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Supramolecular Hydrogels Instantaneously Formed by Inclusion Complexation between Amphiphilic Oligomers and α-Cyclodextrins

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Abstract: Supramolecular hydrogels were instantaneously fabricated by mixing aqueous solutions of α-cyclodextrins (α-CDs) and amphiphilic methoxy (polyethylene glycol) (MPEG)-ε-caprolactone (CL) oligomer, which was synthesized via the ring-opening polymerization of the CL monomer using low-molecular-weight MPEG (M_n of MPEG=2,000 g/mol) as an initiator. The supramolecular structure of the hydrogels was revealed by X-ray diffraction (XRD) analyses. Rheological studies of the hydrogels revealed an elastic character when the number of CL units in the oligomer was more than 2, and the obtained hydrogels showed high storage modulus but relatively low shearing viscosity due to the low-molecular-weight character of the oligomer, which was more preferable for use as an injectable delivery system. The physical properties of the hydrogels could be modulated by controlling the chain morphology and concentration of the oligomers, as well as the feed molar ratio of the oligomer to α-CD. The components of the supramolecular hydrogels are biocompatible and can readily be eliminated from the body. These features render the supramolecular hydrogels suitable as drug delivery systems and tissue engineering scaffolds.

Keywords: hydrogels, cyclodextrin, inclusion complexation, rheological properties.

Introduction

Physical hydrogels have attracted much attention in the biomedical field, particularly for the delivery of delicate protein drugs and cells due to their generally favorable biocompatibility and other unique properties.[1,2] Such hydrogels can be achieved by noncovalent cohesive interactions including hydrophobic interaction, ionic complexation, stereocomplex formation, crystallization, etc. Therefore, pharmaceutical drugs can be entrapped into hydrogels *in situ* in aqueous media without chemical crosslinking and any contact with organic solvents. Jeong *et al.* have developed a series of novel thermoplastic biodegradable physical hydrogel systems based on poly(ester-ether) block copolymers (A-B type, A-B-A type, B-A-B type, and star-shaped). Aqueous solutions of these block copolymers form gels at high concentrations and elevated temperatures due to the formation of close-packed micelles of amphiphilic copolymers. These hydrogels exhibited reversible sol-gel transitions and were studied as injectable drug delivery systems.[3-5]

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of six to eight glucose units linked by α-1,4-linkages and named α-, β- and γ-CD, respectively. They are water-soluble but have hydrophobic internal cavities.[6] Such cavities can selectively include various guest molecules ranging from small compounds to polymers.[7-10] In pharmaceutical applications, various CDs and their derivatives have been widely used to increase solubility, bioavailability, and stability of low-molecular-weight hydrophobic drugs via supramolecular associations.[11,12] Since it was firstly reported that a crystalline inclusion complex (IC) named as "molecular necklace" was formed between CD and poly(ethylene glycol) (PEG),[9] CDs have extensively been investigated as useful building blocks for constructing novel supramolecular architectures, such as polyrotaxanes or polypseudorotaxanes.[10] These supramolecular self-assemblies could potentially be applied in the design of new and efficient DNA delivery vectors and in the manipulation of DNA sequences due to their novel chemical and physical properties.[13-15]

Recently, the supramolecular hydrogels based on the polypseudorotaxane formation of various CDs with linear polymers have attracted a great deal of attention due to their potential biomedical applications as tissue engineering scaffolds and drug delivery carriers. Previously, Li *et al.* prepared CD-based hydrogel materials for injectable drug delivery using linear polymers, such as poly(ethylene oxide) (PEO) or Pluronics (PEO-PPO-PEO triblock copolymers), to partially penetrate the inner cavity of α-CD.[16,17] However, only high-molecular-weight PEO or Pluronics could lead to stable

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hydrogels with CDs, which can not be readily eliminated from the body through the kidney due to the large hydrodynamic radius.[5] Recently, Huk *et al.* obtained thermoreversible supramolecular hydrogels by introducing short PEG or PPG chains as grafts to hydrophilic dextran or chitosan backbones, which improved the stability of the hydrogel structures.[18-20]

More recently, we reported that supramolecular hydrogels could be rapidly fabricated in aqueous solutions by complexing amphiphilic water-soluble poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCL-PEG-PCL) block copolymers with α-CD, even at a low concentration of the copolymer and low feed molar ratio.[21] Li *et al.* described a supramolecular hydrogel system formed from biodegradable PEO-PHB-PEO triblock copolymer with α-CD, which was suitable for the long-term sustained release of drugs.[22] It was thought that the hydrophobic interaction between PCL or PHB segments in the copolymers facilitated the formation of the polymer network.

