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Homogeneous synthesis of linoleic acid-grafted chitosan oligosaccharide in ionic liquid and its self-assembly performance in aqueous solution

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ABSTRACT: A water-soluble amphiphilic derivative of chitosan oligosaccharide (COS) modified with linoleic acid (LA)-grafted COS (LCOS) has been synthesized in the ionic liquid 1-butyl-3-methylimidazolium acetate ([BMIM]Ac). The effects of the ionic liquid on the degree of substitution (DS), surface activity, and self-assembly behavior of LCOS have been investigated. The results showed that the ionic liquid homogeneous system led to a relatively higher DS compared with the product synthesized in a traditional organic solvent. Furthermore, the LCOS synthesized in the ionic liquid had better surface activity (cmc = 1.1×10^{-4} g·mL^{-1}), and could also self-assemble into nanomicelles with better-defined spherical shape and a narrower particle size distribution (30–40 nm) in aqueous solution. These results suggest that an effective and environmentally friendly synthesis method for COS derivatives has been established and, moreover, the obtained LCOS micelles meet the basic requirements for use as an improved drug transduction vector.
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INTRODUCTION

Recently, functional polymeric nanomicelles have been widely used as transduction vector in drug delivery system, since they not only maintain the biological activities of the drug itself in the body but also introduce new desirable properties.[1] Polymeric nanomicelles are invariably composed of a hydrophobic inner core serving as a reservoir for hydrophobic drugs and a hydrophilic outer shell protecting the drug from inactivation.[2] Researchers are increasingly making great efforts to exploit ideal polymeric nanomicelles for drug delivery systems with specific characteristics. The raw materials need to be inherently biocompatible and nontoxic, and the polymeric micelles should have a uniform small size (<200 nm in diameter), which may be suitable to attain an appreciable enhanced permeability and retention (EPR) effect. The production process should also be environmentally friendly as far as possible.[3,4] Therefore, natural polymer nanomicelles have attracted much attention owing to their many favorable characteristics.

Chitosan (poly-β-1-4-*N*-glucosamine), the second most abundant natural biopolymer,[5] has attracted much attention in drug delivery system due to its favorable properties, such as biocompatibility, biodegradability and nontoxicity.[6,7] However, the insolubility of the chitosan macromolecule at physiological pH severely limits its application in drug delivery systems.[8] Therefore, much of the research in this area has been focused on water-soluble chitosan oligosaccharide (COS), a depolymerized product of chitosan, that shows good biocompatibility and excellent bioactivity.[9,10] Compared with high molecular weight chitosan, COS has better physiological characteristics. However, COS itself is neither able to form self-assembled micelles nor transfer drug molecules directly as it shows no amphiphilicity.[11] One strategy is to modify COS by forming derivatives with hydrophobic groups, such as oleic acid,[12] hexanoic acid,[13] arachidic acid,[14] and so on. These derivatives have been studied and confirmed to form polymer micelles by self-assembly in aqueous solution. To date, such hydrophobic modification processes have always been performed in conventional organic solvents (such as DMSO), which have several limitations such as limited efficiency, complex synthetic processes, long reaction times, serious corrosion, environmental pollution, and health risk to humans. These issues would restrict widespread application and large-scale production.[15,16] In this context, novel, recyclable, and green ionic liquids have

been proposed as potential alternative media to traditional organic solvents.[17,18]

Ionic liquids are molten salts with many advantageous properties, such as negligible vapor pressure, good chemical stability, nonpolluting, excellent dissolution power for organic and inorganic compounds, and ease of recovery.[19,20] Ionic liquids are able to dissolve COS by disrupting its crystalline nature and the inter- and intramolecular hydrogen bonds involving the -NH_2 and -OH groups in its backbone.[21] Ionic liquids can not only reduce dissolution times, but also function as homogeneous reaction media to improve the efficiency of organic reactions.[22,23] However, literature reports on the use of ionic liquids as reaction media for the synthesis of COS-based drug transduction vectors are scarce. This prompted us to investigate in detail the effect of ionic liquid homogeneous system on the synthesis and basic capabilities of a COS-based drug transduction vector material.

In order to achieve accurate results and obtain pure products, COS with the narrow molecular weight distribution ($\overline{M}_w = 3700$, $M_w/M_n = 1.20$) was used as the starting material, and the ionic liquid 1-butyl-3-methylimidazolium acetate ([BMIM]Ac) was used as the reaction solvent to prepare amphiphilic *N*-linoleyl COS (LCOS).[24] For comparison, the same product (LCOS) was also synthesized in a traditional organic solvent (DMSO). The chemical structures of the LCOS were characterized by ^{1}H-NMR and Fourier transform infrared (FTIR) spectroscopies. The effects of the ionic liquid on the degree of substitution (DS), surface activity, and self-assembly behavior of LCOS were studied in detail by size exclusion chromatography (SEC), surface tension, contact angle, fluorescence measurements and transmission electron microscopy (TEM). The hydrophobic model drug ibuprofen (IBU) was encapsulated within the LCOS micelles through a simple and convenient route. The results suggest that this method of preparing LCOS with an ionic liquid as solvent is very simple and reliable, and the obtained product LCOS is suitable for use as a potential drug transduction vector.

