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Vesicle aggregation in aqueous mixtures of negatively charged polyelectrolyte and conventional cationic surfactant

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Abstract

Vesicle aggregation induced by different environmental factors, including the addition of divalent metal ions, decrease of pH, and increase of temperature—was investigated through turbidity measurement, fluorescence measurement, and transmission electron microscope observation in aqueous solutions of hydrolyzed styrene–maleic anhydride copolymer (HSMA) mixed with dodecyltriethylammonium bromide ($C_{12}Et_3$). The vesicle aggregation can be explained by the dehydration of the vesicle surface through cations addition or temperature increase based on an analysis of the interaction between vesicles. Moreover, the steric repulsion was introduced to the system and the control of vesicle aggregation was achieved.

Keywords: Vesicle; Aggregation; Dehydration; Steric repulsion

1. Introduction

Vesicles have been widely used as models for cell membranes, drug delivery systems and microreactors [1–3]. Generally, different function relies on different properties of vesicles. For example, it is desirable for vesicles to be stable when they are used as templates [4], while vesicle aggregation and fusion are usually beneficial to the release of entrapped drugs [5]. However, the properties of vesicles in aqueous solution were often affected by the variation of environmental factors. Hence, prediction and control of the vesicle stability, especially against aggregation or fusion are necessary for applications of vesicles.

Vesicle aggregation can be induced by several ways such as addition of salts [6–16] or polymer [17–19], variation of pH [20] or temperature [21,22]. The mechanism was also investigated by analyzing the interactions between two approaching vesicles [23–25]. Among them, DLVO theory was often used to describe electrostatically stabilized systems. For example, salt addition induced vesicle aggregation in dilauroylphosphatidic acid (DLPA) system [10] and pH decrease induced vesicle aggregation in a kind of glycolipid system [20] were attributed to screening of the electrostatic repulsion through addition of salt or H^+. However, this is not applicable to the aggregation of electrically neutral vesicles, especially those composed of lipid with more complicated head groups such as phosphatidylcholine (PC) [7]. Considering that vesicles are more complex than rigid particles, some other interactions such as hydration force should be taken into account in a more rational explanation [11–14]. Webb and coworkers [13] found that salt can induce the reversible aggregation of DGDG vesicles and explained the phenomenon by a reduction of hydration repulsion due to salt induced surface dehydration. Inoue et al. [7,14] also thought that PC liposome aggregation induced by cations was a result of the hydration shell destruction by the hydrolysis of the cations.

In recent years, vesicles formed in mixtures of cationic and anionic surfactant have attracted much attention due to their peculiar advantages such as spontaneous vesicle formation and high time stability [26–28]. In these systems, vesicle composition was considered to be more close to 1/1 than that in the

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bulk solution [29], implying that the electrostatic repulsion is weaker than that in single composition systems. Besides, the combination of cationic and anionic headgroups is similar to zwitterions, and therefore the existence of dipole moment on the vesicles surface makes the interaction between the vesicles and water more complicated [30]. Vesicles aggregation occurs frequently in such systems, however, compared with liposome systems, investigations of vesicle aggregation and fusion in synthetic surfactant system were rather scarce [6,21,22]. Thus further systematic studies of environmental factors induced vesicle aggregation are necessary to understand how the factors work and to control the aggregation. In our previous paper [31], vesicle formation and stability against some environmental factors including aging, addition of NaBr and ethanol were investigated in systems of hydrolyzed styrene–maleic anhydride copolymer mixed with conventional cationic surfactant. It was found that vesicles can form spontaneously in this kind of systems and show super time stability, which is very similar to that in mixtures of cationic and anionic surfactants. What was superior to catanionic vesicles is that these vesicles can resist more concentrated NaBr. Recently, we found that these vesicles are sensitive to some other factors. Addition of divalent cation, decrease of pH, and increase of temperature can induce vesicle aggregation. In this paper, the vesicle aggregation induced by these environmental factors was systematically investigated for a better understanding of the vesicle properties in such systems and mechanism of general vesicle aggregation.

2. Experimental

2.1. Materials

Styrene–maleic anhydride copolymer (CAS 26762-29-8) was purchased from Aldrich Co. The molecular weight and polydispersity were $M_n = 1600$ and $M_w/M_n = 2.1$. The carboxyl content after hydrolysis in the polymer was determined through potentiometric titration described previously [31]. *n*-Dodecyltriethylammonium bromide ($C_{12}Et_3$) and *n*-dodecyltributylammonium bromide ($C_{12}Bu_3$) were prepared by reaction of *n*-dodecyl bromide and triethylamine or tributylamine. The crude product was recrystallized five times from mixed solvents of ethanol–acetone or ether–acetone. The purity of the surfactant was examined, and no surface tension minimum was found in the surface tension curve. *N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-1,2-dihexadecanoyl-sn-glycero-3-phosphoethanolamine, triethylammonium salt (NBD-PE) and Lissamine™ rhodamine B 1,2-dihexadecanoyl-sn-glycero-3-phosphoethanolamine, triethylammonium salt (Rh-PE) were purchased form Invitrogen Molecular Probe Co. The water used was redistilled from potassium permanganate. Other reagents were products of A.R. Grade of Beijing Chemical Co.

