Functionalization of Colloids with Robust Inorganic-Based Lipid Coatings

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ABSTRACT: Core−shell colloids, particles covered with polyelectrolyte (PE) multilayer films and lipid bilayer membranes, were prepared through self-assembly processes. The PE multilayer films were fabricated by the layer-by-layer (LbL) assembly of poly(diallyldimethylammonium chloride) (PDDA) and poly(sodium 4-styrenesulfonate) (PSS) onto colloidal particles. The inorganic-based synthetic lipid, *N*-[*N*-(3-triethoxysilyl)propylsuccinamoyl]dihexadecylamine (Si-lipid), was employed for membrane formation and was deposited onto the PE-coated particles through electrostatic interaction. The naturally occurring lipid, dimyristoylphosphatidic acid, sodium salt (DMPA), was also used for comparison. Multilayer film buildup on the particles was monitored stepwise by microelectrophoresis, and formation of the lipid bilayers was confirmed by fluorescence microscopy as well as scanning and transmission electron microscopy. The morphological stability of the Si-lipid and DMPA membranes to the surfactant Triton X-100 and ethanol was examined by fluorescence measurements. The Si-lipid bilayer coating was found to be highly stable upon exposure to Triton X-100 and ethanol solutions, even at high concentrations, whereas the DMPA membranes delaminated from the particle surface at low surfactant concentrations and low ethanol content aqueous solutions. The enhanced stability of the Si-lipid film is attributed to the polymerized moiety in the headgroup of the synthetic lipids and H-bonding interactions between adjacent Si-lipid molecules. The Si-lipid systems described here are attractive because of the potential to prepare robust inorganic lipid-based films with controllable properties, for example, thickness, permeability, and stability, both in the form of coatings on particles and as capsular colloids.

Introduction

It has been well-known for more than 30 years that lipid molecules can spontaneously aggregate into spherically closed bilayer membranes.[1−4] These lipid assemblies, known as liposomes, have been studied extensively as cell membrane models, drug carriers, and gene transfection agents.[5−7] Although liposomes offer a number of advantages with respect to physical properties, for example, tunable permeability based on the lipid components and their packing, problems are often encountered with their stability. In addition, it is often difficult to control their size distribution and membrane thickness, especially when conventional preparation methods are employed.

One approach that can be used to control the size of spherical lipid colloidal entities is by employing a template, such as colloidal particles, for the deposition of lipid films. Both inorganic and polymer particles have been utilized as supports for the deposition of single layers and bilayers of various phospholipids.[8−13] For example, single lipid layers spontaneously assemble onto octadecyl-hydrophobized silica particles,[8,9] while lipid bilayers form on hydrophilic silica particles.[10−12] In a study involving phospholipid bilayers deposited onto ∼8 μm hydrolyzed poly(methyl methacrylate) particles, it was shown that the outer lipid layer can be removed by washing with a detergent solution or organic solvents.[13] More recently, the biological significance of lipid membranes in contact with polymers has led to a number of studies focusing on the formation of lipid layers on polyelectrolyte-coated supports.[14−17] In studies involving polyelectrolyte multilayer-coated colloids, Moya et al. reported that dipalmitoylphosphatidic acid forms bilayers while dipalmitoylphosphatidylcholine most likely forms multilayers.[14,15] Optically homogeneous lipid coatings were observed on the particle surfaces. Despite these previous studies, the morphological stability of particle-supported lipid membranes has not been examined. The morphological stability of lipid coatings on particles is of particular interest for potential applications of these colloidal materials in, for example, drug delivery and the food and cosmetics industries. Therefore, there is considerable interest in the preparation of particles that are coated with stable lipid bilayer membranes.

