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ORIGINAL CONTRIBUTION

Thermal-responsive self-healing hydrogel based on hydrophobically modified chitosan and vesicle

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Abstract High-performance polymer materials with stimulus-responsive, self-healing and controllable features are expected to have diverse applications. In this paper, we report a novel, thermal-switchable self-healing hydrogel which can be obtained simply by mixing the hydrophobically modified chitosan (hm-chitosan) with the thermal-responsive vesicle composed of 5-methyl salicylic acid (5mS) and dodecyltrimethylammonium bromide (DTAB). Temperature stimuli points to a sol–gel phase transition in the supramolecular hydrogel and such transition can be reversibly performed for several cycles. In particular, the gelation temperature can be easily controlled by varying the ratio of DTAB to 5mS. Aside from the temperature responsive ability, the original feature highlighted in this work is that such a vesicle-based hydrogel exhibits interesting self-healing feature in a matter of seconds through the autonomic reconstruction without the use of healing agent. Thus, hydrogels based on hm-chitosan and functional vesicle may have potential application in a wide range of areas.

Keywords Thermal-responsive · Self-healing · Supramolecular hydrogel · Hydrophobically modified polymer · Vesicle-to-micelle transition

Introduction

Smart polymer materials are the subject of increasing interest due to their ability to undergo desirable and reversible transitions in microstructure or macrostructure upon small changes in their environment. Recently developed smart hydrogels possessing switching, self-healing and self-oscillating features are expected to have diverse applications, such as drug delivery systems, remotely actuated, biosensors and shape memory materials [1–4]. Although lots of smart hydrogels have been constructed, it is still difficult to create multi-functional hydrogel owing to complicated designs and syntheses.

The physical cross-linked hydrogels, known as supramolecular hydrogels, have been exploited to show a promising class of functional hydrogels [5, 6]. Compared to chemically cross-linked hydrogels, supramolecular hydrogels demonstrate better reproducible feature and adaptive property. In particular, the presence of responsiveness together with self-healing within the identical hydrogel acquires increasing interest. Currently, a novel redox-responsive self-healing supramolecular hydrogel, based on the inclusion complex between the host polymer-poly(acrylic acid) (PAA) possessing β-CD, and the guest polymer-PAA modification of ferrocene (Fc), was reported by Nakahata et al. [7]. It has been shown that the redox potential can induce a reversible sol–gel phase transition and such supramolecular materials formed by host–guest interactions exhibit self-healing and self-repairing properties. Besides, He et al. [8] reported the synthesis and characterization of pH-responsive, self-healing hydrogels based on boronate–catechol complexation. The dynamic nature of the boronate ester linkages gives rise to self-healing hydrogels exhibiting high stability at alkaline pH but low stability under acidic conditions.

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Alternative to the hydrogels constructed by host–guest or boronate ester linkages, the vesicle-based hydrogels are expected to achieve the multi-functional properties as well. Unlike “hard” nanoparticles, vesicles (or liposomes) are “soft” self-assembled structures that can be essentially considered as nanocontainers with a bilayer membrane enclosing an aqueous core. For this reason, vesicles thus are of great interest within the enormous body of research due to application in the encapsulation and targeted release of drug and DNA molecules [9–11]. The association of macromolecules with membranes has proven to be an efficient means of achieving remarkable effects [12]. Research groups of Raghavan have provided a detailed explanation for the interaction between vesicle and biopolymer [11, 13, 14]. According to the study, the addition of hydrophobically modified biopolymer into the vesicle can result in a “permanent” gel [14]. Specifically, we consider one resultful method of developing functional materials is to combine the hydrophobic polymer with stimuli responsive vesicle. Responsive vesicle has been extensively studied for some potential application in biology and medicine. For example, vesicle-to-micelle transition (VMT), as well as the micelle-to-vesicle transition (MVT), is of particularly interesting for loading substances or providing a biomimetic environment. Sarrazin-Cartalas et al. [15] have ever used the MVT to prepare thermal reversible solution, and the thickening property is correlated with the vesicles which used as cross-links. Recently, Dowling et al. [16] have embedded sodium oleate (NaOA) which undergoes VMT upon pH changes within gelatin. When pH changes from 8.3 to 10, a vesicle-to-micelle transition releases hydrophilic solutes encapsulated within the vesicles into the bulk gel, and in turn these solutes can rapidly diffuse out of the gel into the external bath.

Compared to the traditional responsive vesicle composed of single special amphiphile, surfactant/hydrotrope systems providing reversible control to the formation and disruption of aggregates such as micelles and vesicles of surfactants in solution by external stimuli have attracted considerable attention [17–20]. Davies et al. [17] have found that the cetyltrimethylammonium bromide/5-methyl salicylic acid (5mS) would form unilamellar vesicles in aqueous solutions .When these vesicles are heated above a critical temperature, they transform into long, flexible wormlike micelles. A similar phenomenon has also been found that the dodecyltrimethylammonium bromide (DTAB)/5mS system could exhibit thermally responsive property as well, even if the DTAB is in a fairly low concentration (below the critical micelle concentration) [19]. Despite lots of responsive vesicles composed of surfactant and hydrotrope are being developed at a rapid pace, studies on the functional gel based on such vesicles are still relatively limited.