2.2. Polyelectrolyte solution

The stock solution of hydrolyzed styrene–maleic anhydride copolymer (HSMA) was prepared by mixing the styrene–maleic anhydride copolymer powder, the required amount of sodium hydroxide, and buffer solution (0.01 M $Na_2B_4O_7 \cdot 10H_2O$, pH 9.2) to yield a 200 mM solution (the concentration refers to the content of carboxyl groups). The mixture was stirred and heated to 90 °C in a water bath for 2 h. HSMA solutions of lower concentrations were obtained by diluting the stock solution with buffer solution.

2.3. Preparation of samples

Surfactant solutions were obtained by dissolving the corresponding surfactant with buffer solution. The samples were prepared by directly mixing the HSMA solution and the cationic surfactant solution. c_T is the total result containing the concentration of the carboxyl content of HSMA and the concentration of cationic surfactants. The molar ratio of the mixture is defined as HSMA/surfactant $= n(\text{HSMA})/n(\text{surfactant})$. For divalent cation induced vesicle aggregation, the concentrated solutions (0.2 or 0.1 M) of alkaline earth nitrate were obtained by dissolving the corresponding alkaline earth nitrate in buffer solution (0.01 M $Na_2B_4O_7 \cdot 10H_2O$, pH 9.2) except $Ba(NO_3)_2$ which dissolved in water. The pH of the vesicle system did not change after adding a small amount of these salt solutions (Fig. S1 in the supplementary material). For pH induced vesicle aggregation part, the pH was adjusted by addition of concentrated HBr (2 M) or NaOH (2 M) solution.

2.4. Turbidity measurement

Turbidity measurements were carried out with a TU-1810 spectrophotometer (PGENERAL, China) at 500 nm. The temperature of turbidity measurement was controlled by an external thermostatic. The absorbance was recorded 2 min after changing the ion concentration or pH in the experiments of divalent cation and pH induced vesicle aggregation. For temperature induced vesicle aggregation, the absorbance was measured 20 min after changing the temperature while the absorbance leveled off.

2.5. Transmission electron microscopy (TEM)

TEM micrographs were obtained with a JEM-100CX II transmission electron microscope (working voltage of 80–100 kV). Samples for TEM were prepared by the negative-staining technique with uranyl acetate solution (1%) as the staining agent. One drop of the solution was placed onto a carbon Formvar-coated copper grid (230 mesh). Filter paper was employed to suck away the excess liquid. Then one drop of the staining agent was placed onto the copper grid. The excess liquid was also sucked away by filter paper.

2.6. Fluorescence probe experiment

The fluorescence resonance energy transfer (FRET) form NBD-PE to Rh-PE was measured using a Hitachi F4500 spectrofluorometer equipped with a thermostated cell holder. The temperature of fluorescence measurement was controlled by an external thermostatic. Both of the two probes were introduced

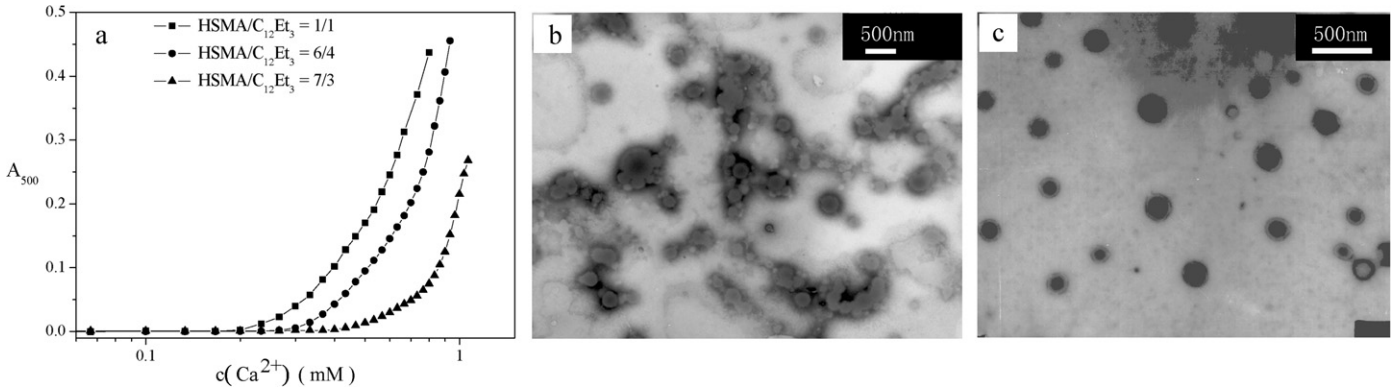

Fig. 1. Turbidity variation (a) caused by the addition of Ca^{2+} to the solution of HSMA/$C_{12}Et_3$ ($c_T = 3$ mM, pH 9.2, 25 °C) and TEM micrographs (b, c) of the solution of HSMA/$C_{12}Et_3$ ($c_T = 3$ mM, HSMA/$C_{12}Et_3$ = 1/1, pH 9.2, 25 °C) system. (b) After adding 0.4 mM Ca^{2+}; (c) after adding 0.4 mM Ca^{2+} and 0.8 mM EDTA.