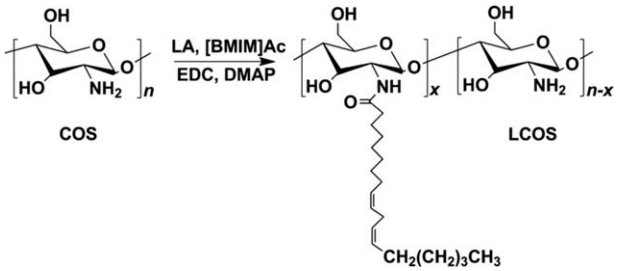
EXPERIMENTAL

Materials

COS with low degree of polymerization and narrow molecular weight distribution ($\overline{M}_w = 3700$, $M_w/M_n = 1.20$) was presented by Hainan Provincial Key Lab of Fine Chemistry. The degree of deacetylation for the COS was 95%. 1-butyl-3-methylimidazolium acetate ([BMIM]Ac, 99% purity) was purchased from Beijing HWRK Chem. *N*,*N*-Dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), ethyl acetate, 1-ethyl-3-(3-(dimethylamino)propyl) carbodiimide hydrochloride (EDC, 99%) and 4-(dimethylamino) pyridine (DMAP, 99%), linoleic acid (LA), and IBU (99%) were purchased from Sinopharm Chemical Reagent Beijing. All other commercial reagents (A.R.) were used as received without further purification and all reactions were carried out under nitrogen atmosphere.

Synthesis of LCOS

The synthetic procedure used to prepare LCOS was as follows: a mixture of COS (0.4 g) in [BMIM]Ac (5.0 g) was heated at 30°C for 30 min with stirring under nitrogen until the COS was completely dissolved. LA (0.3 g) was then added, along with DMAP (0.26 g) and EDC (0.41 g) as catalysts and the mixture was continuously stirred for 6 h at 30°C under nitrogen atmosphere. After completion of the reaction, the mixture was cooled to room temperature and anhydrous ethanol (100 mL) was added to remove the remaining DMAP and EDC. The crude product was collected by filtration. The ionic liquid [BMIM]Ac was recovered from the filtrate and the crude product was dialyzed in distilled water for 3 days in a dialysis bag (MWCO 4000). The remaining dialyzed solution was freeze-dried to obtain the pure LCOS brown powder (yield: 89%). Similarly, LCOS was also prepared in DMSO (yield: 78%). The DS, defined as the number of acyl groups per 100 sugar residues of chitosan, was determined by ^{1}H-NMR using the ratio of alkene protons ($\delta = 5.32$) to H-2 protons ($\delta = 2.71$) of chitosan and SEC. The synthetic route was presented in Scheme 1.



Scheme 1. The synthetic route of LCOS in [BMIM]Ac.

Characterization and Instrumentation

^{1}H nuclear magnetic resonance (^{1}H-NMR) spectra were obtained on a Bruker AVANCE II 400MHz spectrometer using DMSO-d_6 as solvent. The FTIR spectra were recorded on a Nicolet Nexus 470 FTIR spectrometer. The weight-average molar masses ($\overline{M}_w$) were determined through SEC equipped with an RI K-2301 refractive index detector and TSK-GEL G4000 PWXL column (30 cm × 7.5 mm) with PBS buffer solution (pH = 7.4) as mobile phase at a flow rate of 0.43 mL·min^{-1}. The $\overline{M}_w$ of the samples were obtained by chromatography workstation according to the standard curves.

Recycling and Reuse of [BMIM]Ac

After the reaction, the filtrate containing [BMIM]Ac was evaporated at 80°C under reduced pressure to leave yellow viscous liquid. The [BMIM]Ac could be recovered and reused directly in the next run for at least three times. However, the yellow color of the [BMIM]Ac gradually became deeper with increasing number of runs, which may have been due to increasing amounts of residual impurities.[23]

Preparation of Self-Assembled LCOS Micelles and Loading with IBU

The self-assembly experiment was performed as follows: LCOS (30 mg) was dissolved in distilled water (10 mL) and sonicated by a probe type sonicator for 20 min. The sonication process was repeated twice to obtain an optically clear solution. The solution was collected and diluted with distilled water to obtain a concentration of 5.0 × 10^{-3} g·mL^{-1}, which was 10 times greater than the cmc. The water-insoluble drug IBU was used as

a hydrophobic model drug, and was loaded into the LCOS micelles through the following steps: IBU (10 mg) in a beaker was dissolved in ethanol (5 mL) and the solution was added to the above aqueous solutions of LCOS, the mixture was then sonicated for 40 min.