However, in these cases, to obtain such stable hydrogel systems, high-molecular-weight PEOs or their block copolymers are needed.[16,17,21,22] Another approach is to graft linear PEG, poly(propylene glycol) (PPG) or poly(ε-lysine) (PL) to hydrophilic polysaccharides, which can improve the stability of macromolecular assembly.[18-20] Therein, high polymer concentration and relatively long gel-induction times were also required. We report here on a stable supramolecular hydrogel system induced instantaneously via self-assembly between α-CD and low-molecular-weight amphiphilic methoxy (polyethylene glycol) (MPEG)-ε-caprolactone (CL) oligomers (MPEG unit M_n=2,000 g/mol) at a low concentration of oligomer. In contrast, no gelation occurred between such MPEG and α-CD in aqueous solutions even at a high MPEG concentration.

Low-molecular-weight PEG exhibits a smaller hydrodynamic radius and lower viscosity than linear high-molecular-weight PEG. The smaller hydrodynamic radius of PEG is important for complete renal excretion when the polyester units are degraded.[23,24] It was reported that α-CD only forms crystalline inclusion complex precipitates with low-molecular-weight PEG from aqueous solution.[25] However, by introducing several CL units with biocompatibility and biodegradability to low-molecular-weight MPEG, an instantaneous gelation occurred when mixing the aqueous solutions of the oligomer and α-CD even at a low concentration of oligomer and low feed molar ratio of oligomer to α-CD. It was suggested that the combination of the inclusion complexation of the amphiphilic oligomers with α-CD and the hydrophobic aggregation of CL units induces an instantaneous gelation, resulting in a stable self-assembly macromolecular network. These hydrogel systems provide an advantage in biomedical applications due to the instantaneous gelation as well as the biocompatibility, biodegradability, and easy clearance of their components.

Experimental

Materials and Measurements. ε-Caprolactone (Aldrich, USA) was dried over CaH_2 for two days and distilled under vacuum just before use. Methoxy(polyethylene glycol) (MPEG, Aldrich, USA) of M_n=2,000 g/mol was used after drying under vacuum at 100 °C for 24 h. Stannous 2-ethyl hexanoate (Sigma, USA) was used as received. α-CD (TCI, Japan) was used after drying under vacuum at 65 °C for 24 h. All other chemicals were analytical grade and used without further purification.

Preparation of MPEG-CL Oligomers. Weighted amounts of MPEG and distilled ε-caprolactone monomer were added into a 100 mL round-bottomed flask. An amount of 0.2 wt% stannous 2-ethyl hexanoate was added to the flask in a nitrogen atmosphere, which was degassed by connecting a vacuum pump for 20 min and purged with nitrogen gas. The degassing and purging process was repeated three times. The mixture was reacted at 125 °C with magnetic stirring for 12 h in a nitrogen atmosphere. After cooling to room temperature, the product was dissolved in trichloromethane and precipitated in anhydrous ethyl ether. This process was repeated twice. The precipitate was filtered and then dried under vacuum for 48 h. The oligomer was obtained with a 90% yield.

Formation of Supramolecular Hydrogels. The general protocol for the hydrogel formation is as follows. A required amount of aqueous solution of MPEG-CL oligomer was added to a predetermined amount of aqueous α-CD solution at room temperature. Various concentrations and compositions of oligomers, and different feed molar ratios of the oligomer to α-CD were used to formulate different hydrogels. The solution was thoroughly mixed by vigorous stirring. In all the systems, gelation instantaneously occurred resulting in a stable network due to the supramolecular self-assembly between α-CD and the MPEG-CL oligomer.

^{1}H NMR Spectroscopy. The ^{1}H NMR spectra for the MPEG-CL oligomers were recorded on a Varian UI500 NMR spectrometer at 500 MHz at room temperature with $CDCl_3$ as the solvent.

Fluorescence Measurement. Steady-state fluorescence spectra were recorded on an AB2 luminescence spectrometer (Aminco-Bowman, France). Pyrene was used as a hydrophobic fluorescent probe. Pyrene solution in THF was added to distilled water, and THF was removed by stirring at 40 °C for 4 h. The final concentration of pyrene was 1×10^{-6} M. The oligomer concentration from 5×10^{-5} to 0.5 mg/mL were prepared by dissolving oligomer and diluting in the pyrene solution. The solutions were kept at room temperature for 24 h to reach the solubilization equilibrium of pyrene in the aqueous phase. Excitation spectra were monitored at 334 nm at 25 °C, and emission spectra were recorded ranging from 350 to 440 nm. Both excitation and emission bandwidths were 8 nm.