In this work, the thermal-responsive self-healing hydrogel was in situ prepared simply by mixing hydrophobically modified chitosan with solution composed of 5mS and DTAB. The DTAB and 5mS were selected mainly due to their ability to form thermal-responsive vesicles, which undergo VMT upon temperature increasing. Temperature can be used to cycle the sample between sol and gel state. In addition, along with the variation of the ratio of DTAB/5mS comes regular changes of the gelation temperature and the lifetime of the cross-links, due to the different stability of the vesicle. Aside from the responsive ability, particular emphasis is placed on the rapid self-healing property which has been rarely studied. A mechanism has been proposed that the vesicles play an important role for acting as multi-functional cross-linkers which associate hydrophobically modified chitosan (hm-chitosan) chains together, as well as in the process of self-healing.

Materials and methods

Materials

Chitosan, with viscosity about 50 ~ 800 mPas and degree of deacetylation about 90 %, DTAB, 5mS, and acetic acid were purchased from Sinopharm Chemical Reagent Co. Ltd. *n*-Dodecyl aldehyde was obtained from Aldrich. Sodium cyanoborohydride was received from Energy Chemical. All the materials were used as received without further purification.

Synthesis of hydrophobically modified chitosan

Hm-chitosan was synthesized by attaching C_{12} tails to the chitosan backbone via reaction with *n*-dodecyl aldehyde. The procedure follows that reported in the literature [14, 21]. Briefly, it involves the addition of *n*-dodecyl aldehyde to an acidic chitosan solution in a water/ethanol mixture, then followed by addition of sodium cyanoborohydride and reacting for 24 h. The hm-chitosan was precipitated by raising the pH and adding ethanol, and the precipitate was purified by washing with ethanol followed by deionized water. The alkylated compound was confirmed by the element analysis (Elemen-tar vario EL cube), and the acetylation and substitution degrees were further determined by ^{1}H NMR spectra, obtained from an AC400 Bruker spectrometer operating at 400 MHz (data are available in Supplementary content). ^{1}H NMR studies on the hm-chitosan have revealed that the degree of hydrophobic substitution was close to that expected from the reaction stoichiometry (2.74 %).

Sample preparation

The DTAB (14, 16, and 18 mM) and 5mS (with concentrations ranging from 8 to 24 mM) were mixed in water. For homogeneous mixing, the mixtures of DTAB and 5mS were thermally agitated at 70 °C and vortex-mixed.

The hm-chitosan was dissolved in acetic acid solution, and the concentration was recalibrated. Surfactant and polymer mixtures of desired composition were prepared by mixing the corresponding stock solutions. Samples were mildly heated at 60 °C for 2 h, followed by centrifugation to remove bubbles.

Rheological measurements

Rheological measurements were conducted to determine the sol–gel transition point on a TA AR-G2 rheometer using a cone-plate of 40 mm diameter with cone angle of 1 °C. The storage modulus (G') and loss modulus (G'') were measured as a function of the temperature at an angular frequency of 1 rad/s within a linear range of viscoelasticity. The measurement temperatures were from 20 to 70 °C.To investigate the recovery properties of the samples in response to applied shear forces, the samples were placed between the para-plate and the platform with special care to avoid evaporation of water. We used the following programmed procedure (applied shear force, expressed in terms of strain; duration in parentheses): $5\% \rightarrow (300\text{s}) \rightarrow 1000\%(120\text{s}) \rightarrow 5\%(300\text{s}) \rightarrow 1000\,\%\,(120\text{s}) \rightarrow 5\%\ (300\text{s}) \rightarrow 1000\%(120\text{s}) \rightarrow 5\%\ (300\text{s})$.

Transmittance measurements

The optical transmittance of the aqueous solution at a wavelength of 500 nm was acquired on a UNICO 2802PCS UV/visible spectrophotometer. The temperature of the cell was controlled using a circulating temperature-controlled bath with an accuracy of ±0.1 °C and monitored by an electronic thermometer. For measurements accurately, the cell holder was flushed with nitrogen each time.

ζ potential

ζ potentials were measured using a temperature-controlled ZetaSizer 2000 (Malvern Instruments Ltd.) potential analyzer.

Result and discussion

Hydrogel based on hydrophobically modified chitosan and vesicle

We perform our initial study with DTAB/5mS mixture at a fixed surfactant concentration of 16 mM with the concentration of 5mS varying from 8 to 24 mM. Similar to the results reported [19], solutions of higher 5mS concentration are rather cloudy and opaque, while for those of low 5mS concentration, they are clear and transparent. Figure 1a shows the dependence of optical transmittance for the DTAB/5mS mixed solutions as a function of the concentration of 5mS. The onset of the bluish color is indicated by the sharp decrease of optical transmittance, which provides preliminary evidence for a transition from micellar structure to vesicle aggregation. Based on the previous works, bluish color exhibited from the cloudy and opaque solution is attributed to the Tyndall effect, which is typical for solution containing large aggregates like vesicles. The vesicles appear to be stable, supported by large absolute values of ζ-potentials presented in Table. 1. Besides, heating the aqueous mixture from 20 to 45 °C also leads to the abrupt increase of optical transmittance, a fact which is interpreted as a result of VMT. Figure 1b also shows temperature-dependent changes of optical transmittance in the heating/-cooling cycle of the sample, indicating that the VMT is quite reversible in nature. The possible mechanism included in the formation of vesicle accompanied by its temperature dependence has been proposed [17, 19]. As suggested, the 5mS molecules have a strong tendency to bind to the surfactant, and thereby give rise to a shielding of the headgroup charges as well as a reduction in effective headgroup area. Thus, the molecular geometry favors the formation of low curvature aggregates (i.e., vesicles). In addition, the thermal response of the 5mS/DTAB vesicles is ascribed to the increase of solubility of 5mS in aqueous solution, which leads to the escape of 5mS from the surfactant, and thus the VMT is observed.