Solubility Analysis

About 40 mg of COS and LCOS were dissolved in 2 mL of [BMIM]Ac, deionized water, PBS buffer solution (pH = 7.4), ethanol, DMF, DMSO, and ethyl acetate at room temperature, respectively. All the samples were shaken every 3 min vigorously, and then the turbidity was observed after 20 min. The test samples with clear solution were regarded as dissolving totally.

Surface Tension Measurement

The surface tension measurement of COS and LCOS aqueous solutions at various concentrations (1×10^{-5}–1×10^{-2} g·mL^{-1}) were carried out on the surface tension instrument (DCAT 11, Dataphysics, Germany) with plate method. All the solutions were kept at room temperature for 24 h before the measurement. Then, a curve based on log *c* and surface tension as abscissa and ordinate, respectively, was plotted.

Contact Angle Determination

In order to determine the surface-wetting properties of LCOS solutions, the contact angles between samples aqueous solutions and the standard polymethyl methacrylate (PMMA) plate were measured on a CAM 200 optical contact angle meter (KSV Instruments, Finland) at room temperature.

Fluorescence Measurement

The fluorescence spectra of the LCOS aqueous solutions using pyrene as a probe to analyze the self-assembly performance in aqueous solutions were measured by a Varian Cary Eclipse. During the measurement, the constant concentration of pyrene was 1×10^{-6} mol·L^{-1} and the concentration of LCOS aqueous solutions was varied from 1×10^{-5} to 5×10^{-3} g·mL^{-1}. Then, a curve based on log c and intensity ratio I_{373}/I_{392} as abscissa and ordinate, respectively, was plotted. The LCOS aqueous solutions for fluorescence measurement were prepared according to the following steps. 0.1 mL 1×10^{-4} mol·L^{-1} of pyrene/ethanol solution was taken and the solvent was removed by flowing N_2. About 10 mL LCOS solution was added and sonicated for 10 min in an ultrasonic bath and then kept at room temperature for 2 h before fluorescence measurement.[25]

TEM and Particle Size Distribution Measurements

The morphology of LCOS self-assembled micelles in aqueous solution were observed by TEM using a PHILIPS Tecnai12 electron microscope.

The size distribution of LCOS self-assembled micelles in aqueous solution was characterized with high concentrations of laser particle size analyzer BI-9000. To ensure the formation of stable self-assembled micelles, the concentration of the LCOS micelles aqueous solution used for measurement was 10 times larger than the cmc.

RESULTS AND DISCUSSION

One Possible Action Mechanism of the [BMIM]Ac on COS

LCOS was prepared by chemical modification of COS in [BMIM]Ac. The results showed that the ionic liquid homogeneous system led to a relatively higher DS compared with the product synthesized in a traditional organic solvent (DMSO). There have been many studies about the mechanism, generally considered that the efficient characteristics of ionic liquids as media are attributed to the large cations and anions. An ionic liquid can weaken the inter- and intramolecular hydrogen bonds of COS chains through its hydrogen bond acceptor properties, especially through coordination of its anions to the -NH_2 and -OH groups of COS. This interaction leads to separation of the -NH_2 and -OH groups of different COS chains, resulting in a homogeneous COS solution and facilitating interactions between the COS and external catalysts and reactants in the ionic liquid. We speculate that the ([BMIM]Ac) ionic liquid on COS has a similar action mechanism. The closest studies reported are Wang *et al.*[26] and Tan *et al.*[27]

Synthesis and Characterization of LCOS

The ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectra of COS and LCOS were shown in Figure 1(a,b), respectively. In Figure 1(a), the signals at $\delta = 4.5$ (H-1), 3.0 (H-2), 3.3–3.8 (H-3, 4, 5, 6) were corresponding to the ring protons of the COS backbones, and that at $\delta = 1.83$ can be assigned to the protons of the attached acetyl groups (-NHCOC$\underline{H}_3$). In Figure 1(b), attachment of the linoleyl moieties is confirmed by the appearance of the new signals at $\delta = 0.85$ due to the terminal methyl groups (-$(CH_2)_{10}C\underline{H}_3$), at $\delta = 1.06$–1.83, and 2.01 due to the methene protons (-$(C\underline{H}_2)_{10}CH_3$), and at $\delta = 5.32$ due to the protons of the ethylenic linkage (-$\underline{H}C{=}C\underline{H}$-). These results demonstrated that LA had been successfully grafted onto the chains of COS. The resonance intensity of the -$\underline{H}C{=}C\underline{H}$- protons varied directly with the DS, while that of H-2 remained unchanged. Therefore, the ratio $I_{\text{-HC=CH-}}/4I_{\text{H-2}}$ could be used to determine the DS of the LCOS. The DS of the LCOS synthesized in [BMIM]Ac was calculated as 37.9%.