X-Ray Diffraction. X-ray diffraction (XRD) measurements were performed on a Rigaku D/Max-2500/PC type X-ray diffractometer. The radiation source was nickel-filtered Cu-Kα radiation with a wavelength of 0.154 nm, and the voltage and current were set to 40 kV and 40 mA, respectively. The proportional counter detector collected data at a rate of $2\theta = 1^{\circ}$ min^{-1} over the range $2\theta = 5$-35°.

Rheological Measurement. The rheological behaviors of supramolecular hydrogels were investigated by a strain-controlled AR2000 rheometer (TA Instruments, New Castle, DE) with a stainless-steel cone and plate geometry (cone angle: 2°, diameter: 40 mm). Measurements were taken at 25 °C and the cone-to-plate distance was 0.2 mm. Storage (G') and loss modulus (G'') of the hydrogels were measured as a function of the frequency under oscillatory shear at a strain of 0.07%, which is within the linear viscoelastic region, as determined by dynamic strain sweep experiments. The viscosity of the hydrogels was measured as a function of shear rate in a steady mode.

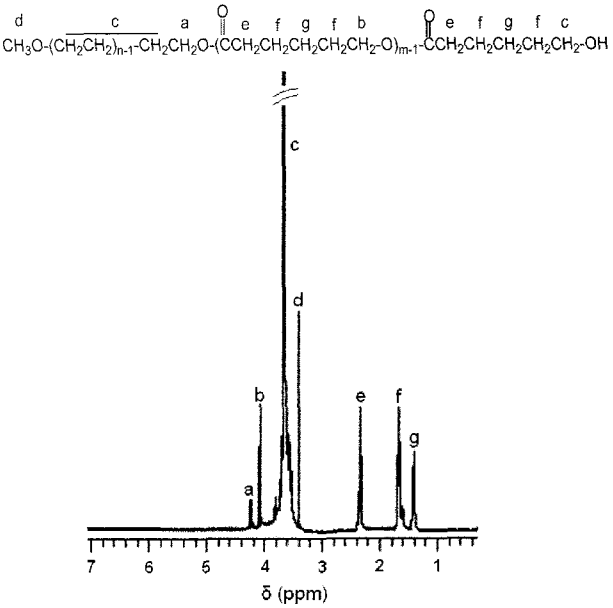

Figure 1. ^{1}H NMR spectrum of EG_{45}-CL_4 oligomer in $CDCl_3$.

Results and Discussion

Synthesis and Characterization of MPEG-CL Oligomers. Three water-soluble MPEG-CL oligomers were synthesized by modulating the feed ratio of ε-caprolactone (CL) monomer to MPEG, namely, EG_{45}-CL_2, EG_{45}-CL_4, and EG_{45}-CL_6, as shown in Table I. To gain insight into the chemical structure of MPEG-CL oligomers, ^{1}H NMR measurements were performed. Figure 1 shows the typical ^{1}H NMR spectrum of EG_{45}-CL_4 oligomer in $CDCl_3$. The characteristic peak at 4.25 ppm belongs to the methylene protons of the MPEG-CH_2-CH_2-O-CO-CL oligomer, indicating the successful synthesis of the MPEG-CL oligomer.[26] The composition of the oligomers was determined from the integration area ratio of the -CH_2- group (peak b, ~4.10 ppm) in the CL units to the -CH_2-CH_2- group (peak c, ~3.63 ppm). Table I shows the structural parameters of the samples. As seen, the oligomer composition calculated from ^{1}H NMR analyses is nearly consistent with the feed composition, indicative of a controlled polymerization reaction (second and third columns of Table I).

The micelle formation of oligomers was verified by the fluorescence probe technique using pyrene.[27,28] The emission spectra of pyrene in the presence of EG_{45}-CL_6 oilgomer are shown in Figure 2(a). The pyrene quantum yield increases due to the decreased polarity of the environment, and the critical micelle concentration (CMC) can be determined using the characteristic peak shifts. Due to the fact that the intensity of I_1 peak gradually decreases with incorporation of pyrene into the hydrophobic core region of the micelles from water, the intensity ratio of I_3/I_1 indicates the change in micelle concentration.