In this study, we report the functionalization of colloidal particles with a new class of lipids, organoalkoxysilane-based lipids (Si-lipids). It was recently reported that this type of lipid assembles in solution to form bilayer vesicles, termed Cerasomes.[18] The morphological stability of Cerasomes is significantly higher than those of other bilayer vesicles, since the membrane surface of the Cerasome comprises a siloxane network to prevent collapse and fusion of the vesicle.[18g] However, the polydispersity of the Cerasomes is quite broad (size 100 nm to several μm), potentially limiting their use in some applications. Herein, we prepare monodisperse lipid-coated colloidal entities by depositing Si-lipid membranes onto polyelectrolyte multilayer-coated poly(styrene) and melamine formaldehyde particles with narrow size distributions (Scheme 1). PE multilayer film formation on colloids, achieved by the layer-by-layer technique,[19−25] was monitored by microelectrophoretic measurements, while the lipid coatings were confirmed

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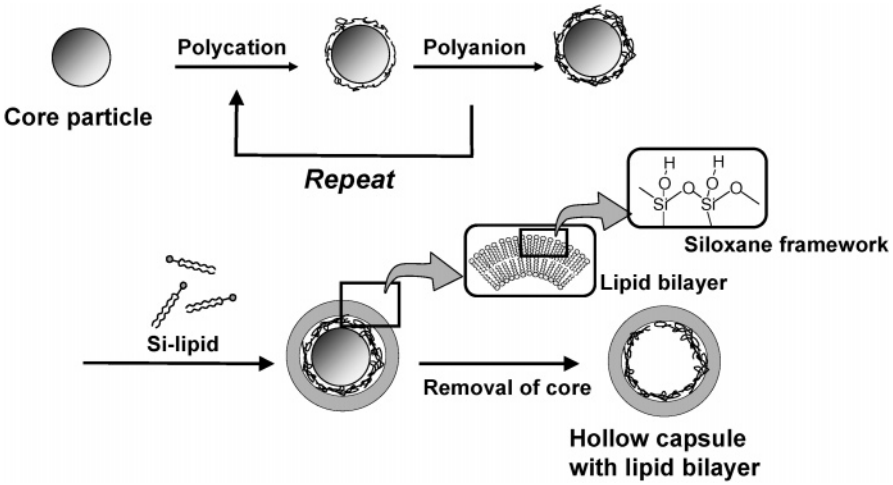
Scheme 1



by fluorescence microscopy and scanning and transmission electron microscopy. The morphological stability of the lipid membranes to surfactant and ethanol was examined by monitoring the fluorescence of membrane-embedded fluorescent lipids. Furthermore, hollow capsules of PE-multilayers and Si-lipid were subsequently produced from the precursor core−shell particles by dissolving the MF cores via treatment with aqueous HCl solution (Scheme 1). The significance of this work lies in the formation of robust lipid coatings on monodisperse colloidal carriers.

Experimental Section

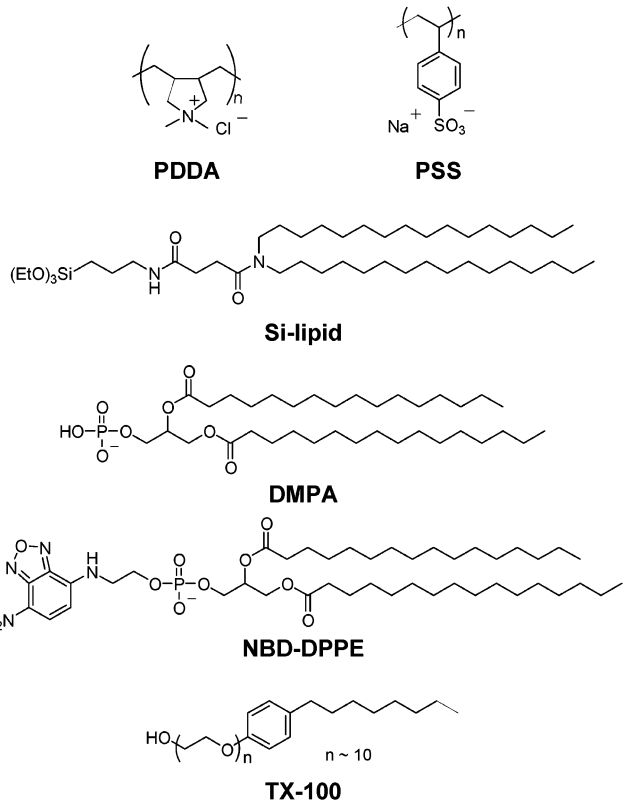
Materials. Negatively charged, sulfate-stabilized polystyrene (PS) particles of approximately 488 nm in diameter and positively charged, weakly cross-linked melamine formaldehyde (MF) particles (diameter = 1.09 or 3.14 μm) were purchased from Microparticles GmbH, Berlin, Germany. The molecular structures of the PEs and lipids used in this study are given in Chart 1.