Once the thermal-response vesicles are introduced to the hm-chitosan solution, the formation of hydrogel is observed (photograph is showed in Fig. 2a). The resultant hydrogel composed of hm-chitosan and DTAB/5mS vesicle is mainly related to the strong hydrophobic interaction. Hydrophobic association rapidly overcomes Coulombic repulsions and the vesicle can function as multipoint cross-links in forming the supramolecular hydrogel [11, 14]. Based on previous works about vesicle-based gel, the likely structure can be demonstrated as a network of vesicles bridged by hydrophobic chains, as depicted in Fig. 2c. Here, parts of the polymer hydrophobes are shown to be embedded in vesicle bilayers, so that each polymer chain is connected to two or more vesicles. The vesicles thus act as cross-links in a polymer gel network. Meanwhile, such gel can hold its gel state for a long time. The permanence of the vesicle gel is due to the slow rate of monomer exchange between vesicle bilayers. That is, in contrast to micelles, vesicles do not break and reform frequently, so that hydrophobes can remain trapped in a given vesicle for a considerable period of time [14]. In particular, for hydrophobic interaction, research groups of Okay have prepared tough and self-healing hydrogels formed between hydrophobically modified polyacrylamide

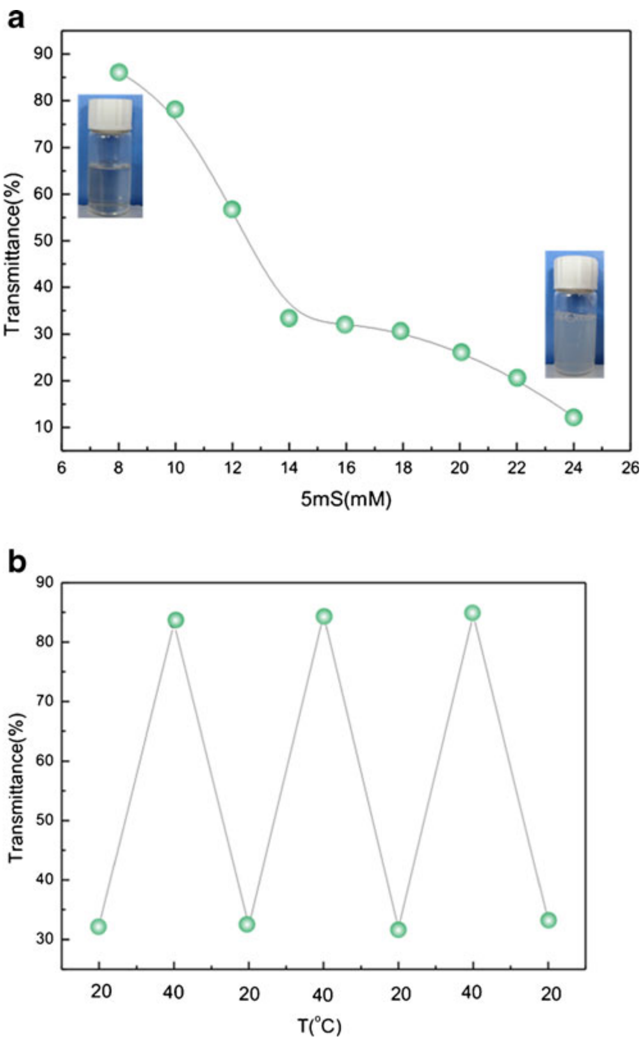

Fig. 1 Optical transmittance behavior and hydrodynamic diameter of DTAB/5mS mixtures. **a** The optical transmittance which quantifies the amount of light scattered from the sample at a fixed DTAB concentration of 16 mM and varying concentrations of 5mS (8, 10, 12,14, 16, 18, 20, 22, and 24 mM). **b** The temperature cycle of optical transmittance for DTAB/5mS aqueous mixture at a fixed DTAB/5mS concentration (16 mM/16 mM)

and sodium dodecyl sulfate (SDS) [22, 23]. Hydrophobic interaction is much stronger that the hydrophobically modified polyacrylamide can itself form tough gel at high polymer concentration without self-healing ability. Then, the additives of SDS could form wormlike micelles and present free, non-associated blocks that endow high self-healing efficiencies in C_{18} hydrogels. Note that in the case of our C_{12} hydrogel, hydrophobic interaction of hm-chitosan itself is not stronger (much lower polymer concentration, lack of amounts of intermolecular hydrophobic association, and different hydrophobe group) that vesicles form the chief cross-links, leads to the weak gels we obtain. However, the rearrangement of physical junctions (i.e., wormlike micelle, vesicle) is the primary process controlling the "self-repairing" properties of the physical network in common, which will be further discussed later.

Table. 1 The ζ potential (in millivolts) of the mixture at different mixing ratio of DTAB/5mS (mM)

DTAB/5mS (mM)	16/16	16/18	16/20	16/22	16/24
ζ-potential (mV)	71.3	74	77.9	79.3	81.4