Figure 2(b) shows the intensity ratio of I_3/I_1 of pyrene excitation spectra as a function of the logarithm of oligomer concentration. Below the CMC, the intensity ratio was low and the slope negligible. When the concentration reached the CMC, the intensity ratio sharply increased. As shown in Figure 2(b), the intersection of the two tangent curves: a horizontal curve at low oligomer concentrations and the inflection, was determined to be the CMC. The CMC value determined for EG_{45}-CL_6 was 3.4×10^{-3} mg/mL, which is quite

Table I. Molecular Characteristics of MPEG-CL Oligomers and Experimental Details of Supramolecular Hydrogels

Designations	MPEG-CL Oligomer		Gel Formulation		Molar Ratio of Oligomer to CD	Gelation Time(s)
	Composition[a]	Number of CL Units[b]	Oligomer (wt%)	α-CD (wt%)		
Gel2-20	EG_{45}-CL_2	1.9	20	12	1:6	58
Gel4-5	EG_{45}-CL_4	3.8	5	12	1:6	45
Gel4-10	EG_{45}-CL_4	3.8	10	12	1:6	35
Gel4-10A	EG_{45}-CL_4	3.8	10	12	1:12	42
Gel4-20	EG_{45}-CL_4	3.8	20	12	1:6	10
Gel6-5	EG_{45}-CL_6	5.7	5	12	1:6	32
Gel6-10	EG_{45}-CL_6	5.7	10	12	1:6	15
Gel6-10A	EG_{45}-CL_6	5.7	10	12	1:4	20
Gel6-10B	EG_{45}-CL_6	5.7	10	12	1:12	25

[a]Theoretical composition based on feed composition. [b]Number of CL units in the oligomers calculated from ^{1}H NMR related integral ratios.

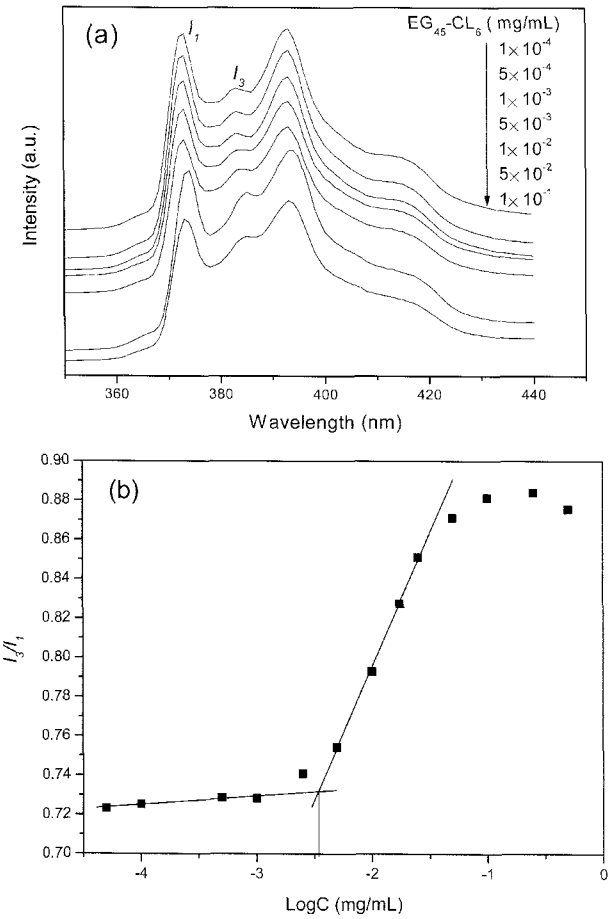

Figure 2. Emission spectra of pyrene in EG_{45}-CL_6 oligomer solution at a fixed excitation wavelength of 334 nm at 25 °C. The concentration of pyrene was 1×10^{-6} M (a) and the intensity ratio I_3/I_1 in the emission spectra as a function of LogC for EG_{45}-CL_6 oligomer at 25 °C (b).

low in comparison with those of linear amphiphilic block copolymers.[22,29] The result indicates that the oligomers have a very strong tendency towards formation of micelles in aqueous solution.