Poly(diallyldimethylammonium chloride) (PDDA, M_w 100 000−200 000) and poly(sodium 4-styrenesulfonate) (PSS, M_w 70 000) were obtained from Sigma-Aldrich. PSS was dialyzed against pure water (M_w cutoff 14 000) and lyophilized before use. Dimyristoylphosphatidic acid (sodium salt) (DMPA) and *N*-(7-nitrobenzofurazan-4-yl)-1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine (NBD-DPPE) were purchased from Sigma-Aldrich. The synthesis of *N*-[*N*-(3-triethoxysilyl)propylsuccinamoyl]dihexadecylamine (Si-lipid) has been described earlier.[18a] The nonionic surfactant used for morphological stability measurements, Triton X-100 (TX-100), was obtained from Sigma-Aldrich. Hydrochloric acid (HCl) and sodium hydroxide (NaOH) were obtained from Merck. The water used in all experiments was prepared in a Millipore Milli-Q Synergy purification system and had a resistivity higher than 18.2 MΩ cm.

PE and Lipid Functionalization of Colloids. PS particles were alternately suspended in an aqueous PDDA solution (1 mg mL^{-1}) containing 0.1 M NaCl and an aqueous PSS solution (1 mg mL^{-1}) containing 0.1 M NaCl. After each PE adsorption step, the samples were washed three times with Milli-Q water. The coating procedure has been detailed elsewhere.[22,23] PE multilayers were deposited onto MF particles using the same procedure, although the first layer adsorbed was PSS, since MF particles are positively charged.

Hydrolysis of the alkoxysilyl part of the Si-lipid was performed by addition of HCl as an acid catalyst to an ethanol solution of Si-lipid, followed by incubation with vortex mixing for 12 h at 25 °C. This incubation time was optimized from a previous report for the preparation of Cerasomes.[18f] The molar ratio of Si-lipid/EtOH/H_2O/HCl was 1:200:19:0.03, and the total

Chart 1



weight of the sol was ca. 250 mg. The solution thus obtained was injected into 1.0 mL of the PE-coated PS (or MF) particle dispersion. The final concentration of Si-lipid was 1.0 mM. Excess lipid was removed by three repeated centrifugation/water wash cycles. In the case of DMPA, ethanolic solutions of lipids were prepared with a concentration of 50 mM. This solution was then injected into 1.0 mL of the PE-coated PS (or MF) particles. The final concentration of lipid was fixed at 1.0 mM. As before, excess lipid was removed by three repeated centrifugation/water wash cycles.

Hollow Capsule Fabrication. Core dissolution of MF was accomplished by exposure of the PE-coated particles (suspended in 0.5 mL of water) to 0.1 M HCl solution (1 mL) for 30 min. The hollow capsules were centrifuged and redispersed in pure water. To ensure complete core removal, this process of HCl exposure/redispersion was repeated a further two times. Finally, the hollow capsules were washed a further three times with pure water.

Microelectrophoresis. Formation of PSS/PDDA multilayer and lipid bilayer coatings on the particles were qualitatively monitored by measuring the ζ-potentials of the coated particles with an electrophoretic light scatterer equipped with a laser Doppler system (Malvern, Zetasizer 2000). An average of five measurements at the stationary level was taken for each data point. The particles for ζ-potential measurements were dispersed in Milli-Q water. For the pH-dependent studies, the solution pH was adjusted by adding HCl or NaOH.

Fluorescence Measurements. Fluorescence microscopy images were taken with an Olympus BH-2 microscope. 3% NBD−DPPE was used as a lipid-fluorescent probe.[26] The excitation wavelength was set at 488 nm.

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) Measurements. The morphology of PE/lipid bilayer-coated particles and the hollow spheres obtained were observed by SEM and TEM. SEM images of Au-sputtered samples dried on silicon substrates were obtained with a Philips XL-30FEG electron microscope at 2.0 kV. TEM measurements were performed with a Philips CM 120 BioTWIN microscope operated at 120 kV. TEM samples were prepared by depositing a droplet of the dispersion on a carbon-deposited copper grid covered with Pioloform film and allowing them to air-dry overnight.

