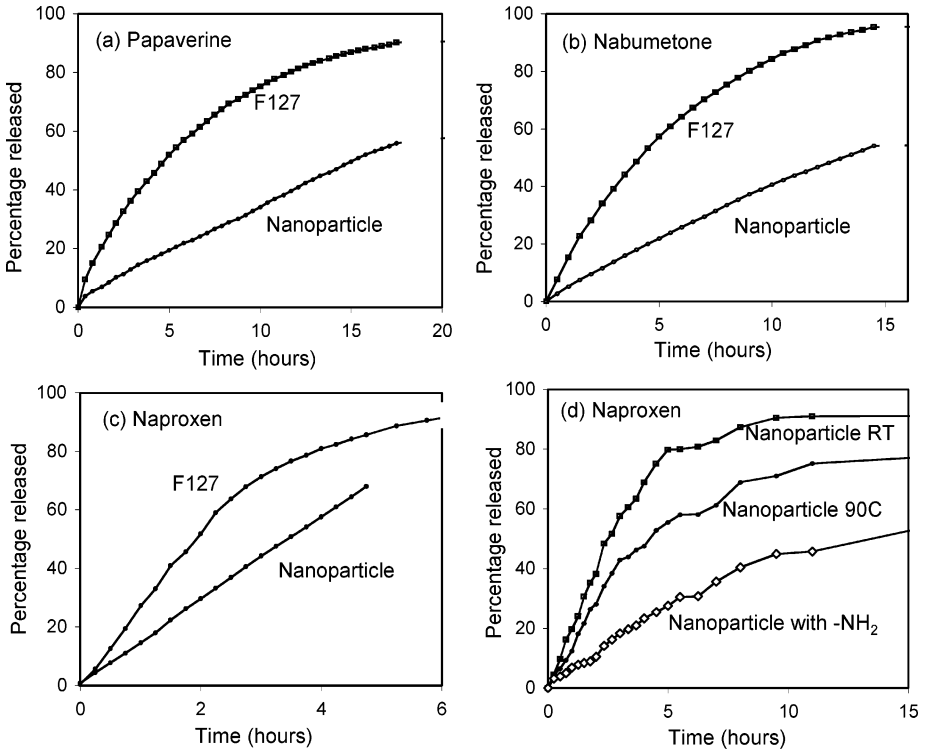

Figure 5. Controlled release results. (a) Papaverine. (b) Nabumetone. (c) Naproxen. (d) Release of naproxen with different nanoparticles.

capacity (close to 200 wt %) in other systems,[36] but these methods cannot be easily applied or compared to the F127 core−shell nanoparticle systems we studied here.

In our studies both the pure F127 surfactant micelles and the silica core−shell nanoparticles have loading capacities similar to what is reported in the literature for the same surfactant (F127) and drugs.[37] Under our experimental conditions, F127 surfactant micelles can achieve a loading of <10 wt % (drug/surfactant) for most agents that are in a solid form (naproxen, for example, 1 wt %), and a much higher (up to 50 wt %) loading for small molecules and agents that are in a liquid form (1,3,5-trimethylbenzene for example). Silica coating on the micelles does not cause significant difficulty in drug loading. In most cases the loading capacity is actually slightly increased as compared to the F127 solutions, sometimes by several times (see Table 1 in the Supporting Information) under the same experimental conditions.

The evaluation of drug release was performed using a dialysis method in which the samples were dialyzed against phosphate buffer solution (pH = 7.4, 0.02 M) at room temperature. The molecular weight cutoff (MWCO = 10 000) of the semipermeable membrane employed allowed the drug or dye to be transported between the inside and the outside of the dialysis bag while retaining the micelles or particles within the dialysis bag. In all the experiments, the experimental parameters were maintained the same for the same group experiments.

The release experiment with dialysis membranes is not a perfect method,[38−40] especially for fast release systems because the diffusion across the membrane becomes the rate limiting step. It is also different from in vivo release conditions where the drugs are instantly diluted into body fluids. However, this method is widely used for studying drug release from micellar systems and has proved useful in comparing the release characteristics of different surfactants. Here, this method is particularly useful for comparing the pure surfactant systems and the silica−micelle core−shell nanoparticles.

Figure 5 shows the release profile of different drugs: papaverine (a basic molecule) (Figure 5a), nabumetone (a neutral molecule) (Figure 5b), and naproxen (an acidic molecule) (Figure 5c,d). In all these cases, pure F127 micelles gave a much faster release profile. This study suggests that the core−shell nanoparticles are not only more stable but also have the potential to hold, maintain, and deliver the drug over a longer period of time. The time required to release 50% of the drug was extended by 2 to 5 times as compared to pure surfactant micelles. The reduced release rate can be either attributed to the slow diffusion though the silica layer, a stronger binding of the drug to the silica species, or to increased stability of the particles.