Hydrogel Formation via Self-Assembly of MPEG-CL Oligomers with α-CD. It is known that α-CD forms crystalline inclusion complex precipitates of a necklace-like supramolecular structure with low-molecular-weight PEG from aqueous solution. The rates of complex precipitation increase as the molecular weight decreases when the molecular weight is more than 1,000 g/mol, and PEG with molecular weight 1,000 g/mol precipitates most rapidly.[25,30] Here, we observed that the solution rapidly became turbid, and the complexes were finally obtained as precipitates (Figure 3(a)) when mixing 20 wt% MPEG (M_n=2,000 g/mol) aqueous solution with 12 wt% α-CD aqueous solution under a feed molar ratio of 1:6 ([MPEG]/[α-CD]). However, gelation occurred instantaneously upon mixing of the oligomer aqueous solution with the α-CD aqueous solution at the same feed composition, even with a low concentration of oligomer.

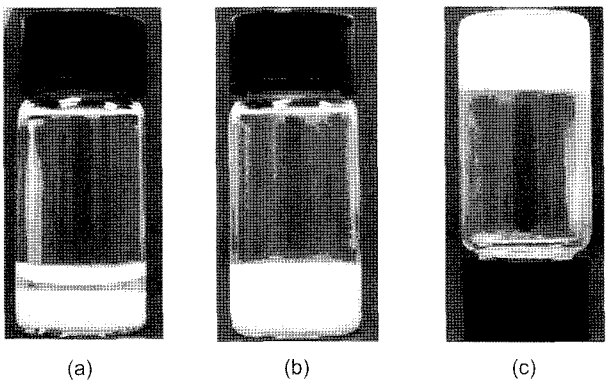

Figure 3. Photographs of the precipitate from the solution containing 20 wt% MPEG and 12 wt% α-CD (a), viscous gel obtained by mixing the solution of 20 wt% EG_{45}-CL_2 and the solution of 12 wt% α-CD (b), and the inverted glass vial of the supramolecular hydrogel formed from the solution of 5 wt% EG_{45}-CL_4 and the solution of 12 wt% α-CD (c).

It has been reported that water-soluble PEG-polyester block copolymers could form micelles in aqueous solution, which leads to the formation of hydrogels at high polymer concentrations and elevated temperature.[3-5] We observed that, despite a very low CMC value for EG_{45}-CL_6 oligomer, a 10 wt% its aqueous solution and 20 wt% aqueous solution of EG_{45}-CL_4 did not form hydrogel even at elevated temperature. It seems that α-CD can aid the gel formation of amphiphilic oligomers at a low concentration at room temperature. While a viscous gel can form between EG_{45}-CL_2 and α-CD (Figure 3(b)), for oligomers EG_{45}-CL_4, and EG_{45}-CL_6, elastic hydrogels could be fabricated in several seconds even at a low oligomer concentration and low feed molar ratio of the oligomer to α-CD. The vial containing the hydrogels could be inverted but exhibited no flow (Figure 3(c)).

It is well known that CDs can quantitatively form inclusion complexes (ICs) with various polymers.[25,31] α-CD forms ICs with PEG and poly(ε-caprolactone) (PCL) in aqueous solution with a stoichiometry of [EG]/[CD]=2:1 and [CL]/[CD] =1:0.9-1.0, respectively. When α-CD aqueous solutions are mixed with the oligomer solutions, they immediately turn into hydrogels within several seconds. This result indicates that α-CD threads onto the PEG segment and/or CL units to form hydrophobic crystalline ICs, which aggregates into microcrystals via hydrophobic interactions. Such microcrystals play an important role in the physical cross-links that result in the formation of the supramolecular-structured polymer network.

To confirm the formation of crystalline ICs between α-CD and PEG segment and/or CL units in the oligomer, we examined the obtained hydrogels by X-ray diffraction. Figure 4 shows the X-ray diffraction patterns for α-CD powder, the EG_{45}-CL_4 oligomer, and the obtained hydrogels. As shown in Figure 4(a), multiple diffraction peaks corresponding to a