Lipid Membrane Stability. The morphological stability of the lipid membranes was evaluated against the nonionic surfactant TX-100. As a lipid-fluorescent probe, 3% NBD−DPPE was added to the lipids. The core (PS)−shell particles were exposed to solutions containing several equivalent concentrations of TX-100 to that of the lipids on the particles in the dispersion. (e.g., 1 equiv corresponds to a molar ratio of TX-100 to lipid of one to one). The number of lipid molecules on the particles was estimated from the particle concentration, particle size, and limited cross-sectional area of the lipid molecules. At concentrations above the critical micelle concentration (cmc), a surfactant partitions into the lipid bilayer and eventually forms mixed micelles of surfactant and lipid.[27,28] Thus, the concentration of TX-100 was set above its cmc. An aliquot of 50 mM TX-100 solution was added to the lipid-coated particle dispersions. TX-100 was added in 1 equiv increments up to a total of 30 equiv. The dispersions were centrifuged, the supernatants were removed, water was added, and the particles were redispersed by gentle shaking. The dispersions were then centrifuged again, the supernatants were removed, and tetrahydrofuran (THF) was added. THF was used to dissolve the PS cores to minimize light scattering. This procedure does not influence the fluorescence intensity of the probe dye. The change of the NBD−DPPE fluorescence intensity at 533 nm upon addition of TX-100 was monitored by fluorescence measurements. The morphological stability of the lipid membranes was also evaluated against ethanol using a similar method.

Results and Discussion

The growth of the PE multilayers on the MF particles was followed by ζ-potential measurements. Figure 1 shows the ζ-potential as a function of PE and lipid layer number for the positively charged MF particles coated with PSS/PDDA multilayers and the Si-lipid. The positively charged (uncoated) MF particles yield a ζ-potential of ca. +55 mV in water. The presence of PSS on the particle surface (layer 1) causes a reversal in ζ-potential to −25 mV. Alternating ζ-potentials are obtained with the further alternate deposition of PDDA and PSS, suggesting that stepwise multilayer growth occurs on the particles. At layer 11, the hydrolyzed Si-lipid was adsorbed onto the PDDA-terminated particle surface (that is, onto five PSS/PDDA bilayers), yielding a ζ-potential of −45 mV. The sign of the ζ-potential is in agreement with that expected for the formation of a Si-lipid bilayer on the particles, while the magnitude is close to that measured for spherical vesicles of the same

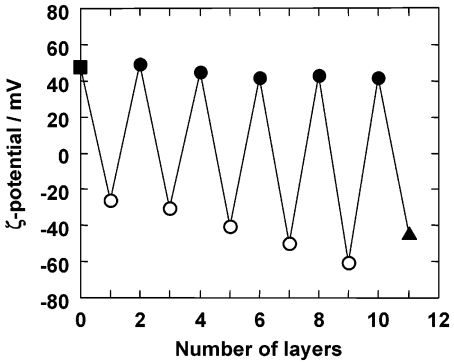


Figure 1. ζ-potential as a function of layer number for MF particles (1.09 mm diameter) coated with PSS/PDDA and Si-lipid layers: square, bare MF particles; open circles, PSS layers; closed circles, PDDA layers; closed triangle, Si-lipid coating. All measurements were performed in water at pH 6.

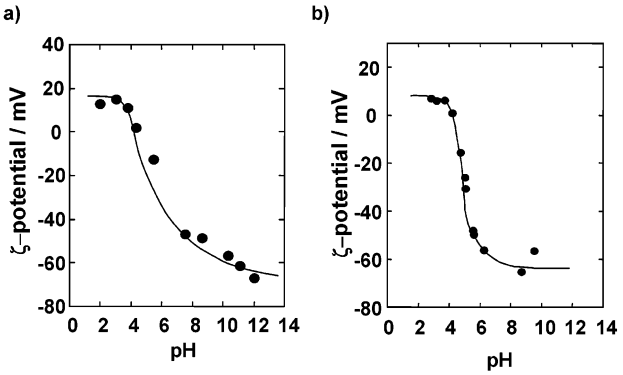


Figure 2. ζ-potential as a function of pH for (a) MF particles (1.09 μm) coated with $(PSS/PDDA)_5$/Si-lipid and (b) Si-lipid bilayer vesicles (Cerasomes). All measurements were performed in water, and the solution pH was adjusted by adding HCl or NaOH.