The FTIR spectra of COS and LCOS were shown in Figure 2. The characteristic peak at 1602 cm^{-1} of COS, attributable to the N-H bending vibration in the -NH_2 group, was no longer seen in the spectrum of LCOS. New peaks at 1559 cm^{-1} (bending vibration of N-H in -CONH group), 1650 cm^{-1} (stretching vibration of C=O in -CONH group), and 3010 cm^{-1} (stretching vibration of -HC=CH-) can be seen in the spectrum of LCOS. In addition, the characteristic peaks at 2928, 2859, and 1465 cm^{-1} due to C-H stretching and C-H bending were significantly intensified. FTIR thus further confirmed that LA had been conjugated onto COS, and indicated that the reaction was highly selective toward N-linoleyl.

Figure 3 shows the weight-average molar masses ($\overline{M}_w$) of COS and LCOS determined by SEC. The retention time (*t*) decreased with increasing $\overline{M}_w$. By comparison, it was found that the difference between the weight-average molar masses ($\Delta\overline{M}_w = 1958$) of COS and LCOS synthesized in [BMIM]Ac was equivalent to the molecular weight of seven LA molecules ($\overline{M}_w = 280.45$). The DS was calculated as 36.8%, consistent with the result from ^{1}H-NMR. Similarly, the difference between the weight-average molar masses ($\Delta\overline{M}_w = 1408$) of COS and LCOS synthesized in DMSO was equivalent to the molecular weight of five LA molecules, and the DS was 26.3%. According

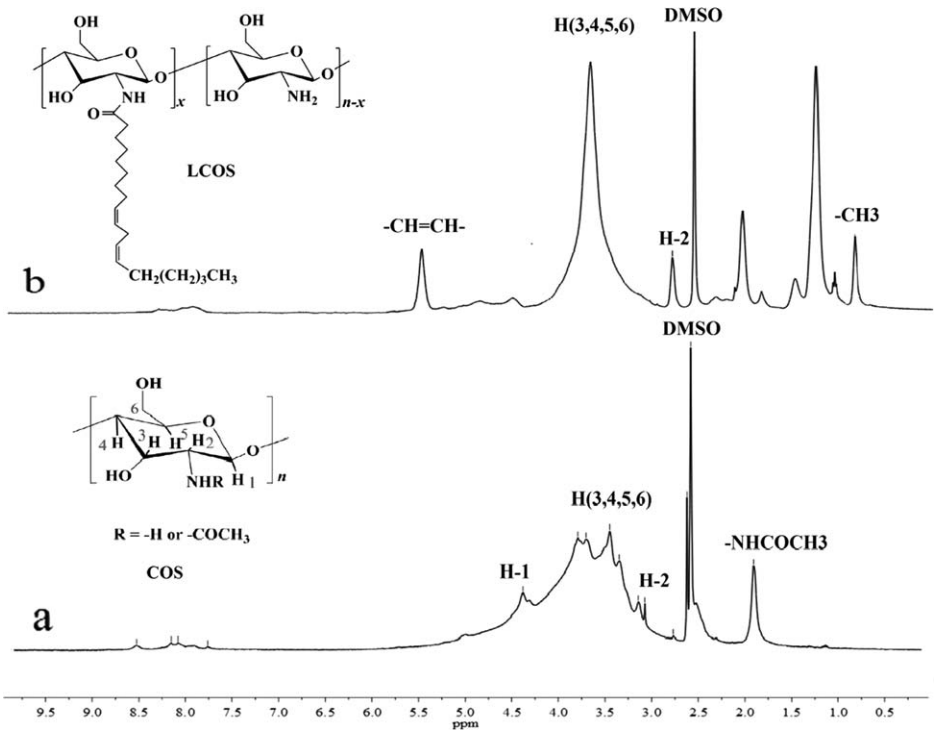


Figure 1. 1H NMR spectra of COS and LCOS.

to those results, more hydrophobic linoleyl groups were grafted onto the COS in the ionic liquid homogeneous system with a relatively higher DS.

The Reusability of Ionic Liquid [BMIM]Ac

One of the important advantages of ionic liquids is their reusability. Figure 4 shows the ^{1}H-NMR spectra of fresh [BMIM]Ac (a), [BMIM]Ac after 1 cycle (b), [BMIM]Ac after two cycles (c), and [BMIM]Ac after three cycles (d). Eight characteristic proton signals at $\delta = 0.66$ (H-10), 1.05 (H-9), 1.62 (H-8), 3.70 (H-6), 4.0 (H-7), 7.27 (H-4), 7.31 (H-5), and 8.61 (H-2) were seen in the ^{1}H-NMR spectra of both the fresh and recycled [BMIM]Ac. The fact that the characteristic signals of [BMIM]Ac were not affected by the recycling process confirmed that its structure was unchanged. Also, the spectra of the recycled ionic liquid displayed only a few weak signals attributable to residual impurities. This indicated that the recycled ionic liquid had a relatively high purity, such that its reuse was feasible.

