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Supramolecular polymeric vesicles formed by *p*-sulfonatocalix[4]arene and chitosan with multistimuli responses†

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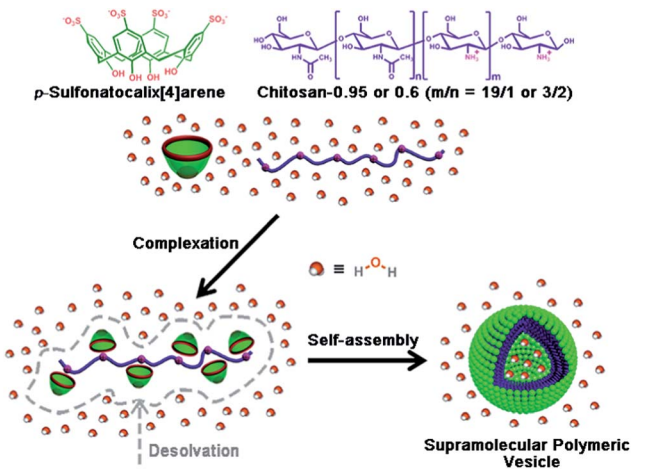
Supramolecular polymeric vesicles are constructed by the complexation of *p*-sulfonatocalix[4]arene and chitosan, where the multivalent electrostatic interactions between the anionic sulfonate tetramer and cationic polyammoniums served as the dominant driving force. The supra-amphiphilic assemblies are disassembled upon exposure to a pH stimulus since the partial deprotonation of chitosan accompanied by a pH increase. Adding a competitive guest can also disrupt the assembly, representing the host–guest inclusion response. Interestingly, an abnormal temperature-response is observed, possibly as a result of the temperature-directed fusion process.

Introduction

Vesicles are ubiquitous building blocks in living systems and are significantly useful in many fields such as chemistry, biology, and materials science.[1] Controllable switching assembly on/off is a prerequisite to achieve potential applications.[2] Consequently, studies on the stimuli-response of vesicles have become an extraordinarily fascinating topic.[3] However, most reported vesicles have only dealt with the response to a single stimulus until now.[4] Multistimuli responsive vesicles are less explored because introducing multi-responsive sites into one amphiphile generally requires tedious and challengeable covalent synthesis.[5]

The supramolecular approach paves a smart, alternative way to build multistimuli-responsive vesicles, benefiting from the reversible nature of non-covalent interactions.[6] We previously constructed a multistimuli-responsive supramolecular vesicle by the complexation of *p*-sulfonatocalix[4]arene (SC4A) with an amphiphilic viologen,[5] driven by calixarene-induced aggregation of tailored guests.[7] Herein, we expand this assembly strategy to build supramolecular polymeric vesicles by the complexation of SC4A with a cationic polyelectrolyte (Scheme 1).[8] Chitosan was employed here as the guest not only due to its natural polycationic character because of the protonation of its free amine groups produced *via* the deacetylation of chitin, but also due to its nontoxic character.[9] The resulting SC4A + chitosan vesicles are expectedly disassembled upon increasing pH or adding a competitive guest. However, upon increasing temperature, it is remarkable that the assembly tends to form a larger one rather than disassemble.



Scheme 1 Schematic illustration of the SC4A + chitosan supramolecular polymeric vesicle.

Experimental

Material preparation

Chitosan with a deacetylation degree of 60% (MV 140 000–220 000) was purchased from Sigma-Aldrich. Chitosan with a deacetylation degree of 95% (MV 10^6) was purchased from Aladdin. D-(+)-Glucosamine hydrochloride was purchased from

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J & K Scientific. 4-Phenolsulfonic sodium was purchased from Acros. Doxorubicin hydrochloride (DOX) was commercially available and used as received. All of these were used without further purification. *p*-Sulfonatocalix[4]arene (SC4A) and 1,4-diazabicyclo[2.2.2]octane (DBO) were synthesized and purified according to the procedures reported previously,[10,11] and identified by ^{1}H NMR spectroscopy in D_2O, performed using a Bruker AV400 spectrometer, and elemental analysis, performed using a Perkin-Elmer 2400C instrument.