Thermal-responsive feature

Here, we investigate the effect of temperature on the structure transition of the hm-chitosan/DTAB-5mS hydrogel. The network of hydrogel exhibits excellent stability under mild temperature, but can be readily destroyed when the temperature stimuli apply. Raising temperature would transform the hydrogel into the sol, while reverted back to the original gel state with decreasing the temperature (digital photographs of samples are presented in Fig. 2). The frequency dependency of *G*′ and *G*″ at temperatures between 15 and 55 °C for the mixture of hm-chitosan (0.4 wt%)/DTAB-5mS (16 mM/22 mM) hydrogel have been plotted in Fig. 3a. At a temperature of 15 °C, the solution exhibits gel-like structure as *G*′ is dominant over *G*″ and weakly frequency-dependent in the range studied. With the increase in temperature both dynamic moduli become frequency-dependent and have a tendency to intersect at a low frequency. Remarkably, at high temperature (55 °C), both *G*′ and *G*″ are increasing functions of frequency, and the loss modulus, *G*″, is dominant over the storage modulus, *G*′, indicative of a liquid-like response. Another way of quantifying the gel strength and gelation is to look at the phase angle, δ, given by the relation $\tan\delta = G''/G'$. The lower the value of δ, the more elastic the material, where a value of $\delta \leq 45°$ is generally indicative of a sample that has gelled while a value of $\delta \geq 45°$ corresponds to a sample in the sol state. On the basis of this criterion, phase angle, as a function of temperature for the same sample has been plotted in Fig. 3b. Clearly, at 15 °C, the solution is a gel; while at 55 °C, it is a typical sol state.

The information contained can be conveyed more visualized. Mechanism of the thermal-switchable ability has been explained by the followings: (1) VMT would occur with the enhanced temperatures at the expense of the cross-links. As mentioned earlier, the DTAB/5mS vesicles could act as the cross-links at the low temperatures, but would transform into the micelles for higher temperatures. In contrast with the vesicle, micelles have a finite lifetime that would rapidly break and reform over a timescale of milliseconds [14]. Therefore, the polymer hydrophobes would not remain embedded in a given micelle for a long period; eventually, the micelle would break and leave the hydrophobes free. Thus, the gel–sol transition can be

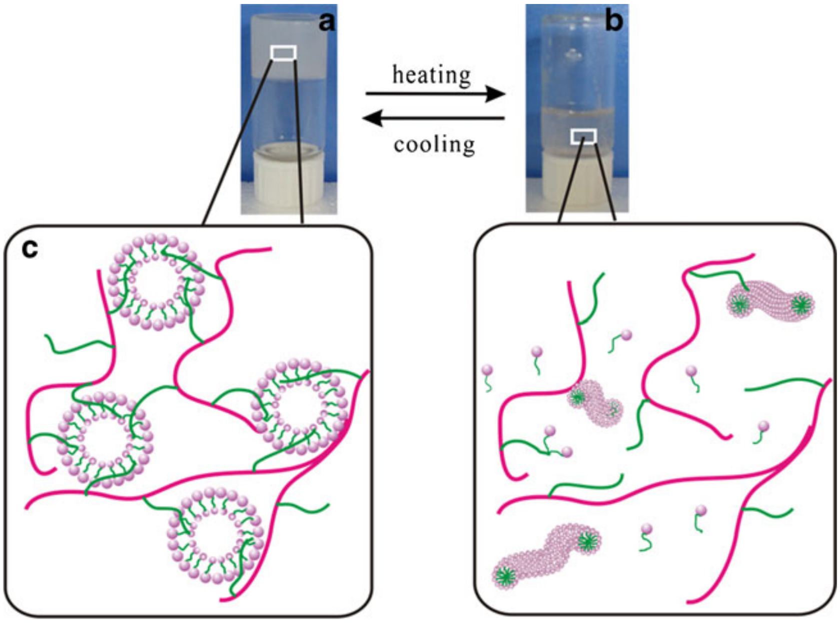

Fig. 2 Thermal-switching of the vesicle-based gel. Photographs of a sample of hm-chitosan (0.4 %) and DTAB/5mS (16 mM/20 mM) in aqueous solution: **a** before and **b** after heating. Before heating, the sample is strongly viscoelastic and holds its weight in the inverted vial. After heating at 55 °C for 10 min, the sample is transformed into a low viscosity fluid that flows easily. **c** Schematic illustration of the sol–gel transition

demonstrated as a concomitant change in the DTAB/5mS aggregates thermal response (from vesicle to micelle, as shown in Fig. 2c). (2) While the temperature decreases, since the VMT is quite reversible, cross-links quickly reform and the gel network reconstruct. As a result, a sol–gel transition is observed. (3) We should note that at the particular lower temperatures, elastic modulus of the sample becomes larger in the temperature range where VMT has not been occurred. This is attributed to the fact that, at higher temperatures, the mobility of polymer chains increase and the hydrophobe groups are prone to pulling out of liposome bilayers, provoke the solution to be more viscous behavior rather than elastic. In some cases, the strength of hydrophobic interactions is usually stronger with enhanced temperature and expected to favor the equilibrium partitioning of hydrophobes to the aggregates [15]. However, the in–out dynamics of the hydrophobes will be faster correspondingly with the increase of temperature, and such effect seems to be more prominent in our case. In other words, the vesicle gel network would decrease to some extent of the effective cross-linking density. Such interpretation coincides with that of other researchers on similar polymer/vesicle mixtures [24, 25].

From consideration of the structure of cross-links it is expected that varying the ratio of DTAB/5mS will cause a shift of the sol–gel transition of our hydrogel. Figure 4a shows storage modulus *G′* and loss modulus *G″* as a function of temperature for hydrogel containing 0.4 wt% hm-chitosan with various concentration ratio of DTAB/5mS. An important aspect with respect to the ratio of DTAB/5mS dependence of the gelation temperature is that, as the concentration of 5mS increases, so does the gelation temperature (Fig. 4b). The above change tendency of gelation temperature is supposed as a result of the stability of cross-links. It has been proposed that the structure transition temperature of DTAB/5mS vesicle depends on the solubility of 5mS in an aqueous solution and the amount of 5mS separating from the DTAB surfactant. That is to say, along with the increase of 5mS/DTAB ratio, an increase in phase transition temperature of 5mS/DTAB would be observed. Thus, the “cross-links” need higher temperature to be destroyed.