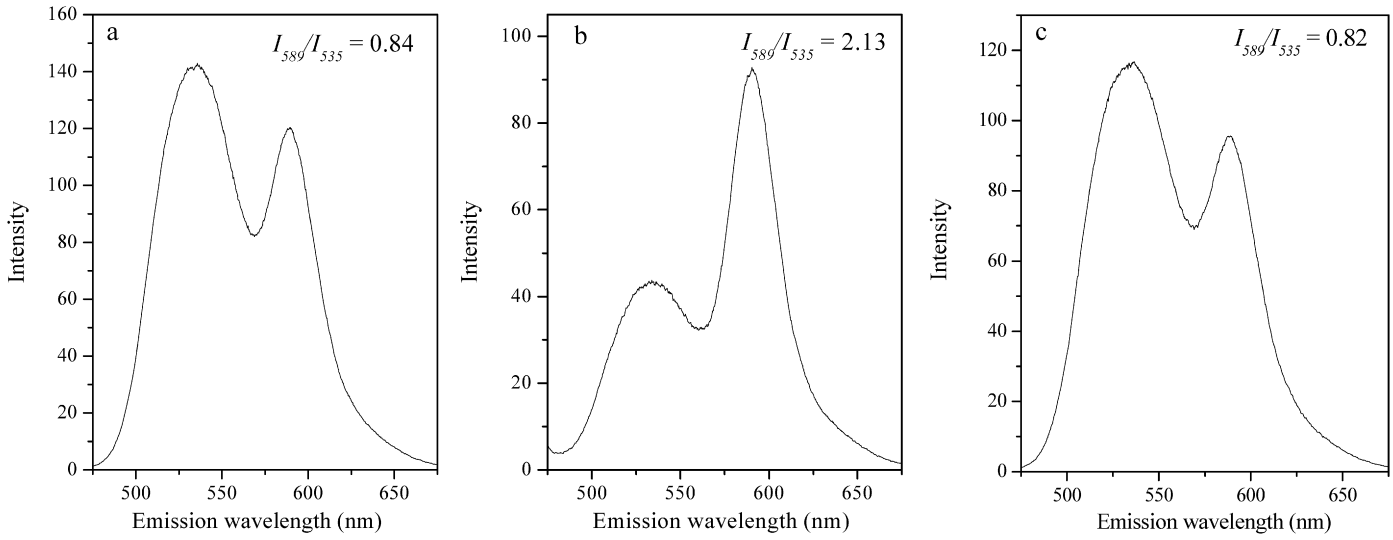

Fig. 2. FRET results of the system of HSMA/$C_{12}Et_3$ ($c_T = 3$ mM, HSMA/$C_{12}Et_3$ = 1/1, pH 9.2, 25 °C): (a) without additive; (b) after adding 0.4 mM Ca^{2+}; (c) after adding 0.4 mM Ca^{2+} and 0.8 mM EDTA.

to a vesicle system. The probe/surfactant molar ratio was 0.6%. The emission spectrum was recorded in the range 475–700 nm at the excitation wavelength of 465 nm. The emission intensity ratio of I_{589}/I_{535} was used to estimate the efficiency of FRET.

2.7. ζ potential

ζ potentials were measured using a temperature-controlled zeta potential analyzer (Brookhaven Instruments Ltd.).

3. Results and discussion

3.1. Polyvalent metal-ion induced vesicle aggregation

At 25 °C, the solution of HSMA/$C_{12}Et_3$ (c_T = 3 mM, HSMA/$C_{12}Et_3$ = 1/1, pH 9.2) is clear. TEM and DLS experiment demonstrated the existence of vesicles with a diameter of 50–200 nm [31]. After the addition of Ca^{2+}, the turbidity of the system increased (Fig. 1a). In the control experiment, Ca^{2+} was added to 1.5 mM HSMA solution and no turbidity change was observed. This indicated that the turbidity increase in HSMA/$C_{12}Et_3$ system after the addition of Ca^{2+} was not due to the decrease of HSMA solubility in the presence of Ca^{2+}. TEM observation showed that vesicle aggregation occurred (Fig. 1b) here.

Vesicle aggregation was confirmed by fluorescence resonance energy transfer (FRET). Experiment as FRET is one of the most effective methods to monitor vesicle aggregation. As an appropriate fluorescence donor/accepter pair, NBD-PE/Rh-PE [32] was introduced to HSMA/$C_{12}Et_3$ system to testify vesicle aggregation (Fig. 2). From Fig. 2, it was found that when 0.4 mM Ca^{2+} was added to the system, the efficiency of the FRET increased (I_{589}/I_{535} changed from 0.84 to 2.13) due to the increase of local density of the two probes. Unfortunately, this method can not distinguish between vesicle aggregation and fusion in this system, which may be attributed to the fast molecular exchange between vesicle and the bulk solution.