Si-lipid (known as Cerasomes), −56 mV. After coating with the Si-lipid, the MF core was dissolved by treatment with HCl. The ζ-potential still remained negative, −38 mV, suggesting that the HCl treatment does not cause significant delamination of the Si-lipid coating.

The ζ-potentials of the MF particles coated with PE-multilayers and Si-lipid as a function of pH are shown in Figure 2a. The corresponding ζ-potentials of Cerasomes as a function of pH are shown in Figure 2b. The Cerasomes were prepared in aqueous HCl solution at pH 3.0 with a lipid concentration of 1.0 mM. The ζ-potential range for the MF particles coated with PE-multilayers and Si-lipid varies from about +10 to −60 mV, depending on the medium pH (Figure 2a). The isoelectric point (IEP) of the coated particles was found to be 4.4. The particles have a large negative value at both neutral and basic conditions, reflecting deprotonation of the silanol groups of the Si-lipid headgroup. The Cerasome ζ-potentials show a similar trend, ranging from approximately +10 at pH ∼ 3 to −70 mV at pH ∼ 9, with an IEP of 4.3 (Figure 2b). The results indicate that the surface electrical state of the PE multilayer-coated particles terminated with a Si-lipid coating resembles that of Cerasomes, supporting that the Si-lipid coating is in the form of a bilayer membrane. Additionally, the pH-dependent ζ-potential data of the corresponding hollow capsules (i.e., after HCl treatment of the MF-core PE/Si-lipid-shell particles) are, within experimental error, identical to those for the core−shell particles (data not shown). This demonstrates that the

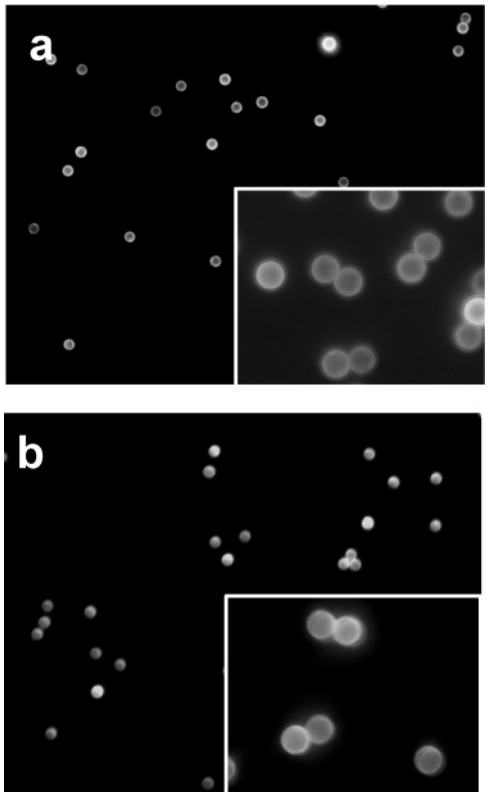


Figure 3. Fluorescence microscopy images of MF particles (3.14 μm diameter) coated with PDDA/PSS multilayers and lipids: (a) MF/$(PSS/PDDA)_5$/Si-lipid; (b) MF/$(PSS/PDDA)_5$/DMPA. All samples contain 3% NBD−DPPE.

core removal step does not significantly delaminate the Si-lipid coating and that the lipid coating is sufficiently permeable to allow removal of the decomposed core (see later).

The deposition of Si-lipid membranes onto PE-coated particles was also observed by fluorescence microscopy. Fluorescence microscopy images of the core−shell particles comprising MF cores coated with 10 layers of PSS/PDDA and a Si-lipid membrane are shown in Figure 3. For comparison, a fluorescence image of the particles coated with 10 layers of PSS/PDDA and DMPA, an unpolymerized lipid coating, is also shown in Figure 3. Homogeneous fluorescence is seen over the particle surface for both the Si-lipid and DMPA-terminated particles. This proves, within the limits of resolution of the fluorescence microscopy technique, the presence and homogeneous distribution of lipids on the particle surface. However, the limited resolution of fluorescence microscopy does not make it possible to discern whether the Si-lipid membrane follows the local curvature of the PE multilayers at the nanoscale or whether there are small lipid-deficient regions on the particle surface.