Rheological characterization

Having described the thermal-responsive behavior of our hydrogel, we now consider the rheological properties of the vesicle-based hydrogel which can provide information on the structure of the gels. Fig. 5a depicts the variations of the storage modulus (*G′*) and loss modulus (*G″*) as a function of frequency, measured in the linear viscoelastic region for hm-chitosan (0.4 wt%) and different ratio of DTAB/5mS .At 25 °C ,from the rheological spectra of *G′* and *G″* of the mixture, it can be seen that *G″* initially exceeds *G′* in lower frequency spectra or equivalently at long time scales, while in a wide higher frequency region or short time scales, the behavior is largely elastic with *G′*>*G″*, revealing that the gels have typical viscoelastic properties. As stated, permanent gels should exhibit a nonzero equilibrium modulus with strict rheological definition. Typically, solutions often considered as “gel-like” or “gels” showing a largely elastic response that its *G′* exceeds *G″* over the entire frequency range and moreover, both moduli are weakly dependent. Somewhat differently, viscoelastic gels (or solutions) often exhibit gel-like behavior at high-enough frequencies and a liquid-like behavior for low frequencies, i.e., *G′* and *G″*

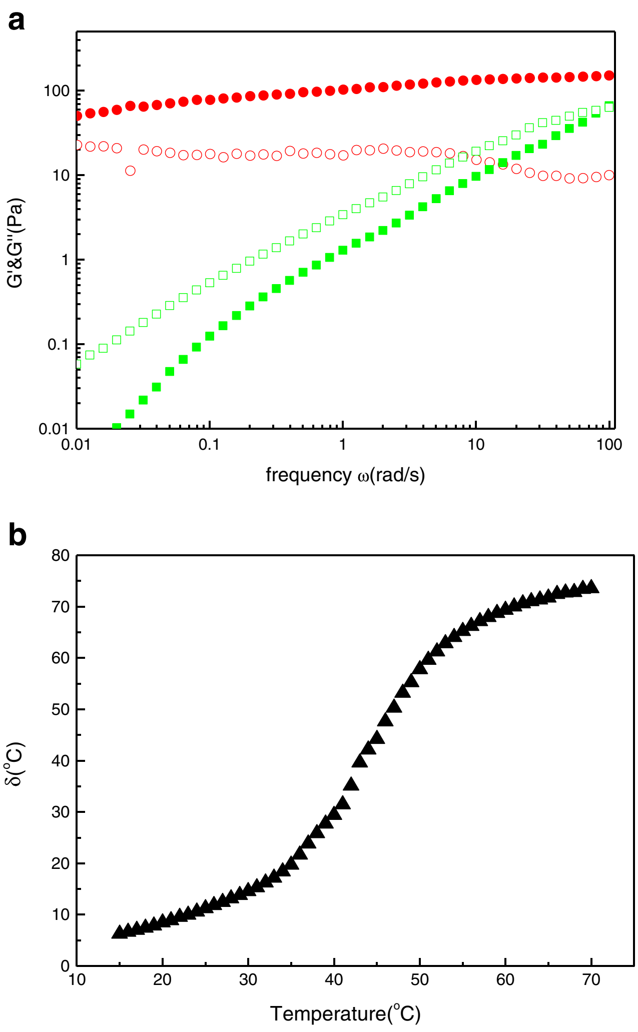

Fig. 3 **a** Linear viscoelastic moduli, $G'(\omega)$ and $G''(\omega)$, for hydrogel (0.4 % hm-chitosan, DTAB/5mS=16 mM/22 mM) at 15 °C and 55 °C; **b** Phase angle, δ, as a function of temperature for the same sample. A heating rate of about 1 °C /min was used

