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Suprarmolecular Hydrogels Based on Low-Molecular-Weight Poly(ethylene glycol) and α-Cyclodextrin

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ABSTRACT: In previous studies, crystalline precipitates, not stable hydrogels, were obtained when low-molecular-weight (MW) poly(ethylene glycol) (PEG; weight-average MW = 400–5000) was used to interact with α-cyclodextrin (α-CD). In this study, the gelation ability of low-MW PEG (number-average MW = 2000, PEG-2000) and α-CD was systematically investigated through the variation in the concentration of PEG-2000 in water ($C_{PEG\text{-}2000}$) and the feeding molar ratio of the PEG repeat unit to α-CD (R). The results show that a stable supramolecular hydrogel could be constructed when $C_{PEG\text{-}2000}$ was kept at 40 mg/mL and R was 6.3. The inclusion complexation between α-CD and PEG-2000 and the effect of $C_{PEG\text{-}2000}$ and R on the stability of the hydrogels were characterized by differential scanning calorimetry, X-ray diffraction, scanning electron microscopy, and rheology measurements. The resulting PEG-2000-based hydrogels retained the basic characteristics of supramolecular physical hydrogels, especially the property of shear thinning. © 2013 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 129: 901–907, 2013

KEYWORDS: biocompatibility; biomaterials; gels; hydrophilic polymers; self-assembly

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INTRODUCTION

Biocompatible supramolecular hydrogels are physical networks self-assembled by biocompatible gelators with macromolecular or low-molecular-weight molecules via noncovalent interactions, including hydrogen bonding, hydrophobic interactions, host–guest recognition, and crystallization.[1,2] They have been extensively explored for applications in biological medicine, genetic engineering, and biomedical materials because of their easy operation, thixotropic reversibility, and good biocompatibility.[3–5] Therefore, the construction of biocompatible supramolecular hydrogels has attracted wide attention recent years. α-Cyclodextrin (α-CD), a kind of cyclic oligosaccharide composed of six glucose units, has a unique architecture of a truncated cone-forming hydrophilic outer surface and a hydrophobic cavity in which guest molecules can be encapsulated.[6–8] So α-CD is a suitable backbone for building one-dimensional, two-dimensional, and three-dimensional supramolecular network structures.[9,10]

Harada and Kamachi[11] first reported in 1990 that poly(ethylene glycol)s (PEGs) with different molecular weights [MWs; weight-average molecular weight (M_w) = 400–90,000] could penetrate the inner cavity of α-CDs to form polymer inclusion complexes (PICs) with necklacelike supramolecular structures called *polypseudorotaxanes*. α-CDs threaded onto PEG chains can further assemble into channel-type crystals, and crystalline precipitates were obtained when PEG with a low MW (M_w = 400–10,000) was used. The driving forces are hydrogen bonding, size matching between the host and guest molecules, the hydrophobic effect, and so on. Since then, supramolecular PICs have been designed to form different supramolecular assemblies.[12–15] Li et al.[16] first reported a hydrogel made of high-molecular-weight PEG and α-CD. Kataoka et al.[17] reported a kind of thermoreversible polyrotaxane hydrogel based on high-MW PEG [number-average molecular weight (M_n) = 35,000] and methylated α-CD. Yui and coworkers[18–20] studied the gel–sol phase-transition behavior of α-CD and PEG-grafted dextran and chitosan. Chen et al.[21] investigated the gelation behavior between a densely PEG-grafted polymer brush and α-CD. Several other such physical hydrogels have also been prepared from PEG-containing block copolymers, star polymers, and hyperbranched polymers.[22–30]

In contrast to these extensive investigations on supramolecular hydrogels made of α-CD and high-MW PEG homopolymers (M_n > 10,000) or PEG-based copolymers with different topologies, only a little work has been conducted on the inclusion complexes of α-CD and low-MW PEG and their ability to gel.[11,16,31,32] In general, crystalline precipitates have been

Table I. MWs and Compositions of PEG and α-CD Reported in the Literature

No.	α-CD (mg/mL)	PEG		—CH_2CH_2O—/α-CD (feed molar ratio)	Result	Reference
		Mg/mL	M_w			
1	145 (saturated)	5	400–10,000	0.8/1	Precipitates	11
2	72.5	6.56	90,000	2/1	Gel	16
3	107	10	600	2/1	Precipitates	31
	102	9	2,000		Precipitates	
	100	12	5,000		Unstable gel	
	102	10	8,000		Stable gel	
4	96.7	30	1100	6.8/1	Precipitates	32
			2000			

obtained when PEG with a low MW (M_w = 400–5000) was used. In fact, the formation and stability of hydrogels are affected by many parameters, including the polymer concentration, the density of the crosslinking points, the hydrophilic chain length of the polymer, and the ratio of hydrophilic to hydrophobic components. However, studies on the inclusion complexes formed by low-MW PEG and α-CD have not taken all aspects of these conditions into consideration. For example, the feeding molar ratio of PEG repeat units to α-CD (R) plays an important role in the formation of hydrogels, but there have been few reports on whether hydrogels can be obtained through the variation of R.