TEM experiments were also conducted to directly visualize the morphology of the PE multilayer and lipid coatings on PS particles. (PS particles were chosen because of their high monodispersity, which helps in comparing size changes before and after coating.) As shown in Figure 4, the uncoated and coated particles exhibit a rather smooth surface, with no discernible changes in surface roughness as a result of PE and Si-lipid coating. No aggregation of the particles was observed as a result of PE and lipid deposition. However, the TEM images revealed a systematic increase in the PS particle diameter upon coating with PDDA/

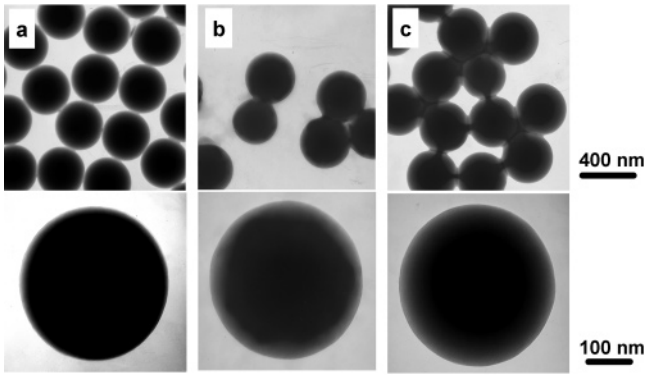


Figure 4. TEM images of PS particles (488 nm diameter) coated with PDDA/PSS multilayers and lipids: (a) bare PS particles; (b) PS particles coated with $(PDDA/PSS)_4$/PDDA; (c) PS particles coated with $(PDDA/PSS)_4$/PDDA/Si-lipid.

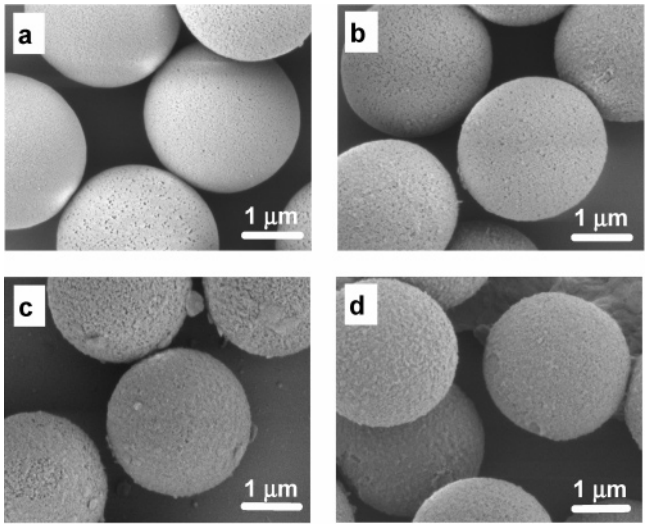


Figure 5. SEM images of MF particles (3.14 μm diameter) coated with PDDA/PSS multilayers and lipids: (a) bare MF particles; (b) MF particles coated with $(PSS/PDDA)_5$; (c) MF particles coated with $(PSS/PDDA)_5$/Si-lipid; (d) MF particles coated with $(PSS/PDDA)_5$/DMPA.

PSS and the lipids. For the nine-layer PDDA/PSS coating, the diameter increase of 16 ± 4 nm (average of 20 particles) corresponds to an average PE layer thickness of ~1 nm, which is similar to values reported earlier for the deposition of PEs under similar conditions.[29] A further increase of 14 ± 4 nm in diameter was observed upon coating with the Si-lipid, corresponding to approximately the unilamellar thickness of the Si-lipid bilayer (i.e., ~7 nm). From SEM images, a homogeneous coating of PEs and lipid on the particles can be seen (Figure 5). In agreement with the TEM data, a uniform coverage of the MF particles was observed. Some pores can be seen on the surface of the bare MF particles (Figure 5a). After coating with five bilayers of PSS/PDDA, these pores are less clearly discernible (Figure 5b), reflecting the deposition of a PE film on the MF particles. However, the deposition of lipid on the PE-coated particles results in rougher surfaces for both the Si-lipid and DMPA systems (Figure 5c,d). No aggregation of the MF particles was observed upon PE or lipid coating.