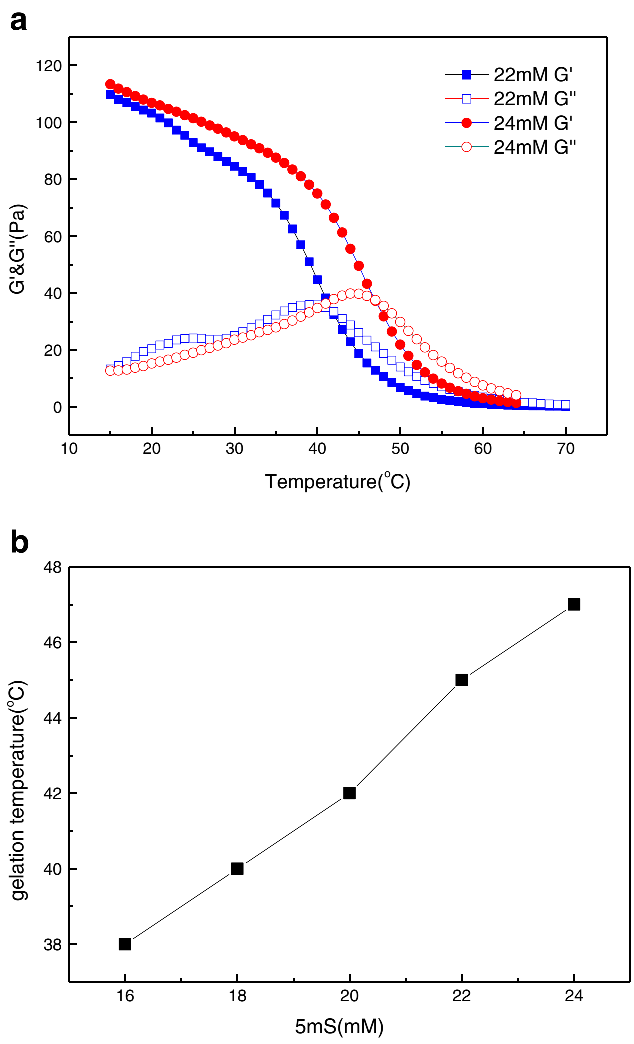

Fig. 4 Effect of the ratio of DTAB/5mS on the sol–gel transition of hydrogel. **a** Storage modulus G' and loss modulus G'' are depicted as a function of temperature for hydrogel containing 0.4 % hm-chitosan with various concentration ratio of DTAB/5mS (DTAB is fixed at 16 mM, the concentration of 5mS are 16, 18, 20, 22, and 24 mM, data of the first three concentration have been provided in support information). A heating rate of about 1 °C/min was used. **b** Dependence of sol–gel transition temperature for vesicle-based gel as a function of the 5mS concentrations

cross and show strong dependence on frequency. It should be noted that for the sample at low temperature, for instance, at 15 °C, G' exceeds G'' over the entire frequency range accessible as shown in Fig. 3a, while the same sample displays viscoelastic solution behavior at 25 °C. From consideration of the gel structure, it is expected that increasing the temperature would cause a major rearrangement of the cross-links and hydrophobes. Thus, samples display a gel-like behavior at low temperature; with increasing temperatures, they are viscoelastic gels with a gel-like behavior at high-enough frequencies and a liquid-like behavior for low frequencies.

Furthermore, the relaxation time τ(s) reflecting the lifetime of the cross-links is introduced to quantify the rheological behavior of hydrogels. The relax time can be determined by $\tau=2\pi/\omega_c$, where ω_c is the crossover angular frequency at which G' equals to G''. Through visual inspection, all the samples have passed the tube inversion test (20 °C), but gels with longer relaxation times behave increasingly elastically and have higher shape stability; noting that the type of vesicle-based network is, however, dependent on the polymer charge density, molecular weight, and hydrophobic chain length, among other parameters [25–27]. Antunes et al. [27] have ever studied the network formation of catanionic vesicles and oppositely charged polyelectrolytes, and suggested that the more long-lived cross-links occur for the more highly charged hydrophilic polymer, the number of cross-links is higher for the hydrophobically modified polymer. Similarly, in our case, the

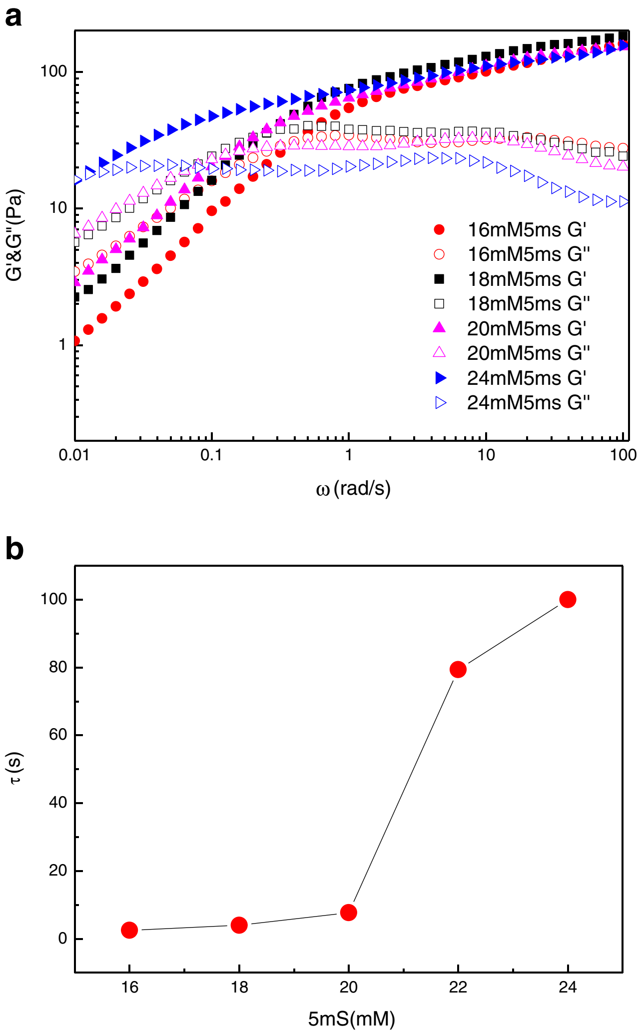

Fig. 5 Dynamic rheological study. (**a**) Storage modulus *G′* (*filled symbols*) and loss modulus *G″* (*open symbols*) as a function of frequency for 0.4 wt% solution of hm-chitosan with different concentration of 5mS (DTAB=16 mM) at 25 °C. (**b**) The relaxation time as a function of the concentration of 5mS at 25 °C, the DTAB concentration is 16 mM

behavior of hydrogel seems to be also governed by the interplay of the hydrophobic attractive interactions and the electrostatic repulsive interactions. Nevertheless, the electrostatic interaction plays a negative part. Figure 5b plots the lifetime of cross-links (τ) as a function of the concentration of 5mS at 25 °C. As shown, the lifetime of cross-link (τ) becomes longer as the concentration of 5mS increases, despite the ζ potential becoming relatively larger. Similar trends carry over to the solutions with various concentration of DTAB (14 and 18 mM, respectively) in which the lifetime of cross-links (τ) behaves as a function of the concentration of 5mS, as illustrated in Table. 2. In the case of the high concentration of 5mS, some of the relaxation times are either below the accessible frequency, characterized by a larger *G′* than *G″* in the investigated frequency range.