Ca^{2+} induced vesicle aggregation was also observed in HSMA/$C_{12}Et_3$ system in other concentration and mixed ratios. The turbidity variation with the addition of Ca^{2+} to different systems was plotted in Fig. 1a. It was obvious that the more the

Table 1
ζ potential of the HSMA/$C_{12}Et_3$ system ($c_T = 3$ mM, HSMA/$C_{12}Et_3$ = 6/4, pH 9.2) after adding different amount of Ca^{2+}

$c(Ca^{2+})$ (mM)	ζ potential (mV)	$c(Ca^{2+})$ (mM)	ζ potential (mV)
0	−29.9	0.3	−27.6
0.1	−29.3	0.4	−25.7
0.2	−29.3		

concentration of the HSMA, the more Ca^{2+} needed for vesicle aggregation.

In order to check the reversibility of the aggregation, ethylenediaminetetraacetic acid disodium salt (EDTA) with twice the concentration of Ca^{2+} was added to the suspension 2 min after the addition of Ca^{2+} to chelate all the Ca^{2+}. We found that the turbidity went back to the original value. TEM observation (Fig. 1c) confirmed that aggregated vesicles were dispersed again. And FRET efficiency (Fig. 2c) also went back to 0.82. All the results showed that the Ca^{2+} induced vesicle aggregation can be reversed by the addition of EDTA. Further experiments revealed that the aging of aggregated vesicles had little effect on the reversibility, at least within 72 h.

Addition of salt will screen the intra- or inter-aggregate electrostatic repulsion, which leads to larger aggregates or flocculation [33,34]. Many reports described vesicle aggregation through classical DLVO theory which explained that the electrostatic double-layer repulsion was screened by addition of salt [9,10]. Therefore ζ potential was measured in HSMA/$C_{12}Et_3$ system with various concentrations of Ca^{2+} (Table 1). It was worth attention that the ζ potential of the vesicles changed only slightly after the addition of Ca^{2+}. When the aggregation occurred, the ζ potential changed for merely 4 mV. The slight decrease of ζ potential indicated that the electrostatic repulsion varied little. Considering that the original ζ potential of the vesicles is small, it can be inferred that these vesicles are not electrostatically stabilized. Hence the Ca^{2+} induced vesicle aggregation cannot be simply explained by the DLVO theory. Some other factors should be involved in the process of the vesicle aggregation.

The efficiency of different divalent cations for vesicle aggregation was examined in HSMA/$C_{12}Et_3$ system (Fig. 3). It was obvious from Fig. 3 that the aggregation was strongly dependent on the ionic properties. Comparing the radius of the divalent metal ions (Table S1 in the supplemental material) [35], we can see that the ability for vesicle aggregation will increase with the decrease of the hydrated radius in the sequence of: $Ba^{2+} > Sr^{2+} \approx Ca^{2+} > Mg^{2+}$. The most effective cation has small hydrated and large crystal radius, while the least effective one has large hydrated and small crystal radius. It is known that the size of the ion affects their concentration in the vesicle diffusion layer: The greater the hydration volume of the ion, the lower the ion concentration in the diffusion layer [36]. And ions binding to the vesicle surface are expected to compete with water for the vesicle surface and destroy the water structure around them. As a result the hydration repulsion should be reduced and vesicle aggregation was promoted. Similar results were also observed in DGDG system [13], in which the structure-breaking ions

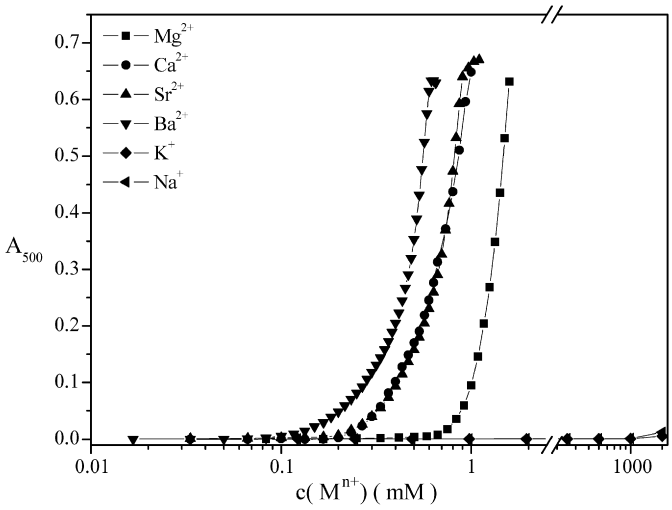

Fig. 3. Turbidity variation caused by the addition of different cations to HSMA/$C_{12}Et_3$ ($c_T = 3$ mM, HSMA/$C_{12}Et_3$ = 1/1, pH 9.2) system.

were also the most effective in promoting vesicle aggregation. Besides, it was found in HSMA/$C_{12}Et_3$ system that monovalent cations with the same or bigger ionic strength cannot induce vesicle aggregation (Fig. 3), which might be due to the different binding capability of monovalent and divalent cations.