Surfactant solubilization is a useful method to evaluate the morphological stability of lipid membranes in aqueous media. For example, Regen et al. reported that polymerized liposomes were morphologically highly

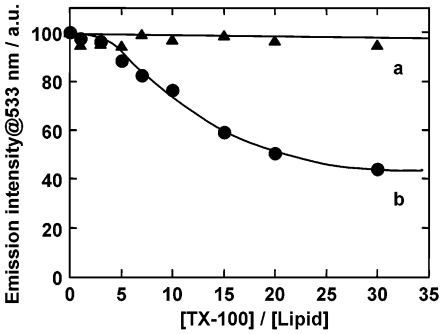


Figure 6. Emission intensity of PS particles (488 nm diameter) coated with PEs and lipids (containing 3% NBD-DPPE). The particles were washed with several equivalents of TX-100 before dissolving in THF, followed by fluorescence measurement: (a) PS particles coated with $(PDDA/PSS)_4/PDDA/$Si-lipid; (b) PS particles coated with $(PDDA/PSS)_4/PDDA/$DMPA.

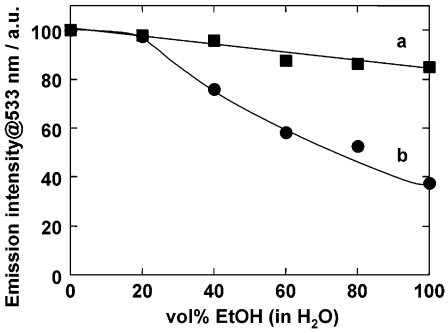


Figure 7. Emission intensity of PS particles (488 nm diameter) coated with PEs and lipids (containing 3% NBD−DPPE). The particles were washed with several concentrations of EtOH before dissolving in THF, followed by fluorescence measurement: (a) PS particles coated with $(PDDA/PSS)_4/$PDDA/Si-lipid; (b) PS particles coated with $(PDDA/PSS)_4/$PDDA/DMPA.

stable against liposome lysing agents such as surfactants (and ethanol).[30,31] Figure 6 shows the resistance of the lipid films on the PE-coated PS particles to the nonionic surfactant TX-100, as evaluated from the fluorescence intensity of the lipid probe, NBD−DPPE. First, the PS particles coated with PE multilayers and DMPA were examined as a control. When 5 equiv of TX-100 was added to the DMPA-terminated particles, the fluorescent intensity decreased, indicating collapse of the lipid film on the PE-coated particles. Typically, liposomes formed from unpolymerized phospholipids disassemble when 2−3 equiv of TX-100 is added.[28,32] For the particles terminated with the Si-lipid, the fluorescence intensity remained constant, within experimental error, even in the presence of 30 equiv of TX-100. The high morphological resistance of the Si-lipid coatings on PE-coated particles toward surfactant is likely to be due to a combination of the two-dimensional inorganic framework of the Si-lipid and H-bonding between adjacent Si-lipid molecules. This finding is in agreement with previous work, which reported higher morphological resistance of Cerasomes toward TX-100, compared with phospholipid-based liposomes.[18g,33]

We also examined the stability of the lipid films on PE-coated particles to the addition of ethanol. Experimentally, lipid-terminated PE-coated PS particles were dispersed in a mixture of water and ethanol. The proportion of ethanol was changed from 0 to 100%. The change of the fluorescence intensity at 533 nm of NBD−DPPE was investigated by fluorescence spectroscopy. Figure 7 shows the resistance of the lipid films supported on the PE-coated PS particles against ethanol. When more than 20% (v/v) of ethanol was added to the DMPA-coated particles, the fluorescence intensity decreased with increasing ratio of ethanol, indicating collapse of the lipid membrane. On the other hand, Si-lipid coated particles retain more than 80% of the original fluorescence intensity, even when the particles were exposed to 100% ethanol. Furthermore, we observed that only the Si-lipid coated particles could be observed under a fluorescence microscope following immobilization in a resin on a glass slide. Since the resin contains xylene, the DMPA films readily delaminated from the particle surface.