Preparation of SC4A + chitosan vesicles. Chitosan was first dissolved in 1% (v/v) acetic acid, and a certain amount of concentrated sodium hydroxide solution was added until the pH of the solution reached 5.3. The pH was verified with a pH meter calibrated with two standard buffer solutions. Then SC4A solution was dropwise mixed with stable chitosan solution to obtain the SC4A + chitosan vesicle. The SC4A + chitosan vesicle would achieve balance in about 1 h.

UV/Vis spectra

The optical transmittance of the aqueous solution was measured in a quartz cell (light path 10 mm) on a Shimadzu UV-3600 spectrophotometer equipped with a PTC-348WI temperature controller.

High-resolution TEM and SEM experiments

High-resolution TEM images were acquired using a Tecnai G2 F20 high-resolution transmission electron microscope equipped with a CCD camera (Orius 832, Gatan) operating at an accelerating voltage of 200 kV. The sample for high-resolution TEM measurements was prepared by dropping the solution onto a copper grid. The grid was then air-dried. SEM images were recorded on a Hitachi S-3500N scanning electron microscope. The sample for SEM measurements was prepared by dropping the solution onto a coverslip, followed by evaporating the liquid in air.

DLS measurements

The samples were examined on a laser light scattering spectrometer (BI-200SM) equipped with a digital correlator (Turbo-Corr) at 532 nm at a scattering angle of 90°.

Zeta potential measurement

The zeta potential of the SC4A + chitosan vesicles was measured by using a nanobrook 173 plus.

NMR spectroscopy

^{1}H NMR spectra were recorded on a Bruker AV400 spectrometer in D_2O at 298 K, using 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (DSS) as a reference. The concentrations of SC4A and D-(+)-glucosamine hydrochloride were 5.00 mM.

Results and discussion

Construction of supramolecular polymeric vesicles

Two chitosans with different deacetylation degrees were employed to obtain deep insight into the host–guest complexation. The amphiphilic assembly based on the complexation of SC4A and chitosan was initially monitored by the optical transmittance around 400 nm. Adding SC4A to a solution of 30 μg mL^{-1} chitosan with a deacetylation degree of 60% (chitosan-0.6) leads to the gradual decrease of optical transmittance, indicating the formation of a large-sized assembly (Fig. S1†). A similar result was obtained for a solution of 30 μg mL^{-1} chitosan with a deacetylation degree of 95% (chitosan-0.95).

It is a prerequisite to determine the preferable mixing ratio between SC4A and chitosan for fabricating supra-amphiphilic assemblies. As shown in Fig. S2,† the transmittance first decreased sharply with increasing chitosan-0.6 concentration, reaching the minimum at 30 μg mL^{-1} chitosan-0.6, and then gradually recovered. In the left-hand portion of inflection, SC4A and chitosan form a higher-order complex with a tendency toward polymeric supra-amphiphilic assembly, whereas in the right-hand portion of inflection, excess chitosan leads to the disassembly of the supra-amphiphilic assembly, accompanied

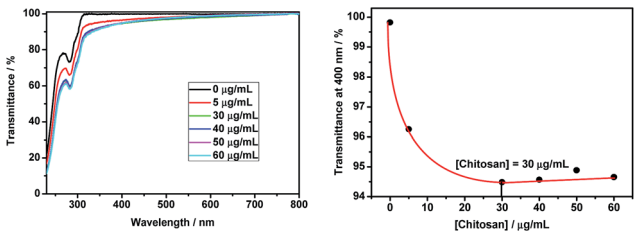

Fig. 1 (a) Optical transmittance of SC4A (0.02 mM) by increasing the concentration of chitosan-0.95 from 0 μg mL^{-1} to 60 μg mL^{-1} at 25 °C in aqueous solution at pH 5.3. (b) Dependence of the optical transmittance at 400 nm on the concentration of chitosan-0.95 with a fixed SC4A concentration of 0.02 mM.