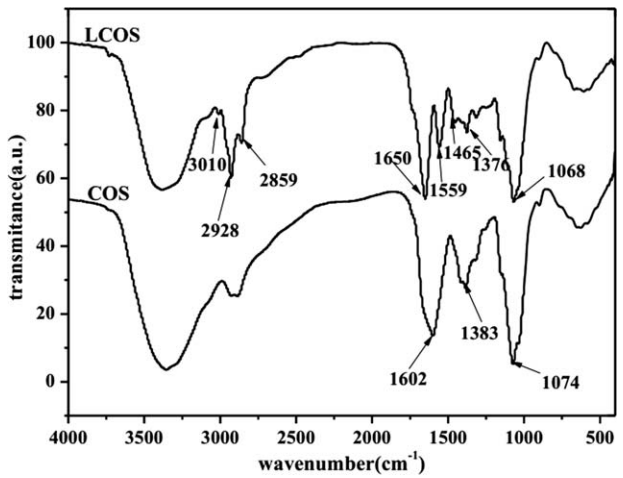


Figure 2. FTIR spectra of COS and LCOS.

Solubility Analysis

The solubility of COS and LCOS in [BMIM]Ac, water, PBS buffer solution (pH = 7.4), and some common organic solvents at room temperature were shown in Table I. The original COS was soluble in [BMIM]Ac, water, and PBS buffer solution

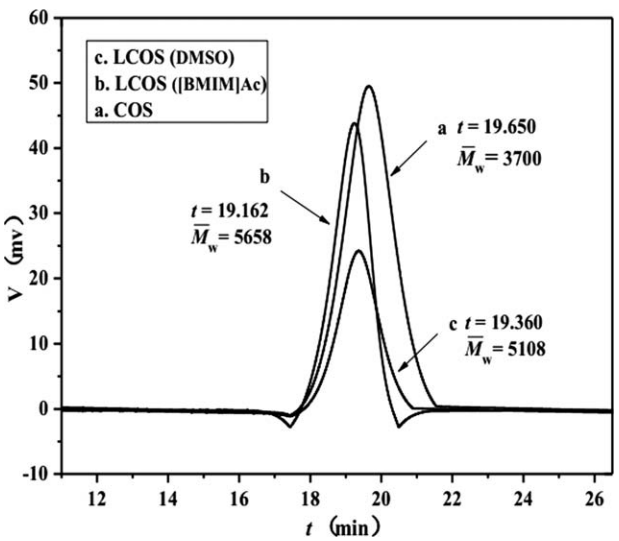


Figure 3. SEC of COS (a), LCOS ([BMIM]Ac, b), and LCOS (DMSO, c) (In each chromatogram, the data indicated the retention time (t) and the weight-average molar mass).

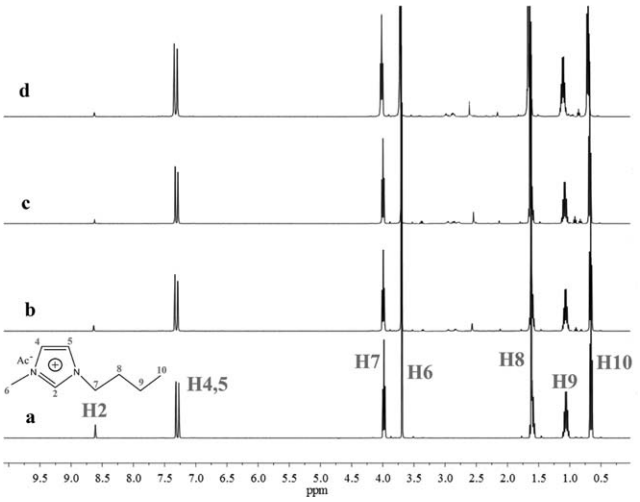


Figure 4. ^{1}H-NMR spectra of fresh [BMIM]Ac (a), [BMIM]Ac after one cycle (b), [BMIM]Ac after two cycles (c), and [BMIM]Ac after three cycles (d).