Table. 2 Relaxation times and ζ-potentials of hm-chitosan/DTAB-5mS systems for different concentration of DTAB and 5mS, the polymer concentration is 0.4 wt%

DTAB (mM)	5mS (mM)	ζ-potential (mV)	τ (s)
14	14	70.9	1
	16	76.9	2.22
	18	80.6	5.6
	20	82	25
	22	84.6	>100
18	18	69.6	1.25
	20	74.3	2.22
	22	79.7	26
	24	81.2	67
	26	84.4	>150

Being composed of “soft” self-assembled structures, the changes of microstructure property are expected to adjust the rheological property. Initially, it should be noted that within the concentration range, the DTAB/5mS vesicles are positive charged, in spite of the much higher concentration of 5mS. For traditional catanionic vesicle, changing the ratio of cationic and anionic surfactant is accompanied by the variation of the ζ-potentials, for example, from positive to negative [28]. However, in our case, the ζ-potential increases monotonically with increasing the concentration of 5mS. This is attributed to the fact that the 5mS, one of the hydrotropes, cannot form well-organized structures, such as micelles, but do increase the solubility of organic molecules in water by several orders of magnitude. Various hierarchically self-assembled structures such as tubes, ribbons, vesicles, and lamellar structures can be fabricated in mixtures of surfactants and hydrotropes. Thus, we can mention that unlike the catanionic vesicle composed of DTAB and SDS, the 5mS only can induce the formation of vesicle constructed by DTAB, but cannot form the particular aggregate itself. Then, as mentioned before, with increasing the concentration of 5mS, the optical transmittance decreases to a large extent as well as the increase of hydrodynamic diameter, due to the increased concentration of vesicle and formation of cluster. The slight increase of the ζ-potential is also associated with this point. Hence, an increase of 5mS concentration promotes closer surfactant aggregates and the possibility of cluster formation. This could explain the increase of the relaxation time since the cluster network is more protected against deformation [26].

Rapid self-healing study

The ability of a material to self-heal damage that occurs during use would be highly desirable for materials. Typically, responsive self-healing viscoelastic gel could be advantageous to the application in many fields owing to its flow ability, injectability and quick self-healable ability [24, 29]. Rao et al. [24].

have prepared self-assembled liposome gel from liposome and cholesterol end-capped polyethylene glycol, and such viscoelastic gel network has a fast, self-healing ability even after high deformation. The gel's fast, self-healing behavior opened the possibility to inject the gel with clinically used syringe equipped with thin needles at room temperature. Holten-Andersen et al. [29] have developed a simple method to control catechol-Fe^{3+} interpolymer cross-linking via pH. The resonance Raman signature of catechol-Fe^{3+} cross-linked viscoelastic gels at high pH displayed elastic moduli (G') that approach covalently cross-linked gels. In particular, they have described in detailed that the tris-catechol-Fe^{3+} viscoelastic cross-linked gels recovered G' and cohesiveness within minutes following failure induced by shear strain, whereas the covalently cross-linked gels did not.

Similarly as for hydrogels containing wormlike micelles or liposomes counterpart[22–24], our thermal-responsive vesicle-based viscoelastic gels could be self-healing as well; considering that the viscoelastic property of the gel, the system is viscous-dominating at low frequency, i.e., the fact that they cannot be held in one's hand or between forceps. Thus, hm-chitosan/vesicle hydrogels are subjected to strain and stress sweep tests under appropriate frequency (ω= 0.6 rad/s) monitoring the storage (G') and loss modulus (G''), respectively. As shown in Fig. 6, under small strain or stress, G' is larger than G'' (elastic-dominating), indicating that the cross-links remain unaffected and the gel network is stable. However, there is a gel–liquid transition point (strain =186 %, stress=158.5 Pa) denoted as a breakdown of the gel state to a quasi-liquid state above a threshold strain (stress). This also indicates the onset of network destruction, in which the hydrophobes of hm-chitosan are forced to pull out of vesicle bilayers under the mechanical deformation and the cross-links are considerably destroyed. Thus, under large strain or stress, the vesicle–gel network is mechanically dissociated into single liposome or small aggregates, leading to an abrupt gel–sol transition. Figure 6c shows the hydrogel under a pulse deformation program that the strain increases from 5 to 1000 % at a certain time point and then returns to 5 % after a certain period. It can be seen that the G' and G'' values are inverted under 1,000 % strain, indicating that the hm-chitosan/DTAB-5mS hydrogel is converted into the sol state. While again placed under 5 % strain, G' and G'' return to their original values within 10 s. This recovery behavior could be repeatable for at least four cycles of varying strains as we studied, indicating that the gels regain their structure quickly after shear.