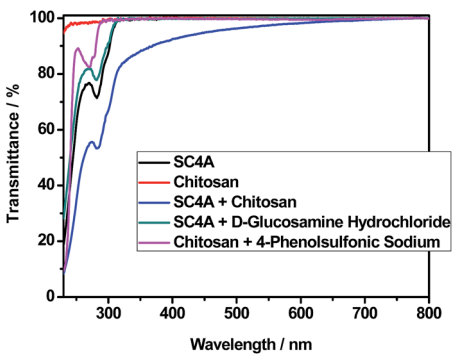

Fig. 2 Optical transmittances of SC4A, chitosan, SC4A + chitosan, SC4A + D-glucosamine hydrochloride, and chitosan + 4-phenolsulfonic sodium at 25 °C in aqueous solution at pH 5.3. [SC4A] = 0.02 mM, [chitosan-0.95] = 30 μg mL^{-1}, [4-phenolsulfonic sodium] = 0.08 mM, and [D-glucosamine hydrochloride] = 34 μg mL^{-1}.

by the formation of a simple inclusion complex. The inflection means that the preferable mixing ratio for supra-amphiphilic assembly between SC4A and chitosan-0.6 is 30 μg mL^{-1} chitosan + 0.02 mM SC4A. For the SC4A + chitosan-0.95 system (Fig. 1), the transmittance minimum was reached at also 30 μg mL^{-1} chitosan-0.95, however, excess chitosan-0.95 cannot disperse the supra-amphiphilic assembly, which indicates that chitosan-0.95 forms a more stable assembly with SC4A than chitosan-0.6. Control experiments show that both free chitosan and SC4A are without any tendency of appreciable self-aggregation under the same conditions and neither replacement of SC4A by its building subunit 4-phenolsulfonic sodium nor replacement of chitosan by its monomer glucosamine could induce the formation of a supra-amphiphilic assembly (Fig. 2 and S3†),[12] indicating that the conical cavity of SC4A and the polycationic structure of chitosan are the crucial factors leading to SC4A + chitosan supra-amphiphilic assembly.

The solution of SC4A + chitosan exhibited a clear Tyndall effect (Fig. 3a and S4a†), indicating the existence of abundant nanoparticles. However, neither free SC4A or chitosan solution nor chitosan + 4-phenolsulfonic sodium or SC4A + glucosamine solution exhibited the Tyndall effect, revealing that not only neither free SC4A nor chitosan can form nanoscaled aggregates under the same conditions, but also neither replacement of SC4A by its building subunit 4-phenolsulfonic sodium nor replacement of chitosan by its monomer glucosamine can induce the formation of nanoscaled supra-amphiphiles, which is in accordance with the above optical transmittance results. Furthermore, dynamic laser scattering (DLS), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) were employed to identify the size and morphology of SC4A + chitosan polymeric supra-amphiphiles. DLS results show that the SC4A + chitosan with different deacetylation degree complex forms well-defined aggregates with a similar size distribution of diameter at a scattering angle of 90° (Fig. 3b and S4b†): from 173 nm to 224 nm for SC4A + chitosan-0.95; from 165 nm to 262 nm for SC4A + chitosan-0.6. The SEM images of SC4A + chitosan complexes show the spherical morphology with an average diameter of 200 nm (Fig. 3c and S4c†). The measured diameters of the aggregates exceed the corresponding extended molecular length, suggesting that these aggregates are vesicular entities rather than simple micelles.[13] The formation of vesicles was convincingly validated by high-resolution TEM images, showing the hollow spherical morphology (Fig. 3d and S4d†). Zeta potential measurement was further performed to identify the SC4A + chitosan vesicular surface charge distribution, giving an average zeta potential of −1.08 mV for SC4A + chitosan-0.6; +35.32 mV for SC4A + chitosan-0.95 (Fig. S5†). The zeta potential is a key parameter affecting the stability of particles. Certain zeta potential values are necessary to keep the amphiphilic assemblies stabilized. The results convincingly indicate that chitosan with a higher deacetylation degree can form more stable polymeric supra-amphiphiles with SC4A. Combining all the aforementioned results, we deduced the mode of formation of SC4A + chitosan supramolecular vesicles as illustrated in Fig. 3e. The inner- and outer-layer surfaces consist of hydrophilic phenol OH groups of