Water-soluble PEG is known to be biocompatible and has been widely used in bioengineering and pharmaceutics. Compared with high-MW PEG, low-MW PEG has a better biocompatibility, which is very important to hydrogels for biomedical applications.[33] Therefore, methods for preparing supramolecular hydrogels based on α-CDs and low-MW PEG have more practical prospects. So, in this study, we systematically investigated the inclusion complexation between α-CD and low-MW PEG (PEG-2000, M_n = 2000) and obtained a kind of stable supramolecular hydrogel via the adjustment of the value of R and the concentration of PEG-2000 in water ($C_{PEG\text{-}2000}$). The resulting hydrogel retained the basic characteristics of a supramolecular physical hydrogel, especially the property of shear-thinning. This research is helpful not only to determine the inclusion complex between α-CD and low-MW PEG but also to provide a new idea for building biocompatible supramolecular hydrogels that should be useful as functional biomaterials for drug delivery.

EXPERIMENTAL

Materials

The α-CD was purchased from TCI Shanghai (Shanghai, China). Methoxy PEG (99%, M_n = 2000 (Aldrich, Milwaukee, WI, USA)) was dried by azeotropic distillation in the presence of toluene. All solvents were used as received.

Preparation of the Hydrogels

α-CD and PEG-2000 were each dissolved in water to form solutions. Then, each of the aqueous solutions of PEG-2000 with various concentrations was added dropwise to each of the aqueous solutions of α-CD with various concentrations. The mixed solutions were ultrasonically treated for 2 min and then were left to stand at room temperature.

Measurements

Scanning electron microscope (SEM) was performed on a TECNAI T20 electron microscope (FEI, Eindhoven, The Netherlands). For SEM observation, the specimens were freeze-dried *in*

Table II. Preparation of Inclusion Complexes of PEG-2000 and α-CD

Sample	α-CD (mg/mL)	PEG-2000 (mg/mL)	—CH_2CH_2O—/α-CD (R)	Time of gelation	Phenomenon
S_1	145	10	1.6/1	—	Precipitate
C_1	17.2	5	6.3/1	—	Transparent solution
C_2	55.5	15.6	6.3/1	2 h	Unstable gel, destroyed after about 6 h
C_3 (or M_2 or T_2)	102	30	6.3/1	5 min	Unstable gel, destroyed after about 48 h
C_4	136.7	40	6.3/1	at once	Stable gel
M_1	44	30	15/1	50 min	Unstable gel, destroyed after about 24 h
M_3	160.7[a]	30	4.1/1	2 min	Stable gel

[a]The saturated solubility in water of α-CD at room temperature is 145 mg/mL, and α-CD was dissolved in preheated water to obtain a homogeneous solution before it was mixed with the PEG solution to prepare sample M_3.

Figure 1. Optical photos of the inclusion complexes of PEG-2000 and α-CD: (1) precipitate S_1, (2) solution C_1, (3,4) unstable gel C_3 (or M_2) before and after destruction, (5,6) unstable gel M_1 before and after destruction, (7) stable gel C_4, and (8) stable gel M_3. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

vacuo. The dried specimens were ground into fine powder, placed on conducting glue, and then coated with gold vapor and analyzed on the TECNAI T20 electron microscope. Differential scanning calorimetry (DSC) measurements were carried out with DSC-60A (Shimadzu, Tokyo, Japan). Each sample capsulated in a metal pan (5 mm in diameter) was first heated from room temperature to 140°C, then cooled to −15°C, and finally heated to 140°C, again under a nitrogen flow. The heating and cooling rate was 10°C/min. The melting temperature (T_m) and crystallization temperature (T_c) were recorded. X-ray diffraction (XRD) patterns were obtained with an X-ray diffractometer (MSAL-XD2, Micro-structure Analysis Laboratory, Beijing, China) with Cu Kα radiation ($\lambda = 0.1541$ nm, 30 kV, 30 mA). The XRD data were collected with 2θ values in the range of 5–50° with a 0.01° step. The steady and dynamic rheological measurements were carried out on a Physica MCR-300 (Anton Paar, Ostfildern, Germany) rheometer with 12-mm parallel-plate geometry. All tests were performed at 25°C.