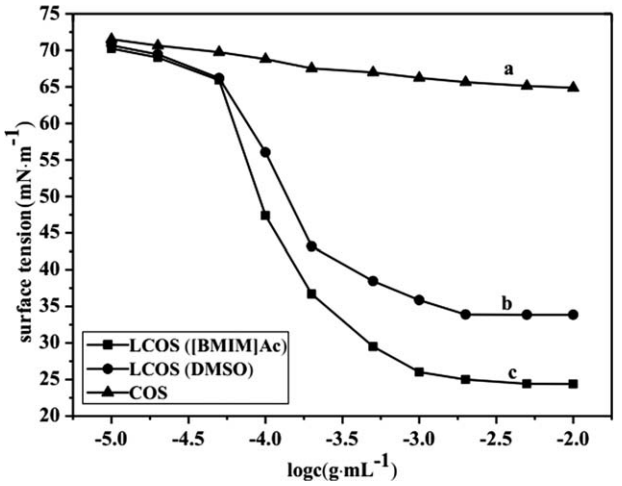


Figure 5. Surface tension versus logarithm concentration of COS (a), LCOS ([BMIM]Ac, b), and LCOS (DMSO, c) in aqueous solution.

(pH = 7.4), slightly soluble in DMSO and DMF and insoluble in ethyl acetate. After modification with hydrophobic LA, both LCOS^{1} (synthesized in [BMIM]Ac) and LCOS^{2} (synthesized in DMSO) were highly soluble in [BMIM]Ac, water, PBS buffer solution (pH = 7.4), DMSO, and DMF. The improved solubility of the COS derivative in common organic solvents could be explained by the fact that its inter- and intramolecular hydrogen bonds were weakened. Furthermore, the NH_2 groups formed amide bonds with the acid functionality of LA, and the conjugation of LA with the linear COS molecules expanded the crystalline structure and rendered the packing of the LCOS more disorganized than that of the original COS. In addition, compared with LCOS^{2}, LCOS^{1} showed better solubility in ethyl acetate. The enhanced DS and the introduction of hydrophobic groups most probably made the critical difference in the solubilities in organic solvents. It can be inferred from such phenomena that water-soluble COS-based derivatives might also acquire better solubility in organic solvents after the incorporation of more hydrophobic groups.

Surface Activities and Self-Assembly Performance

Figure 5 shows the equilibrium surface tensions of COS and LCOS aqueous solutions at different concentrations. The surface tension of the COS solutions showed no obvious change with increasing concentration due to the lack of hydrophobic groups on the COS backbones. After modification with LA, the surface tensions of LCOS aqueous solutions were lower than that of COS aqueous solution at all concentrations, and decreased dramatically with increasing concentration. Above a certain concentration of LCOS aqueous solution, the surface tension reached a plateau value because the hydrophobic chains moved toward and self-assembled for preventing the free energy from increasing further.[28] This showed LCOS to be more effective in reducing the surface tension of the solutions than the unmodified COS. It was also obvious from Figure 5 that the LCOS synthesized in [BMIM]Ac gave a more pronounced decrease at the same concentration than LCOS synthesized in DMSO. This was because LCOS ([BMIM]Ac) had a higher degree of hydrophobic substitution and more hydrophobic groups could move to the surface of the solution to reduce the surface tension. Furthermore, the higher degree of hydrophobic substitution may have resulted in enhanced stability of the self-assembled micelles in aqueous solution. Therefore, the LCOS synthesized in [BMIM]Ac was considered to improve the surface activity and lead to higher stability and more compact self-assembled micelles in aqueous solution.

Table I. The Solubility of COS and LCOS at Room Temperature

Solvents	COS	LCOS^{1}	LCOS^{2}
[BMIM]Ac	a	a	a
Water	a	a	a
PBS buffer solution (pH = 7.4)	a	a	a
DMSO	b	a	a
DMF	b	a	a
Ethyl acetate	c	b	c

Note: a–soluble, b–slightly soluble, c–insoluble.
LCOS^{1}: synthesized in [BMIM]Ac.
LCOS^{2}: synthesized in DMSO.

Another manifestation of the surface activity of LCOS is its wetting ability on a solid surface. The contact angles between LCOS aqueous solutions (0.01 g·mL^{-1}) and the standard PMMA plate were presented in Table II. The measurements were repeated six times and the average contact angles for LCOS^{1} (synthesized in [BMIM]Ac) and LCOS^{2} (synthesized in DMSO) aqueous solutions were 60.8° and 72.1°, respectively. The lower contact angle of LCOS^{1} aqueous solution on the standard PMMA plate compared to that of LCOS^{2} may be attributed to the increased ability of the molecules to destroy the water film arising from the strong interaction between water molecules and the standard PMMA plate surface. Thus, a lower contact angle means a better wetting ability.[25,29] The results indicate that LCOS synthesized in [BMIM]Ac had a better wetting ability than that synthesized in DMSO.