In addition, in most cases the release rate for the silica cross-linked core−shell nanoparticles was more or less constant even after more than 50% of the drug was released, approaching a "zero-order" release profile. The zero-order kinetics is highly desirable for drug delivery, wherein the release rate remains constant throughout the delivery period, but few systems have

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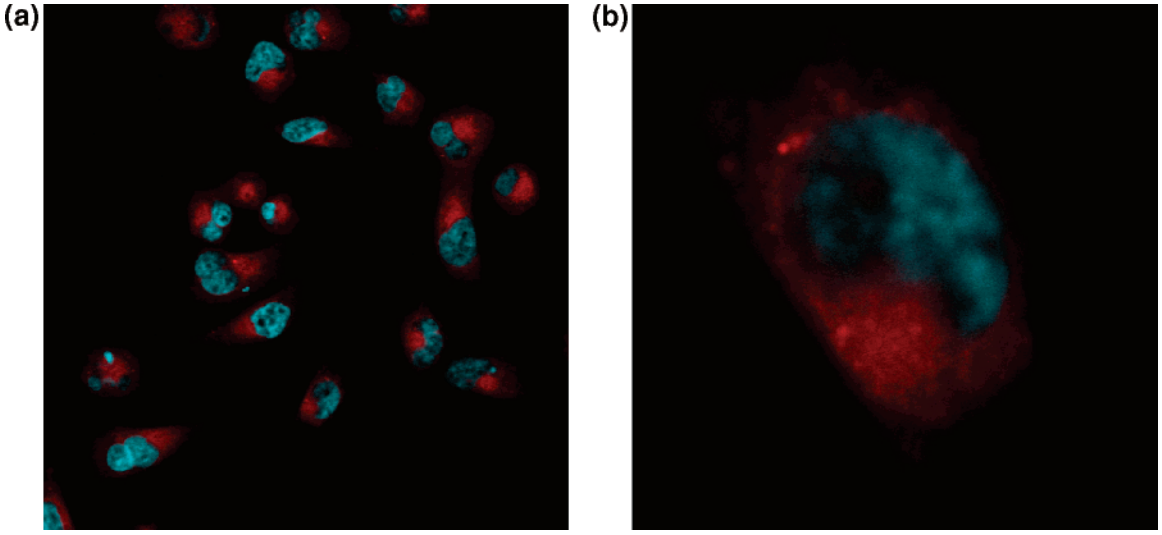

Figure 6. Delivery of Nile Red into prostate cancer cells. (a) A wide view with a 60× objective lens and (b) a view of a single cell, showing the red contrast inside the cell but outside the cell nuclei. The cell size ranges from 3 to 5 μm.

attained such constant release profile. On the other hand, pure F127 micelles normally have a faster release in the early stage, and they can hardly maintain a constant release rate at all. For all the samples, the release rate gradually levels off when more than 70% of the drugs are released. More than 95% of the drug can be released after an extended period of time (see Figure 2 in the Supporting Information), only it takes a much longer time for the core−shell nanoparticles to achieve this level of release.

3.4. Effect of Silica Chemistry and Sample Treatment. The interactions among the drug, the surfactant, and the silica matrixes affect the loading and the release of the drug. There can be three main types of interactions that can affect the release rate:[41] (1) hydrophobic interactions, (2) electrostatic interactions, and (3) hydrogen bonding. In the silica−micelle system, we can manipulate these interactions to change the release profile. For example, heating the particles increased the degree of condensation of the silicates (cross-linking density) as well as the hydrophobicity of the silica matrix. As a result, the drug loading increased, and the release rate decreased (Figure 5d, and Table 1, rows 18−21, in the Supporting Information).

Another way of controlling drug loading and release is to introduce additional groups in the silica matrix. In addition to the hydrophobic solvation, electrostatic interaction also increases drug−micelles interaction.[42,43] The extent of drug solubility depends on the compatibility between the drug and the micelle core. To increase the drug loading capacity of micelles, copolymers containing functional groups, such as carboxylic acid, were used by Lee et al.[43] Babonneau et al.[44] performed ^{13}C NMR experiments on ibuprofen molecules encapsulated in mesoporous MCM-41 type-silica functionalized by amino groups, and they found reduced mobility for ibuprofen due to the binding with the amino groups. Based on these results, we modified our core−shell nanoparticles with different functional groups. We found that the modified core−shell nanoparticles with functional groups had a higher loading capacity and a slower release rate for those matched drugs. Figure 5d compared naproxen release from nonmodified nanoparticles and amino group modified nanocomposite. Table 1 in the Supporting Information, rows 22−24, gives a summary of the naproxen loading capacity on different nanocomposites.