It was reported that the hydration force between vesicles was affected by the hydrophobicity of the vesicle surface [11]. The repulsive hydration force will decrease with the increase of surface hydrophobicity. Thus, if the vesicle surface is more hydrophobic in HSMA/cationic surfactant systems, the hydration repulsion will be weaker and the divalent cation induced vesicle aggregation will occur more easily. Based on this consideration, the effect of surface hydrophobicity on Ca^{2+} induced vesicle aggregation was investigated in HSMA/cationic surfactant systems. The hydrophobicity of the vesicles surface was adjusted by replacing partial $C_{12}Et_3$ to $C_{12}Bu_3$ and the results was shown in Fig. 4. As expected, when 10% $C_{12}Et_3$ was re-

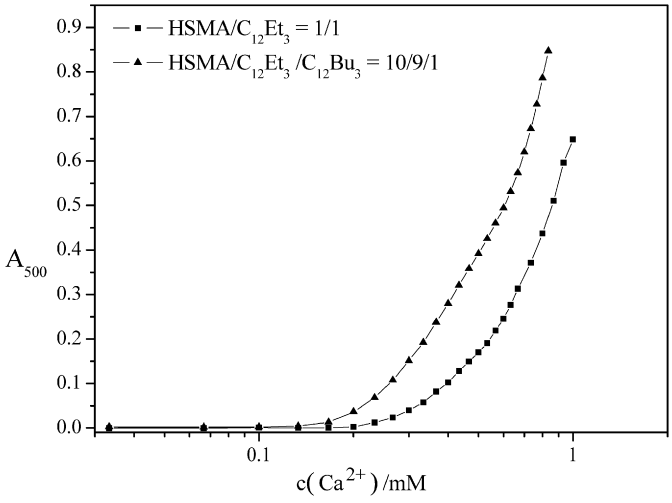

Fig. 4. Turbidity variation caused by the addition of Ca^{2+} to HSMA/$C_{12}Et_3$ ($c_T = 3$ mM, HSMA/$C_{12}Et_3$ = 1/1, pH 9.2) and HSMA/$C_{12}Et_3$/$C_{12}Bu_3$ ($c_T = 3$ mM, HSMA/$C_{12}Et_3$/$C_{12}Bu_3$ = 10/9/1, pH 9.2) systems.

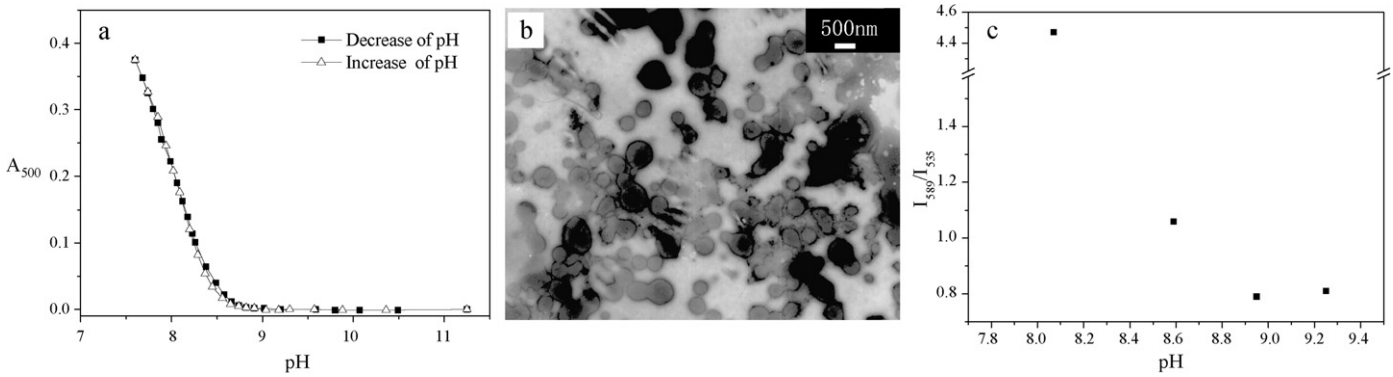

Fig. 5. Vesicle aggregation caused by the variation of pH of HSMA/$C_{12}Et_3$ ($c_T = 3$ mM, HSMA/$C_{12}Et_3$ = 1/1) system: (a) turbidity curve; (b) TEM image at pH 8; (c) FRET results.