Table II. The Contact Angles Between LCOS Aqueous Solutions (0.01 g·mL^{-1}) and the Standard PMMA Plate

Simples (0.01 g·mL^{-1})	DS (%)	Contact angles (°)						Average value	Standard errors
		1	2	3	4	5	6		
LCOS^1	36.8	60.5	60.8	61.1	61.3	60.7	60.8	60.8	0.27
LCOS^2	26.3	72.1	72.3	71.5	72.5	71.9	72.0	72.1	0.32

Note: LCOS^1: synthesized in [BMIM]Ac.
LCOS^2: synthesized in DMSO.

Fluorescence measurements using pyrene as a fluorescent probe were carried out to study the self-assembly behavior of LCOS in aqueous solution. The emission spectrum of the pyrene monomer strongly depends on the polarity of the microenvironment. There are five peaks in the emission spectrum of pyrene, and the ratio of the emission intensities of the first peak (I_{373}) and the third peak (I_{392}) is sensitive to the microenvironment. If micelles are formed in an aqueous solution, pyrene preferentially lies close to these microdomains and shows strong emission. In a polar solvent, there is an enhancement in the intensity of I_{373}, but no effect on that of I_{392}. Therefore, the emission intensity ratio of the first peak (373 nm) and the third peak (392 nm) of pyrene can be used to monitor the solution behavior of polymer micelles. A smaller I_{373}/I_{392} ratio indicates lower polarity of the solution around pyrene.[30] Figure 6 shows the change in fluorescence intensity ratio I_{373}/I_{392} versus the logarithm of the LCOS concentration. The crossover point can be used to determine the critical micelle concentration (cmc).[28] The cmc of the LCOS ([BMIM]Ac) was determined as about 1.1×10^{-4} g·mL^{-1}, approximately one quarter of that of LCOS (DMSO) (4.5×10^{-4} g·mL^{-1}). This result could be attributed to the increased hydrophobicity arising from the introduction of a larger amount of hydrophobic groups. The lower cmc of LCOS ([BMIM]Ac) in aqueous solutions indicates that a small amount of LCOS synthesized in [BMIM]Ac may form more compact and stable self-assembled micelles under dilute conditions as compared with LCOS (DMSO) aqueous solutions. A higher degree of hydrophobic substitution on the COS backbones favors the formation and stability of self-assembled micelles in aqueous solution.

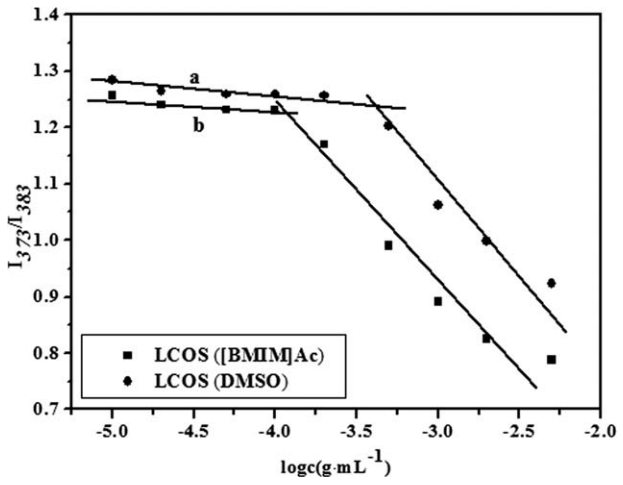


Figure 6. Intensity ratio (I_{373}/I_{392}) of pyrene emission spectra versus logarithm of the concentration for LCOS in aqueous solution.

Figure 7 shows a TEM image (a) and a size distribution histogram (b) of LCOS ([BMIM]Ac) micelles in aqueous solution. For comparison, the corresponding TEM image and size distribution histogram of LCOS (DMSO) micelles were shown as insets in the upper right-hand corners of Figure 7(a,b), respectively. It is evident from Figure 7(a) that the LCOS synthesized in [BMIM]Ac self-assembled into better-defined spherical