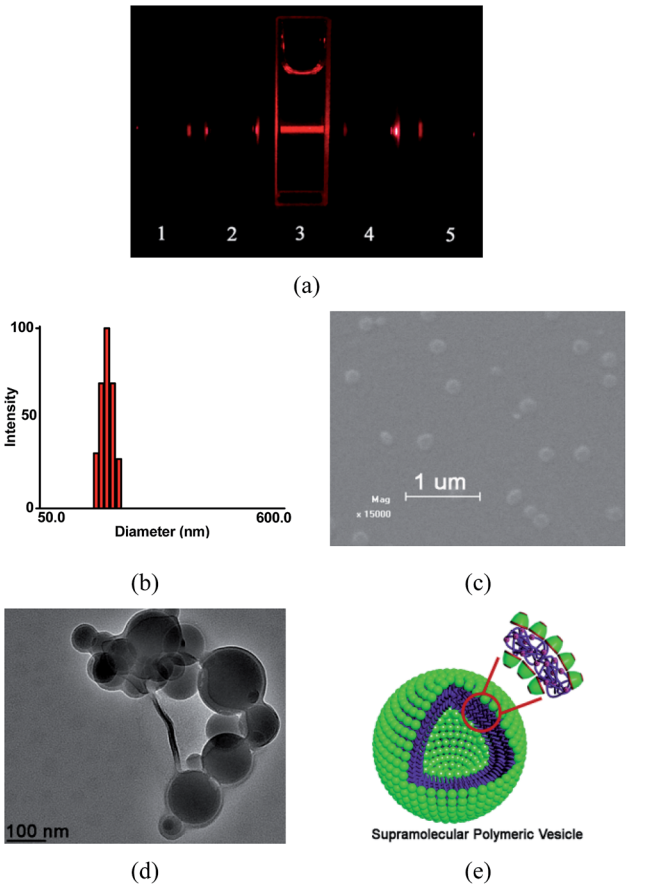

Fig. 3 (a) Tyndall effect of free SC4A (1), free chitosan (2), SC4A + chitosan (3), SC4A + D-glucosamine hydrochloride (4), and chitosan + 4-phenolsulfonic sodium (5). (b) DLS data of the SC4A + chitosan assembly. (c) SEM and (d) high-resolution TEM images of the SC4A + chitosan assembly. [SC4A] = 0.02 mM, [chitosan-0.95] = 30 μg mL^{-1}, [4-phenolsulfonic sodium] = 0.08 mM, and [D-glucosamine hydrochloride] = 34 μg mL^{-1}. (e) The deduced mode of the supramolecular polymeric vesicle.

SC4A, which are exposed to the aqueous solution, and SC4A and chitosan are connected together by electrostatic interactions, as well as host–guest interactions.

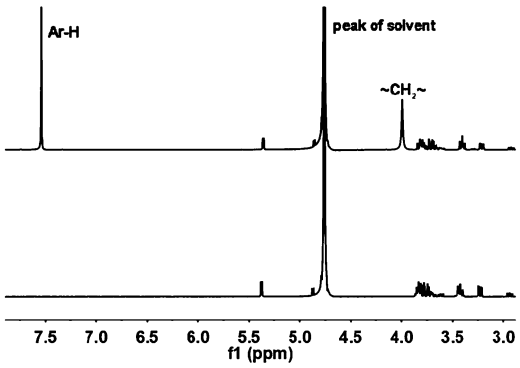

Fig. 4 Partial ^1H NMR spectra (400 MHz, D_2O, 298 K) of (a) SC4A + D-glucosamine, (b) D-glucosamine. The peaks without labeling are assigned to the signals of D-glucosamine.

NMR experiments (Fig. 4) of glucosamine (the monomer of chitosan) in the absence and presence of SC4A were performed to evaluate the binding structure between SC4A and chitosan. No appreciable complexation-induced shift was observed for all glucosamine protons, giving no evidence of encapsulation into the calixarene cavity. Thus, the formation of the present supramolecular polymeric vesicle is dominantly driven by the electrostatic interactions. Both SC4A and chitosan are highly hydrophilic blocks with opposite charges in water. The neutralization between the positive charges and the negative charges leads to the formation of a supra-amphiphilic complex.[6,9,14] The SC4A + chitosan system is somewhat similar to the polyelectrolyte–surfactant assembly.[15] We also envisage that the pre-organized conic structure of calixarene is a crucial factor for the formation of the supramolecular polymeric vesicle.