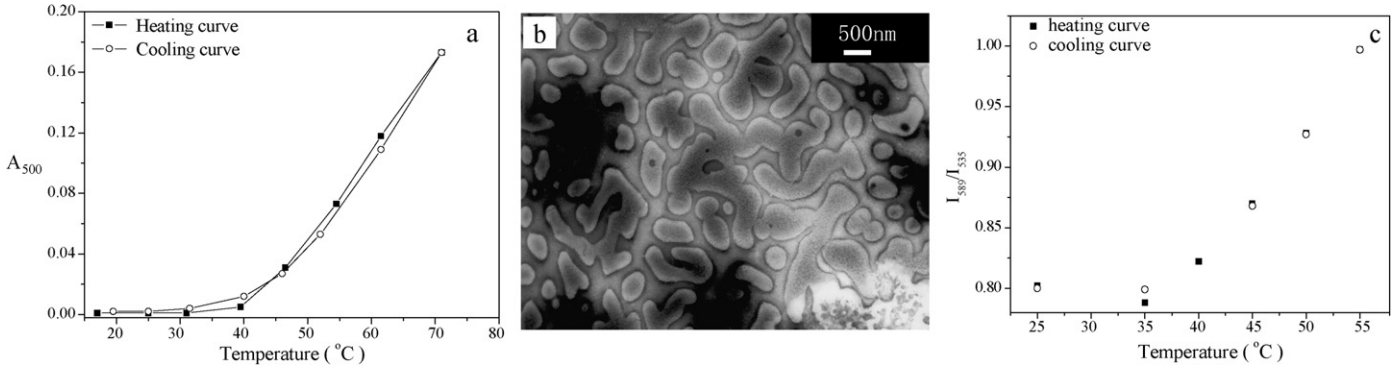

Fig. 6. Vesicle aggregation caused by increase of temperature in HSMA/$C_{12}Et_3$ ($c_T = 3$ mM, HSMA/$C_{12}Et_3$ = 1/1, pH 9.2) system: (a) turbidity curve; (b) TEM image at 60 °C; (c) FRET results.

placed by $C_{12}Bu_3$, the vesicle aggregation occurred at the lower Ca^{2+} concentration.

3.2. pH induced vesicle aggregation

Since HSMA is a weak acid, the following equilibrium exists in the aqueous solution of HSMA:

$$R\text{–}COO^- + H^- \rightleftarrows R\text{–}COOH.$$

Therefore, $RCOO^-$ and RCOOH coexist in the solution, and their relative concentrations will vary with pH. It is expected that decrease the solution pH will increase the concentration of R–COOH and lower the vesicle charge density. Meanwhile, the binding of H^+ to the vesicle surface will make the vesicle surface more hydrophobic and thus decrease the hydration repulsion between vesicles. So vesicle aggregation induced by pH decrease could be expected.

Fig. 5a showed turbidity variation with respect to pH variation of the HSMA/$C_{12}Et_3$ ($c_T = 3$ mM, HSMA/$C_{12}Et_3$ = 1/1) system. From Fig. 5a, it was obvious that the turbidity was very low and kept constant in the area of pH $\geqslant$8.8. However, when pH decreased to 8.6, the turbidity began to increase. TEM observation revealed that vesicles existed dispersedly when pH >8.8, but aggregated when pH <8.6 (Fig. 5b). FRET also demonstrated this result (Fig. 5c). And pH decrease induced vesicle aggregation was reversible by the addition of NaOH (Fig. 5a).

3.3. Temperature induced vesicle aggregation

As is known, increase of temperature is effective to remove hydration water and decrease the hydration repulsion between colloid particles. If the hydration repulsion became so low that the total interactions changed from repulsive to attractive, the aggregation of the colloids will take place. Such effect was utilized in several micelle systems [37–40], but rarely in vesicle systems [21,22]. In HSMA/$C_{12}Et_3$ systems the influences of temperature on vesicle aggregation were investigated. It was interesting that turbidity increase with increase of temperature (Fig. 6a). Considering that each component of the system did not show turbidity variation with temperature increase, this phenomenon should be attributed to the increase of aggregate size in mixed systems. TEM observation and FRET results confirmed the vesicle aggregation and fusion then (Figs. 6b and 6c). Further investigation shows that this process is reversible when the temperature of the system was adjusted (Figs. 6a and 6c).

The effect of additives which can change water structure was also investigated in this kind of system. Urea was known as a "water-structure breaker," which can cause loss of water "structure" and facilitate the hydration of a nonpolar solute [41]. The glucose may have the opposite effect. As a "water-structure maker," it can strengthen hydrophobic interactions [42]. Thus, addition of urea or glucose should make the vesicle aggregation take place at a higher or lower temperature. As expected, glucose can promote the temperature induced vesicle aggregation