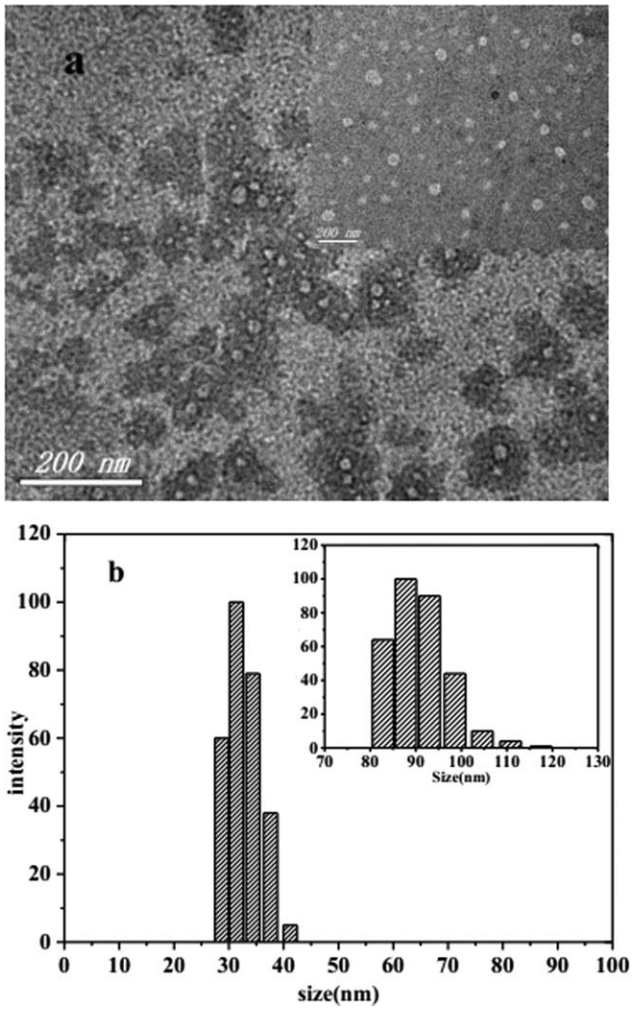


Figure 7. TEM image (a) and size distribution histogram (b) of LCOS ([BMIM]Ac) micelles and TEM image (a, inset) and size distribution histogram (b, inset) of LCOS (DMSO) micelles in aqueous solution.

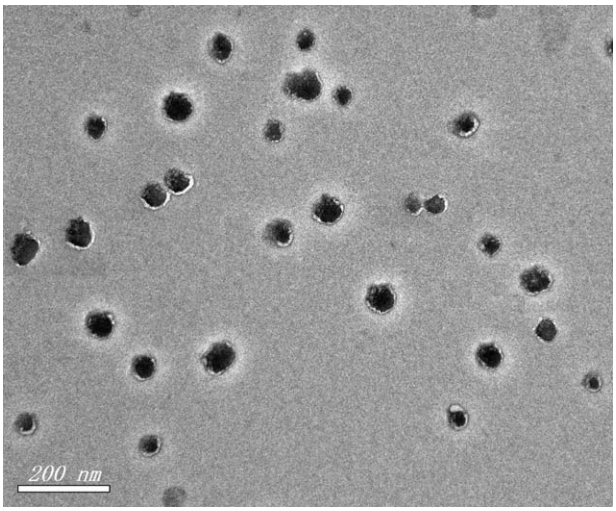


Figure 8. TEM image of ibuprofen-loaded LCOS micelles in aqueous solution.

micelles, which were better dispersed without any aggregation at room temperature. This indicated that more hydrophobic substitution resulted in compact hydrophobic cores and more stable micelles. Figure 7(b) shows that the LCOS ([BMIM]Ac) micelles were of smaller size and had a narrower size distribution (30–40 nm). The sizes of the self-assembled micelles decreased with the increasing DS, indicating that more hydrophobic substitution resulted in more compact and stable micelles. This phenomenon was consistent with the results reported by Kwon *et al.*[31] and Jiang *et al.*[32] that an increase in DS may enhance the chances of hydrophobic interactions among hydrophobic pendant groups, resulting in the formation of more compact hydrophobic cores.

Figure 8 shows the TEM image of IBU-loaded LCOS ([BMIM]Ac) micelles in aqueous solution. It depicted that the morphologies of IBU-loaded LCOS ([BMIM]Ac) nanomicelles were still regular, and that their sizes were significantly greater than those of the pristine LCOS nanomicelles, confirming that the drug has been accommodated internally. Similar findings have been reported by other authors. Additionally, the diameters of both the LCOS micelles and the IBU-loaded LCOS micelles were less than 200 nm, as is required to survive both rapid renal filtration and elimination by the EPR effect, which is crucial to optimize their chances of reaching disease sites. The TEM and size distribution results suggested that the LCOS synthesized in the ionic liquid met the requirements of a potential drug transduction vector.

CONCLUSIONS

In conclusion, the amphiphilic LA-grafted COS, which represents a promising polymeric nanomicelle drug transduction vector, has been successfully synthesized in [BMIM]Ac as a green solvent. This novel ionic liquid homogeneous system led to a relatively higher DS than conventional solvent-based approaches, making it an environmentally friendly and efficient approach for the synthesis of COS derivatives. The cmc of the LCOS aqueous solution was 1.1×10^{-4} g·mL^{-1}, indicating that it could readily form self-assembled micelles in aqueous solution at low concentration. Furthermore, the LCOS micelles in aqueous solution had a narrow size distribution and an average size less than 200 nm, which is suitable for intravenous administration. Our results highlight the potentiality of LCOS nanomicelles for application as a promising drug transduction vector.

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