Next, we intended to compare the stability of the resulting polymeric supra-amphiphiles constructed by the host–guest interactions between SC4A and chitosan with different deacetylation degrees. As shown in Fig. 5a, there was no change in either the optical transmittance or the Tyndall effect of the SC4A + chitosan-0.95 solution over 12 h at room temperature. Furthermore, neither the optical transmittance nor the Tyndall effect can be disturbed by centrifuging the solution for several minutes at 2500 rpm (Fig. S6a†). It is well-known that salt concentration would affect the stability of the assembly driven by electrostatic interactions. However, as shown in Fig. 5b, there was even no change in either the optical transmittance or the Tyndall effect of the SC4A + chitosan-0.95 assembly in 100 mM NaCl solution over 6 h at room temperature. All the above experimental results convincingly indicate that the SC4A + chitosan-0.95 assembly is quite stable at room temperature. For the SC4A + chitosan-0.6 assembly, although centrifugation could not change its optical transmittance and Tyndall effect either (Fig. S6b†), the optical transmittance and the Tyndall effect of that solution could not be changed within only 6 h at room temperature (Fig. 5c). Furthermore, as shown in Fig. 5d, the optical transmittance of the SC4A + chitosan-0.6 assembly increased dramatically upon gradual addition of NaCl as a result of the disassembly of the supra-amphiphiles, and only *ca.* 80 mM NaCl concentration is required to fully disrupt the nanoparticles. All these results convincingly indicate that chitosan with a higher deacetylation degree can form more stable polymeric supra-amphiphiles with SC4A. The same conclusion was obtained from zeta potential measurements. One reasonable explanation is that chitosan with a higher deacetylation degree possesses a higher positive charge density under acidic conditions, affording stronger electrostatic interactions with SC4A.

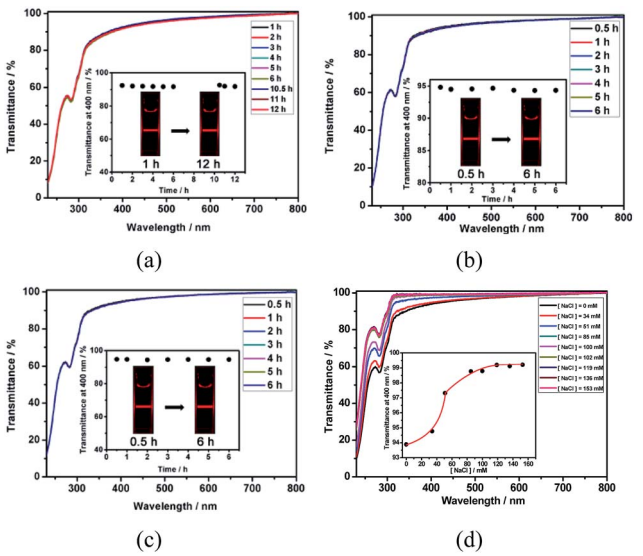

Fig. 5 (a) Optical transmittance of the SC4A + chitosan-0.95 solution at different times within 12 h at 25 °C at pH 5.3. Inset: dependence of the optical transmittance at 400 nm on time, and the Tyndall effect of the SC4A + chitosan-0.95 assembly after preparation for 1 and 12 h. (b) Optical transmittance of the SC4A + chitosan-0.95 solution at different times within 6 h at 25 °C in 100 mM NaCl solution. Inset: dependence of the optical transmittance at 400 nm on time, and the Tyndall effect of the SC4A + chitosan-0.95 assembly after preparation for 0.5 and 6 h. (c) Optical transmittance of the SC4A + chitosan-0.6 solution at different times within 6 h at 25 °C at pH 5.3. Inset: dependence of the optical transmittance at 400 nm on time, and the Tyndall effect of the SC4A + chitosan-0.6 assembly after preparation for 0.5 and 6 h. (d) Optical transmittance of SC4A + chitosan-0.6 solutions at different concentrations of NaCl solution. Inset: dependence of the optical transmittance at 400 nm on NaCl concentration. [SC4A] = 0.02 mM, [chitosan-0.95] = 30 μg mL^{-1}, [chitosan-0.6] = 30 μg mL^{-1}.