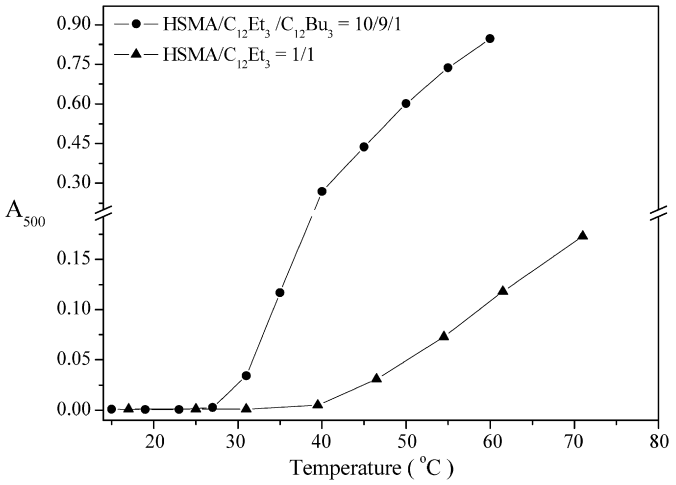

Fig. 7. Turbidity variation caused by changing temperature of the HSMA/$C_{12}Et_3$ and HSMA/$C_{12}Et_3$/$C_{12}Bu_3$ systems ($c_T = 3$ mM, pH 9.2).

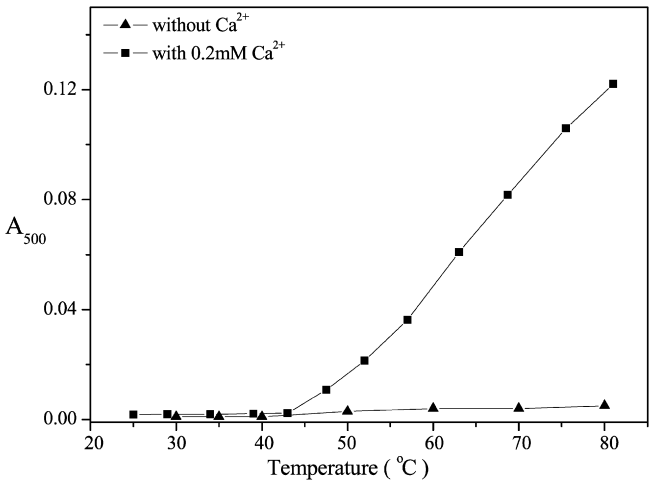

Fig. 8. Turbidity variation caused by changing temperature of the HSMA/$C_{12}Et_3$ system ($c_T = 3$ mM, HSMA/$C_{12}Et_3$ = 6/4, pH 9.2) with and without 0.2 mM Ca^{2+}.

while urea is unbeneficial to it (Fig. S2 in the supplementary material), which confirmed that the dehydration played a key role in the process of temperature induced vesicle aggregation.

Considering that the hydrophobicity of vesicle surface greatly influences the hydration force between vesicles, we investigated the effect of the surface hydrophobicity on temperature induced vesicle aggregation in HSMA/$C_{12}Et_3$ system (Fig. 7). As shown in Fig. 7, vesicle aggregation occurred at a lower temperature when 10% $C_{12}Et_3$ was replaced by $C_{12}Bu_3$ in the system of HSMA/$C_{12}Et_3$ ($c_T = 3$ mM, HSMA/$C_{12}Et_3$ = 1/1, pH 9.2), indicating that the increase in surface hydrophobicity was helpful for temperature induced vesicle aggregation. Such effect was also confirmed in mixtures of cationic and anionic surfactants. In 2005, vesicle aggregation induced by temperature increase was reported in *n*-dodecyltributylammonium bromide ($C_{12}Bu_3$)/sodium *n*-dodecylsulfate (SDS) system [21]. However, heating induced vesicle aggregation cannot occur in $C_{12}Et_3$/SDS system [22]. It seems that the hydrophobicity of vesicle surface plays an important role in such phenomenon.

It was worth to point out that, the heating induced vesicle aggregation was found in mixed system of SDS and cationic surfactant only when the headgroup of the cation surfactant was tributyl [21,22]. However, aggregation can still occur in a mixture of negatively charged polyelectrolyte and positively charged surfactant when the surfactant headgroup was triethyl. The difference between the two systems should be analyzed from their structure differences. In mixture of cationic and anionic surfactants, the vesicle surface was composed of the headgroups of the two surfactants, but the hydrophobicity of the vesicle surface was mainly contributed by the hydrocarbon part of cationic surfactant headgroup [21]. However, in HSMA/$C_{12}Et_3$ system, the vesicle membrane structure is different from that in catanionic systems. The main chain of HSMA stretched on the vesicle membrane near the hydrophilic region [31]. Thus the hydrophobic main chain of HSMA would contribute extra hydrophobicity to the vesicle surface, which reinforced the hydrophobicity contributed by hydrocarbon part of cationic surfactant headgroup. So the temperature induced vesicle aggregation can occur in HSMA/cationic surfactant systems when the headgroup of the cationic surfactant is smaller than that in mixtures of cationic and anionic surfactants.

Temperature induced vesicle aggregation is also found to be sensitive to the vesicle composition. For example, when the concentration was kept 3 mM but the mixed ratio was changed from 1/1 to 6/4 or 7/3, the temperature induced vesicle aggregation cannot occur. This may be attributed to the increased charge density of the vesicle surface and corresponding strong hydration repulsion between vesicles. Considering the fact that Ca^{2+} addition can decrease the hydration force, it should be helpful to temperature induced vesicle aggregation. As expected, heating induced vesicle aggregation occurred when 0.2 mM Ca^{2+} was introduced to the system (Fig. 8) with the mixed ratio of 6/4.