3.5. Dye Delivery into Cells. The core−shell nanoparticles were examined for their ability to deliver dye molecules into DU-145 human prostate cancer cells. Nile Red was chosen as a model hydrophobic molecule, while carboxyfluoroscein was used for its hydrophilic character. Nile Red is a hydrophobic phenoxazine dye with limited water solubility, and it is known to cross cell membranes. It has been used to stain neutral lipids and lipoproteins,[45,46] and it has been shown to be useful for staining liposomal phospholipids inclusions. Fluoroscein is known to have limited uptake into cells and is water soluble.

In this study, solutions of Nile Red loaded nanoparticles (1 μM total dye) were added to DU-145 human prostate cancer cell lines for varying times, and the transfer of the dye from the nanoparticle into the cell was determined by fluorescence microscopy. Hoechst 33258 was used as a nuclear co-stain, while independent studies with propidium iodide confirmed that cells maintained their viability under these conditions. The nanoparticles were found to be biocompatible, and fluorescent staining of the cells was apparent within 5 min. The uptake slightly increased at longer incubation. Qualitatively, uptake was slightly decreased when the experiments were conducted in full growth media as compared to 1% FCS (fetal calf serum)/PBS (phosphate buffered saline). This was likely due to the higher protein content of the cell media, which would also bind to the hydrophobic dye. For convenience, studies were typically conducted with 1 h incubation time. Figure 6 shows that the Nile Red permeated to the inside of the cell (red color), but stayed outside of the nuclei (blue color). Analogous studies with fluoroscein showed essentially no cellular uptake, even after 3 h. As fluoroscein is not able to readily cross cell membranes, while Nile Red can, these studies suggest that the nanoparticles themselves are not endocytosed (taken up by the cells) in this

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time frame by DU-145 cells. Most likely the hydrophobic Nile Red was first released from the particles and then taken up by the cells. It should be pointed out the Nile Red itself does not readily dissolve in water, and this experiment shows the potential of this approach to deliver hydrophobic agents into live cells. Non-nuclear intracellular staining of DU-145 cells by Nile Red was also confirmed with confocal microscopy. Patterns were consistent with the dye being contained within the cell and not the outer lipid membrane.

4. Conclusion

In this study, we have synthesized a new class of robust core−shell nanoparticles based on silica cross-linked individual block copolymer micelles and have shown that these nanoparticles could be a good candidate for nanomedicine applications. The easy in scale-up and low cost of production will make the silica−micelle core−shell particles available for wide applications. The new core−shell nanoparticles maintain the attributes of polymer micelles (biocompatibility), but they have additional advantages. (1) The silica cross-linked micellar core−shell nanoparticles have a much high stability due to the presence of the cross-linked silica layer. The stability of silica can be maintained against dilution, and it will not be readily affected by a temperature change and by other environmental factors. (2) The silica layer reduces the diffusion rate from the micelles, therefore decreasing the release rate and potentially increasing the circulation time. (3) The synthesis of nanoparticles, addition of functional group, and drug loading are simple and reliable and can be done either in one step or in several simple steps in an aqueous solution at room temperature. The tailoring of physicochemical properties can be easily achieved by varying the processing conditions and parameters. (4) Silica core−shell particles can be designed to be intrinsically multifunctional (either on silica or polymer) and thus can be combined covalently or noncovalently with drugs. Extremely rich chemistry is available to functionalize silica surface either through "one-pot" synthesis or post-treatment for attaching targeting groups on the particle surface. (5) We should be able to extend this approach to hydrophilic, hydrophobic drugs or dyes, or multiple agents, therefore making them potentially useful not only in drug delivery but also in molecular imaging, biomarkers, and biosensors.

Currently, the detailed structure of the silica cross-linked micellar particles, including the exact location of silica, the thickness of the silica layer, and the density (or porosity) of the silica matrix, is still under investigation. Methods to control the particle sizes and to adjust the silica layer thickness and rigidity are also being developed. Major efforts to study the biocompatibility and conduct practical studies of such core−shell nanoparticles to carry imaging contrast agents and drugs and their cellular interactions will be pursued. In addition to the nanomedicine application, the robust, uniform core−shell particles can be used to trap a range of organic and inorganic species to perform chemical reactions in the confined environment. Such techniques could be used to control the size and dispersion of the nanoparticles produced inside the micelles. The core−shell nanoparticles could also be used as new fundamental units to form high level self-assembled materials with built-in functionality, using approaches similar to the preparation of self-assembled mesoporous materials.[19]

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Supporting Information Available: Detailed experimental procedures as well as dynamic light scattering and drug loading studies are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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