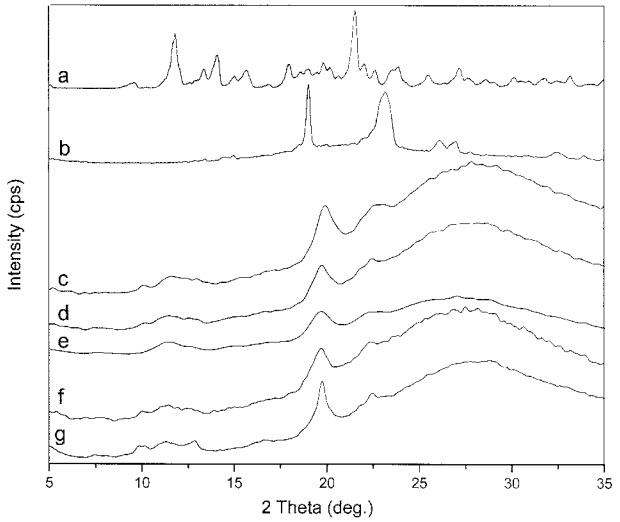

Figure 4. X-ray diffraction patterns of α-CD powder (a), EG_{45}-CL_4 oligomer (b), Gel4-20 (c), Gel4-10 (d), Gel4-5 (e), Gel6-10 (f), and Gel6-10B (g).

crystalline form were observed for pure α-CD, and the EG_{45}-CL_4 oligomer showed two strong diffraction peaks at 2θ=19.1° and 23.2° (Figure 4(b)). However, the patterns for all supramolecular hydrogels investigated exhibited a number of peaks, with the main one at 19.7° (Figures 4(c)-(g)), which are different from those for pure α-CD and the EG_{45}-CL_4 oligomer. The strong peak at 19.7° is a typical peak for the ICs of α-CD and PEG or PCL, suggesting the existence of an inclusion complex of α-CD with PEG and/or CL units in the oligomer in the obtained hydrogels.[25,32-34]

On the basis of the above observation, Figure 5 shows the graphical illustrations of the plausible gelation mechanism. In the case of the low-molecular-weight MPEG (M_n=2,000 g/mol), all the PEG chains could be easily included by α-CDs, and the unoccupied EG units might be too short to form a hydrogel. Meanwhile, for the oligomer, α-CD preferentially included CL units due to a greater inclusion affinity for more hydrophobic molecules,[35] so more EG units were remained as hydrophilic framework to form gel. The oligomers could form micelles in aqueous solution due to the amphiphilic property of diblock copolymers,[26,36,37] which can also play an important role in the instantaneous gelation of α-CD with the oligomer in aqueous solution. A cooperative effect of rapid complexation rate of α-CD with the oligomer due to the low-molecular-weight character, hydrophobic interactions between crystalline inclusion complexes, as well as the hydrophobic aggregation between the CL units can result in instantaneous gelation and formation of a stable supramolecular hydrogel.

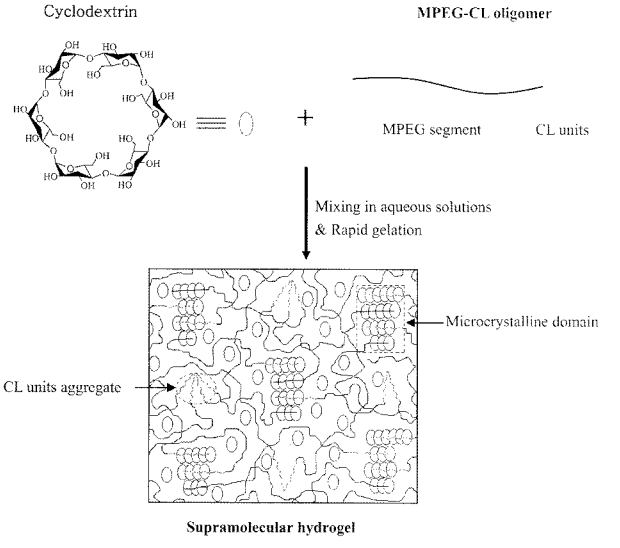

Figure 5. Graphical description of the gelation mechanism of the supramolecular hydrogel.

Rheological Properties of Supramolecular Hydrogels. The variations of G' and G'' as a function of the frequency for the supramolecular hydrogel samples are shown in Figures 6-7. We observed that the storage modulus is slightly higher than the loss modulus over the entire frequency region for Gel2-20, indicating that the material exhibits a viscoelastic response. However, for Gel4-20 at the same feed composition and concentration, the storage modulus is much higher than the loss modulus over the entire region, and its G' and G'' values are higher than those of Gel2-20, indicating that the hydrogel is more elastic. The trends were similar for all the hydrogel samples of EG_{45}-CL_4, and EG_{45}-CL_6 oligomers. These hydrogels (except Gel2-20) display a predominantly elastic solid-like behavior.[38] At the same concentration and feed molar ratio, the G' values increased with an increase in the number of CL units in the oligomer (Figures 6-7). As mentioned above, the precipitate was obtained from a mixture of 20 wt% MPEG solution and 12 wt% α-CD solution. These results indicate that the introduction and the number of CL units in the oligomer are critical for the formation and stability of supramolecular hydrogels.