3.4. Control of vesicle aggregation

As mentioned above, vesicle aggregation induced by environmental factors in HSMA/$C_{12}Et_3$ system is correlated with the concentration and mixed ratio. Thus the vesicle aggregation can be regulated by changing the composition of the mixture. Besides, introduction of steric repulsion provided another way to control vesicle aggregation.

Steric repulsion is kind of repulsion between two approaching colloids where the colloids was coated with hydrophilic polymer chain [43,44]. PEG-containing surfactant with a molecular weight range from 1000 to 5000 of PEG chain was usually used for such application [45]. In this work, a kind of nonionic surfactant Brij35 ($C_{12}EO_{23}$) was selected to regulate vesicle aggregation. The hydrophilic part of this surfactant, PEG1000, was used to provide steric repulsion. Moreover, the large hydrophilic part of Brij35 may enhance the surface hydration. Fig. 9 showed that the effect of Brij35 on vesicle aggregation in HSMA/$C_{12}Et_3$ system ($c_T = 3$ mM, HSMA/$C_{12}Et_3$ = 1/1) by turbidity measurement. These results showed that addition of Brij35 can inhibit vesicle aggregation induced by adding Ca^{2+},

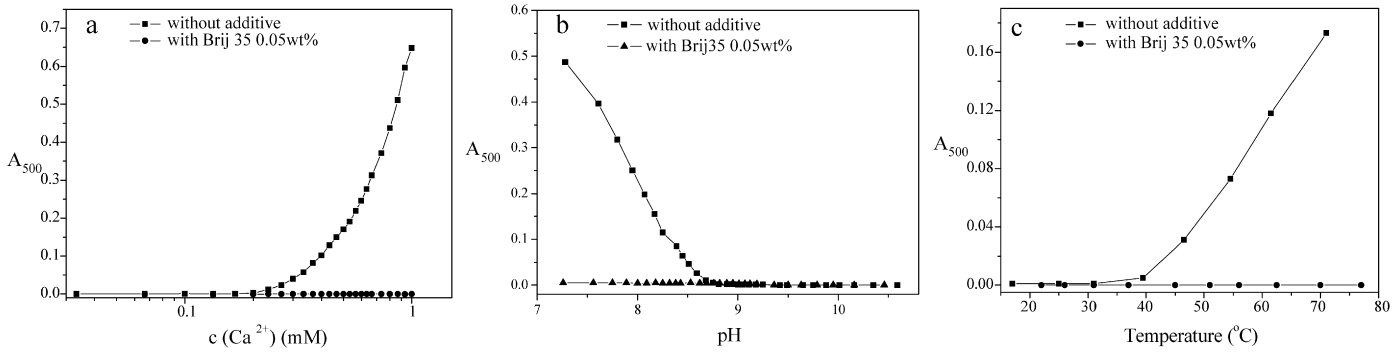

Fig. 9. Turbidity variation caused by: (a) addition of Ca^{2+}; (b) changing pH; (c) changing temperature of the HSMA/$C_{12}Et_3$ system ($c_T = 3$ mM, HSMA/$C_{12}Et_3$ = 1/1, pH 9.2) with and without Brij35.

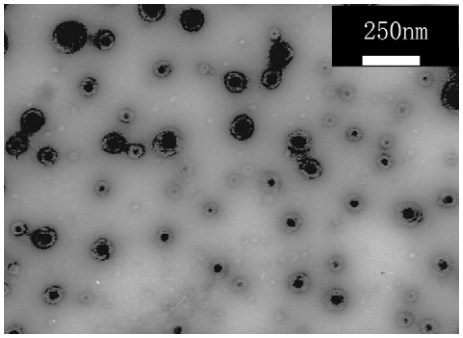

Fig. 10. TEM micrographs of the HSMA/$C_{12}Et_3$ system ($c_T = 3$ mM, HSMA/$C_{12}Et_3$ = 1/1, pH 9.2) after adding 0.05 wt% Brij35 and 0.4 mM Ca^{2+}.

decreasing pH and increasing temperature effectively. As an example, TEM image (Fig. 10) showed that the vesicles of this system were still disperse after adding 0.4 mM Ca^{2+}. This provided an effective method to control vesicle aggregation in such systems by introduction of steric repulsion.

4. Summary

A multi-factor induced vesicle aggregation was found in polyelectrolyte–surfactant system. By an analysis of the interaction between vesicles, the cause of aggregation was considered to be the decrease of hydration repulsion. Moreover, the hydrophobicity of vesicle surface had great influence on hydration force between vesicles. Steric repulsion was introduced to the system to control vesicle aggregation, and vesicle aggregation was inhibited successfully. We hope this work may advance the understanding of vesicle stability against aggregation and promote the application of vesicles in related fields.

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Supplementary material

The online version of this article contains additional supplementary material.

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