Multistimuli-response of the supramolecular polymeric vesicles

We further tested the pH, host–guest inclusion and temperature responses of the present vesicle. For the pH response, as shown

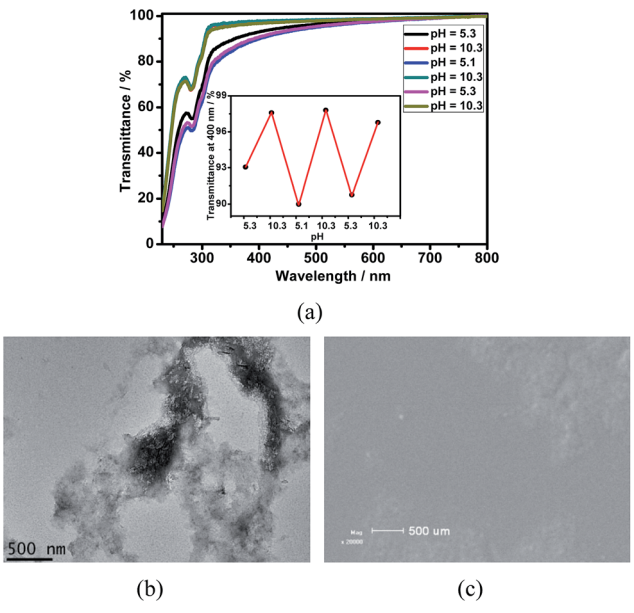

Fig. 6 (a) Optical transmittance of the SC4A + chitosan-0.95 solution observed upon several cycles under acidic and alkaline conditions. (b) High-resolution TEM, and (c) SEM images of the SC4A + chitosan-0.95 solution under alkaline conditions. [SC4A] = 0.02 mM, [chitosan-0.95] = 30 μg mL^{-1}.

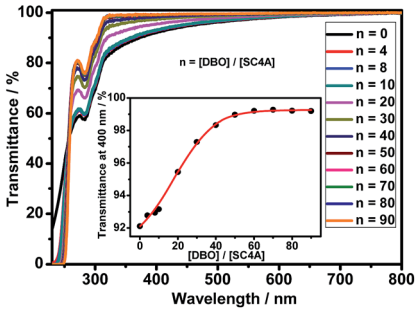

Fig. 7 Optical transmittance of the SC4A + chitosan-0.95 solution at different concentrations of DBO. Inset: dependence of the optical transmittance at 400 nm on DBO concentration with a fixed SC4A concentration of 0.02 mM. [chitosan-0.95] = 30 μg mL^{-1}.

in Fig. S7,† the optical transmittance of the SC4A + chitosan solution increased dramatically with increasing pH from acidity to alkalinity accompanied by the disassembly of the SC4A + chitosan vesicle. This process is reversible and the reversible assembly/disassembly process can be modulated repeatedly several times (Fig. 6a and S8†). The disassembly of the SC4A + chitosan vesicle under alkaline conditions is further convincingly proven by the disappearance of the Tyndall effect and DLS signal (Fig. S9†). Concurrently, no vesicle could be found in TEM and SEM images any more (Fig. 6b and c and S10†). The pH response of the vesicle is acceptable for the protonation and deprotonation of the amine groups in chitosan under acidic and alkaline conditions. Alternatively, the SC4A + chitosan vesicle can also be disrupted by adding a competitive guest, 1,4-diazabicyclo[2.2.2]octane (DBO) (Fig. 7 and S11†). Although the binding affinity of SC4A with DBO is high up to 10^7 M^{-1},[10] 50 equiv. DBO is still required to fully disrupt the vesicle, which further confirms the strong electrostatic interactions between SC4A and chitosan. It is in well accordance with the result reported by Nau *et al.* that SC4A forms an extremely stable complex with the polycationic protamine (1.24×10^9 M^{-1}).[16]