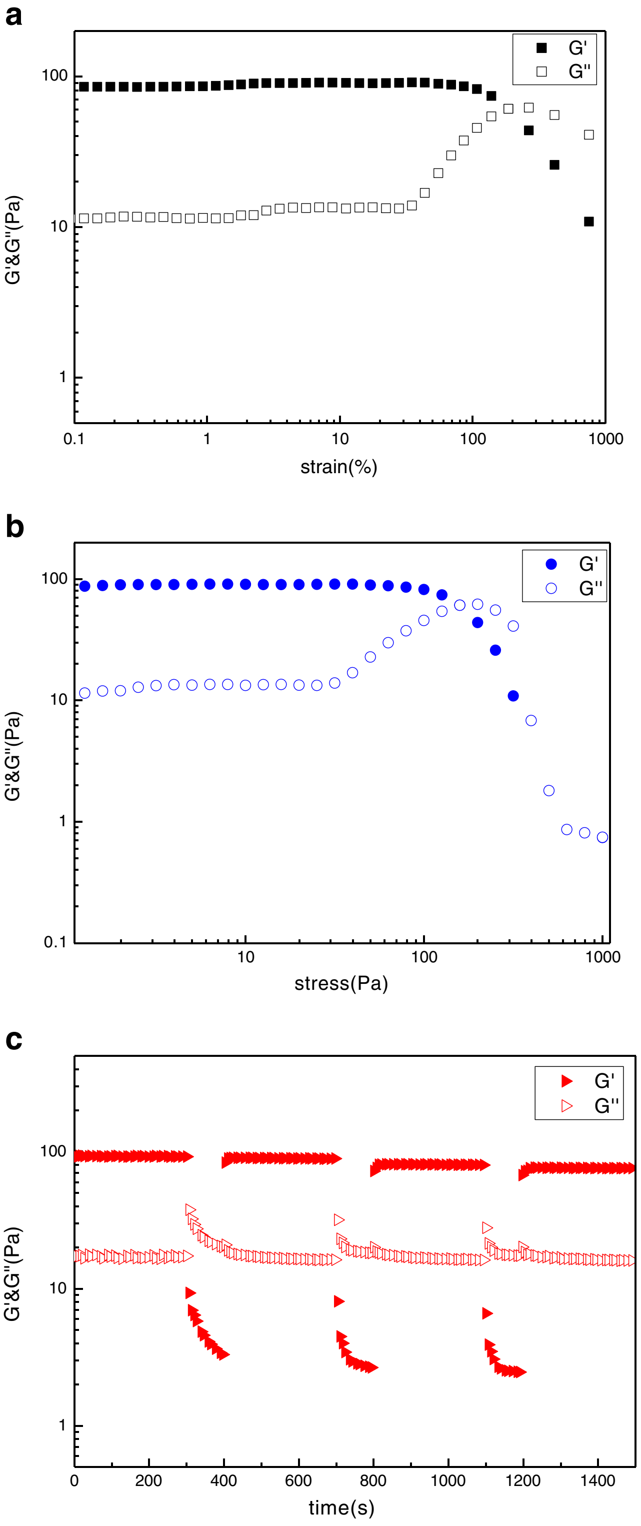

Fig. 6 Storage modulus G' and loss modulus G'' of hydrogel (0.4 % hm-chitosan, 16 mM DTAB/24 mM 5mS) as a function of **a** strain and **b** stress at 20 °C. **c** Evolution of storage G' and loss modulus G'' of hydrogel with time following two successive pulses of high deformation

The rapid self-healing capability after shear of hm-chitosan/DTAB-5mS gels may be rationalized in terms of the unique polymer/vesicle network structure. On the one hand, the characteristics of the polymer/vesicle network structure are summarized as follows: (1) neighboring vesicles are linked by a number of hydrophobic chains. Unlike the previous hydrogels reported [23, 24], vesicles are the main cross-links instead of intermolecular association of hydrophobic chains. Thus the influence of intermolecular hydrophobic associations has been weakened to a large extent in our case. (2) The interaction between polymer and vesicle is ascribed to the non-covalent bond (hydrophobic interaction). Thus here, the vesicle serves as reversible "dynamic" cross-links that hydrophobic chains can be either embedded into the bilayers of vesicle or pulled out. Furthermore, unlike the cyclodextrin inclusions or dynamic bonds (such as metal-dopa bond), vesicles can afford multi-action sites for hydrophobic interaction, indicating that the self-healing rate of such a hydrogel would be much faster. Upon destroying the hm-chitosan/DTAB-5mS gel may generate lots of unsaturated vesicles, as well as many hydrophobic chains. When the large stress applied stopped, the input of mechanic force subsides, allowing the hydrophobic chains to diffuse into each other and interact with neighboring vesicle by hydrophobic driving. Consequently, a number of new cross-links reform, and thus the gel network reconstruct. Therefore, the evolution of the self-healing of polymer/vesicle gels arises from the mutual diffusion of hydrophobic chains and their subsequent interactions with vesicle. The multi-action sites provided by vesicle accentuate the process of self-healing.

Conclusions

In the present work, a novel non-covalent thermal-switchable self-healing hydrogel was developed simply by mixing hydrophobically modified chitosan with vesicles composed of DTAB and 5mS. Hydrogel can be switched into sol state at enhanced temperature while reverted back to gel state with lowering the temperature. The sol–gel phase transitions can be reversibly performed for several cycles in a similar way of a supramolecular gel. In particular, the gelation temperature can be easily controlled by varying the ratio of DTAB to 5mS. Evaluation of the frequency dependence of the storage and loss moduli for the two systems show the average lifetime is dependent on the ratio of DTAB to 5mS with respect to the strengthening hydrophobic interaction. Of practical relevance to construct hydrogel with high-performance, vesicle-based hydrogel has also shown attractive rapid self-healing property. Mechanism has been proposed in related to the supramolecular interaction and special shape of the vesicle for the first time. Thus, our supramolecular hydrogels involved the vesicle-to-micelle transition, hydrophobic interaction, and macromolecular recognition that show multi-functional features may have general implications in the designs and preparations of the stimulus-responsive self-healing materials.

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