This high morphological stability of the Si-lipid films on the PE-coated particles is attributed to the development of a siloxane network, that is, cross-linking of the Si-lipids, which occurs through hydrolysis and condensation during Si-lipid deposition on the particles (data not shown). For the spherical liposome analogue, Cerasomes, the formation of a siloxane network was confirmed by FT-IR, MALDI−TOF-MS spectroscopy, and cryoscopic measurements.[33] A stretching band assigned to the Si−O−Si group was observed around 1100 cm^{-1} in FT-IR measurements. In addition, oligomers (tetramers and pentamers) were detected by TOF-MS spectra for the Cerasome incubated for 24 h. These studies suggest that similar cross-linking is likely to occur in the case of the Si-lipid coatings deposited on particles, thus enhancing the morphological stability of the films. Additionally, the silanol groups and the amide bonds present on the Si-lipids provide the opportunity for hydrogen bond formation, possibly further stabilizing the Si-lipid films.

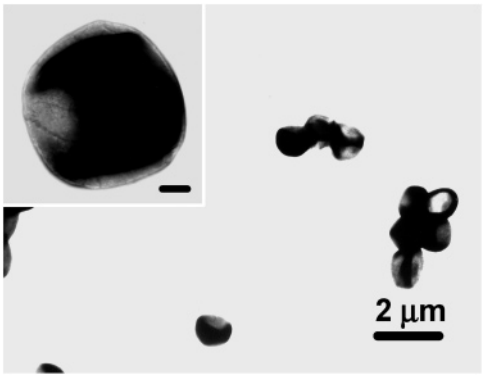


Figure 8. TEM images of hollow capsules of $(PSS/PDDA)_5/$Si-lipid formed after dissolving the MF core (diameter = 1.09 μm) from corresponding core−shell particles by exposure to 0.1 M HCl solution. The scale bar in the inset corresponds to 200 nm.

Exposing the PE multilayer- and lipid-coated MF particles to HCl solution resulted in dissolution of the MF core templates. The dissolved MF was expelled from the core via permeation through the PE-multilayer and lipid membrane. TEM revealed that the large majority of capsules are continuous films. The average diameter is ca. 1.1 μm, which is similar to that of the corresponding core−shell particles. For the Si-lipid system, the ζ-potential values of the capsules were similar to those of the corresponding core−shell particles (see earlier). In contrast, when DMPA was employed for lipid bilayer

formation, the ζ-potential switched from the original negative charge to a positive value, indicating removal of the DMPA coating. In the case of the Si-lipid, the phase transition temperature from the gel to the liquid crystalline (LC) state occurs at 10.5 °C. It is postulated that in the LC state the permeability of the lipid membrane is sufficiently high for the decomposition products of the MF spheres, which are of the order of a few nanometers in size,[34] to be removed. It is also possible that inhomogeneities in the lipid coating permit removal of the core components. We note that the Si-lipid can also be deposited on PE capsules to prepare Si-lipid-terminated PE capsules; this will be the subject of future investigations. Future studies will focus on examining the degree of cross-linking in the Si-lipid-coated particles and on the control of permeability through deposition of multiple Si-lipid bilayers alternating with PE multilayers.

Conclusions

We have demonstrated that the use of an organoalkoxysilane-type lipid (Si-lipid) with a polymerizable moiety in the headgroup yields robust lipid coatings on PE-coated particles. Microelectrophoresis, fluorescence microscopy, and electron microscopy experiments suggest that a lipid bilayer of the Si-lipid forms on the particle surface. The particle-supported Si-lipid membranes are highly stable upon exposure to surfactant and ethanolic solutions. Removal of the core from Si-lipid-terminated PE-coated particles proceeds without significant delamination of the Si-lipid, providing a viable approach to the preparation of lipid-functionalized capsules. The high stability exhibited by the Si-lipids is crucial in areas where subsequent processing of these colloidal materials is required, for example, the insertion of membrane-bound proteins and ion-channels and for the attachment of surface receptors. In addition, the silanol group has an affinity for bone and promotes hydroxyapatite (i.e., the main inorganic component of bone) formation in simulated body fluid,[35−37] potentially making these particles covered with Si-lipid membranes biocompatible. Further, capsules coated with Si-lipids are potentially excellent candidates as delivery systems, especially for controlled release.

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