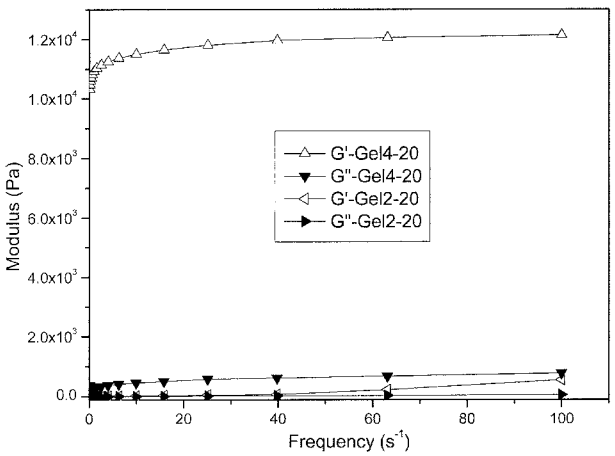

Figure 6. Storage modulus (G') and loss modulus (G'') evolutions as a function of frequency for the supramolecular hydrogels.

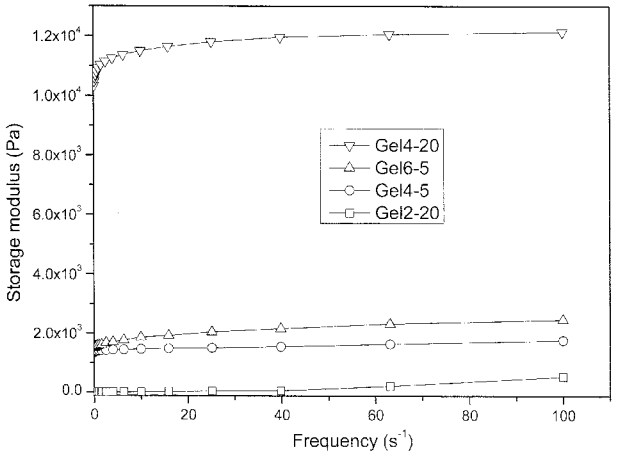

Figure 7. Comparison of the storage moduli (G') of various supramolecular hydrogels.

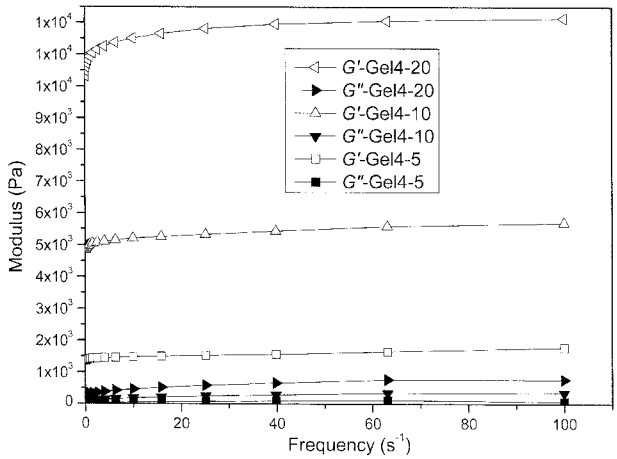

Figure 8. Storage modulus (G') and loss modulus (G'') evolutions as a function of frequency for supramolecular hydrogels.

The hydrophobic interactions between CL units seem to facilitate the formation of the macromolecular network, which further supports the plausible mechanism of instantaneous formation of hydrogel network.

Figure 8 presents the storage and loss modulus evolutions of the hydrogels formed from different concentrations of oligomer EG_{45}-CL_4 and 12 wt% of α-CD aqueous solution as a function of frequency. With the increase of oligomer concentration (5, 10, and 20 wt%), the G' value increases while the G'' value increases only slightly, which could be attributed to an increase in the amount of crystalline IC micro-domains. In some cases, the G' value is even greater than that for the hydrogels formed from PCL-PEG-PCL block copolymers of high-molecular-weight PEG, possibly because of more cross-linking points provided by more chain ends of the low-molecular-weight oligomers.[21]

Figure 9 shows the influence of the feed molar ratio of oligomer to α-CD on the rheological property. The storage modulus (G') increases when changing the feed molar ratio