The previously reported SC4A-based supra-amphiphilic aggregates disassembled upon increasing temperature because both the host–guest complexation and assembly are driven by an enthalpy term.[5,7] However, we surprisingly found that the optical transmittance of the SC4A + chitosan solution remained unchanged with temperature increasing from 10 to 30 °C and then decreased sharply with further increase in temperature (Fig. 8a and S12a†). DLS results show that the diameters of the resulting nanoparticles at a higher temperature (55 °C) are larger (Fig. 8b and S12b†): from 406 nm to 625 nm for SC4A + chitosan-0.95; from 293 nm to 424 nm for SC4A + chitosan-0.6, which results in the decrease of the optical transmittance of the SC4A + chitosan solution with increasing temperature. SEM and TEM images show that the larger SC4A + chitosan nanoparticles at a higher temperature are also vesicles (Fig. S12c and d†). Interestingly, SEM and TEM images show the ellipsoid-like morphology and cross-link between spheres (Fig. 8c and d). We therefore infer that a vesicle fusion process occurred upon increasing temperature.[17] For the abnormal temperature-response, one possible explanation is that the complexation between SC4A and chitosan is entropy-driven, accompanied by an unfavorable enthalpy term. According to the Van't Hoff equation, increasing temperature is favorable for the system with positive enthalpy change to form a more stable assembly. The entropy-driven complexation, accompanied by a positive enthalpy change, is not rare in SC4A cases, originating from the extensive desolvation effect of charged residues involved in electrostatic interactions.[18] However, we did not obtain valuable information from the calorimetric measurement under the present assembly conditions, where the concentrations of SC4A and chitosan were too low to generate an appreciable heat effect. On the other hand, increasing temperature favors the vesicle fusion, resembling the membrane fusion process.[19]

Control experiments showed that this temperature response was not observed for chitosan itself. Furthermore, increasing the concentration of nanoparticles could lead to a much more

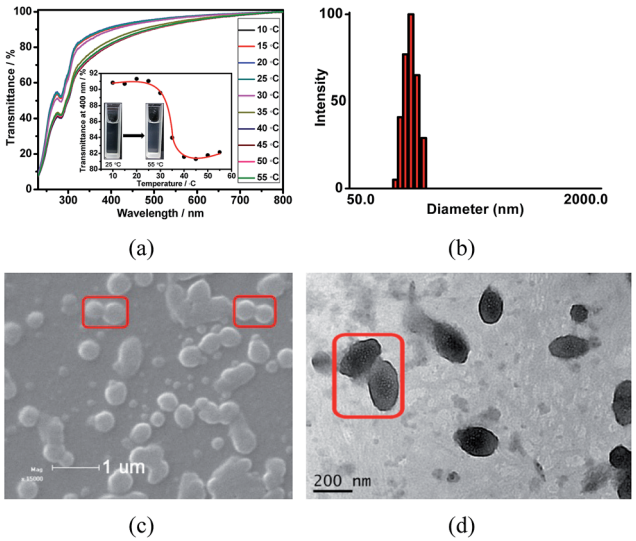

Fig. 8 (a) Optical transmittance of the SC4A + chitosan-0.95 assembly with temperature increasing from 10 to 55 °C. Inset: dependence of the optical transmittance at 400 nm on temperature, and the corresponding turbidity photos at 25 and 55 °C. DLS data (b), SEM (c), and high-resolution TEM (d) images of the SC4A + chitosan assembly at 55 °C. [SC4A] = 0.02 mM, [chitosan-0.95] = 30 μg mL^{-1}.

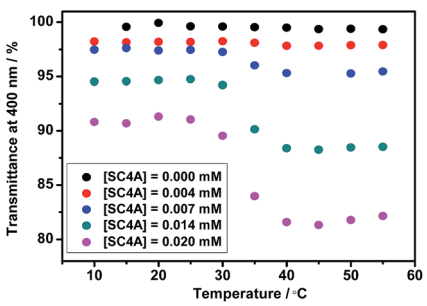

Fig. 9 Dependence of the optical transmittance at 400 nm on temperature in the presence of different concentrations of SC4A with a fixed chitosan-0.95 concentration of 30 μg mL^{-1}.