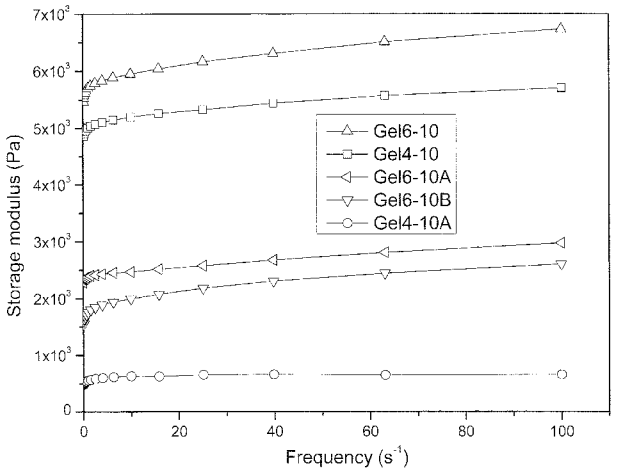

Figure 9. Storage modulus (G') evolutions as a function of frequency for various supramolecular hydrogels.

of the oligomer to α-CD monomer from 1:4 (Gel6-10A) to 1:6 (Gel6-10). However, the value decreases when the molar ratio increases to 1:12. This can be explained by the fact that the enhanced crystalline micro-domain formed from more IC aggregation due to the increase of feed molar ratio leads to more stable hydrogel formation. However, while the concentration of the oligomers and α-CD were fixed, a further increase of the molar ratio of the oligomer to α-CD leads to a decrease in the amount of crystalline micro-domains in the hydrogel system. Nevertheless, a low feed molar ratio of oligomer to α-CD monomer could still lead to the rapid formation of stable hydrogel. This result is quite different from that for hydrogels formed from MPEG modified chitosan with α-CD, where no gelation was observed at a molar ratio of [EG]/[CD] =4.[19]

Figure 10 shows the viscosity of the hydrogel systems as a function of shear rate. The viscosity of the hydrogel greatly diminished with shearing, and it was observed that the dimin-

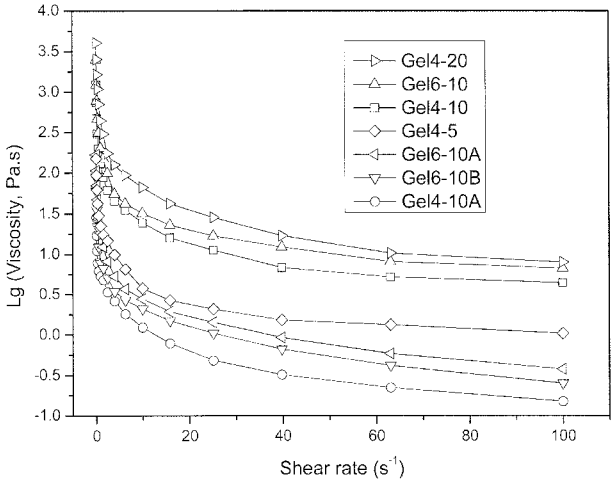

Figure 10. Apparent viscosity as a function of shear rate for the hydrogels.

ished viscosity of the hydrogels could be reversibly restored towards its original value after a particular period of time without shear force. This property renders the drug delivery matrix injectable through fine needles. Moreover, in some cases, the hydrogels based on the oligomer exhibit higher modulus and lower shearing viscosity than the hydrogels formed from PCL-PEG-PCL triblock copolymers of high-molecular-weight PEG,[21] which is preferable for actual applications such as injectable delivery systems. In addition, the viscosity of the hydrogels can be modulated by controlling the concentration and composition of the oligomers as well as the feed molar ratio of the oligomer to α-CD.

Conclusions

Supramolecular hydrogels were rapidly constructed by mixing low-molecular-weight amphiphilic MPEG-CL oligomers and α-CDs at room temperature. α-CDs can instantaneously induce amphiphilic oligomers to form a macromolecular network at a low oligomer concentration and low feed molar ratio of oligomer to α-CD due to the inclusion complexation of α-CD with the oligomer, as well as the hydrophobic association among the CL units in the oligomer. The rheological properties could be finely modulated by controlling the oligomer concentration, the feed molar ratio of oligomer to α-CD, and the composition of the oligomers. All the components of the hydrogels are biocompatible and can be readily eliminated from the body, and the hydrogels exhibit high modulus and low shearing viscosity due to the low-molecular-weight character of oligomer. These properties render the hydrogel systems more advantages in biomedical applications such as injectable platforms.

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