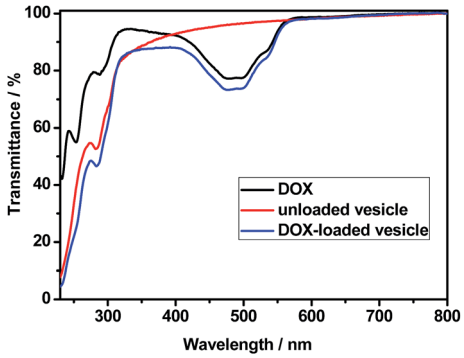

Fig. 10 Optical transmittances of DOX, unloaded vesicles, DOX-loaded vesicle at 25 °C in aqueous solution at pH 5.3. [SC4A] = 0.02 mM, [chitosan-0.95] = 30 μg mL^{-1}.

effective temperature response (Fig. 9 and S13†). This also supports the above experimental results and discussion well.

Loading of drug molecules by the vesicle and its stability

According to the multistimuli-responsive character of binary SC4A + chitosan vesicles, we selected doxorubicin hydrochloride (DOX), one kind of water-soluble fluorescence dye and anticancer drug molecule, as a model molecule to investigate its capability of entrapment and stability after loading. DOX was encapsulated into supramolecular vesicles using a previously established encapsulation method.[5] In comparison with that of the unloaded vesicle, the transmittance of the DOX-loaded vesicle becomes much stronger within the wavelength range of 400 to 550 nm (Fig. 10 and S14†), attributing to the characteristic absorption of DOX. Furthermore, we carried out the dialysis experiments of DOX-loaded vesicles with and without DBO, and compared the fluorescence intensity of DOX outside the dialysis bag. As shown in Fig. S15,† without DBO, the fluorescence intensity of DOX outside the dialysis bag showed a very little change within 1 h, indicating that the DOX-loaded vesicles are highly stable toward leakage at room temperature. However, the fluorescence intensity of DOX outside the dialysis bag significantly enhanced when treating the vesicles with DBO, demonstrating that the DOX-loaded vesicle could be disrupted by adding DBO to release DOX.

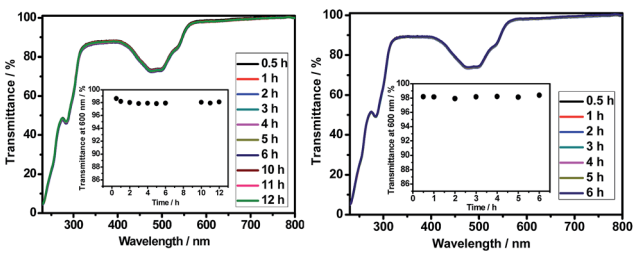

Fig. 11 (a) Optical transmittance of the SC4A + chitosan-0.95 assembly loaded with DOX at different times within 12 h at 25 °C at pH 5.3. Inset: dependence of the optical transmittance of the SC4A + chitosan-0.95 assembly loaded with DOX at 600 nm on time. (b) Optical transmittance of the SC4A + chitosan-0.6 assembly loaded with DOX at different times within 6 h at 25 °C at pH 5.3. Inset: dependence of the optical transmittance of the SC4A + chitosan-0.6 assembly loaded with DOX at 600 nm on time.

Then, we compared the stability of the resulting DOX-loaded polymeric supra-amphiphiles constructed between SC4A and chitosan with different deacetylation degrees. As shown in Fig. 11a, the optical transmittance of the SC4A + chitosan-0.95 vesicle showed no changes after loading DOX over 12 h at room temperature, and a similar phenomenon was also observed in the case of the DOX-loaded SC4A + chitosan-0.6 vesicle (Fig. 11b). These results convincingly indicate that the loading of DOX could not affect the stability of the supramolecular polymeric vesicle.

Conclusions

In conclusion, supramolecular polymeric vesicles were constructed by the complexation of SC4A and chitosan. Chitosan with a higher deacetylation degree can form a more stable assembly with SC4A because it can afford stronger multivalent electrostatic interactions with SC4A. These obtained vesicles exhibit multistimuli responsiveness, disassembled by increasing pH or adding a competitive guest. An unusual temperature-response was observed that the vesicles were capable of fusing around human physiological temperature. In addition, we successfully loaded DOX in vesicles and the loading of DOX could not affect the stability of the supramolecular polymeric vesicle. The present supra-amphiphilic assembly promises potential applications in the biomedical field such as controlled release and tissue engineering.

Acknowledgements

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