RESULTS AND DISCUSSION

The narrow side of the α-CD cavity was 4.7 Å in diameter, whereas the sectional size of PEG was 3.1 Å. Therefore, the PEG chains should have been able to thread into the α-CD cavity and form inclusion complexes. Because the height of the α-CD cavity (7.9 Å) was about twice the contour length of the PEG repeat unit (—CH_2CH_2O—), more α-CDs could thread onto the PEG chains and form necklacelike inclusion complexes or pseudopolyrotaxanes. It was reported that low-MW PEG (M_n < 10,000) could form stoichiometric whole complexes with α-CDs in which two ethylene glycol units of PEG were bound in a single α-CD cavity; however, only partial PEG chains units that were close to both ends could penetrate into α-CD, even when the α-CDs were excessive when high-molecular-weight PEG was used.[11]

Table I lists the previously reported inclusion complexes between α-CD and PEG with various MWs.[11,16,31,32] It was found that crystalline precipitates were mostly obtained when low-MW PEG with a low concentration was used to interact with α-CD with a high concentration. It is known that the polymer concentration, the density of the crosslinking points, and the ratio of hydrophilic to hydrophobic components are all important parameters in the formation and stability of hydrogels. If all the components are hydrophobic, they cannot form a hydrogel but easily precipitate from water. For example, precipitate S_1 [Table II and Figure 1(1)] rather than a homogeneous hydrogel was obtained when PEG-2000 with a low concentration (10 mg/mL) was mixed with a saturated α-CD solution (145 mg/mL). This was because each hydrophilic PEG chain was wholly included in the cavities of the α-CDs under these conditions, and the obtained polypseudorotaxane became hydrophobic and easily precipitated from water. To solve this problem, a PEG chain partially covered by α-CDs was selected in our study. The gelation ability was investigated through the variation of $C_{PEG\text{-}2000}$ and R.

Table III. Preparation of the Inclusion Complexes of PEG-2000 and α-CD with the α-CD Concentration Kept at 102 mg/mL

Sample	α-CD (mg/mL)	PEG-2000 (mg/mL)	—CH_2CH_2O—/α-CD (R)	Phenomenon
T_1	102	20	4.3/1	Unstable gel, destroyed after about 8 h
T_2	102	30	6.3/1	Unstable gel, destroyed after about 48 h
T_3	102	40	8.7/1	Unstable gel, destroyed after about 24 h
T_4	102	69.3	15/1	Unstable gel, destroyed after about 24 h

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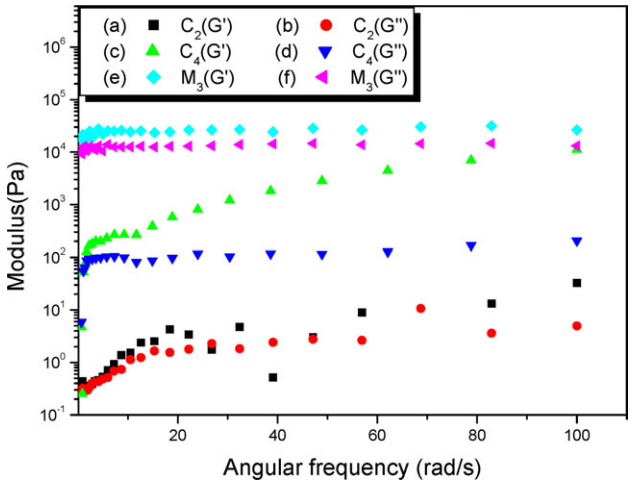


Figure 2. G' and G'' evolution as a function of frequency for the inclusion complexes: (a,b) G' and G'' of C_2, (c,d) G' and G'' of C_4, and (e,f) G' and G'' of M_3. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Effect of $C_{PEG\text{-}2000}$ on Gelation

With R kept at 6.3, the ratio of hydrophilic to hydrophobic components kept at about 2, and increasing $C_{PEG\text{-}2000}$, a series of inclusion complexes were further obtained, and the results are shown in Table II and Figure 1. The mixture of α-CD and PEG-2000 with a low concentration (5 mg/mL) was a transparent aqueous solution [Figure 1(2)], and the solution became gradually turbid and sticky with increasing $C_{PEG\text{-}2000}$. Hydrogel C_2 was observed when $C_{PEG\text{-}2000}$ reached 15.6 mg/mL. However, it was not stable, and the network was disturbed after 6 h. With increasing $C_{PEG\text{-}2000}$, the lower the time of gelation was, longer the time that it took for the network to be destroyed [Figure 1(3,4)]. A stable hydrogel, C_4, was obtained when $C_{PEG\text{-}2000}$ reached 40 mg/mL [Figure 1(7)]. Therefore, we concluded that the concentration of PEG played an important role in the formation of the hydrogels. Only when enough polymer chains were provided in the aqueous solution was it possible for a stable hydrogel to be formed.

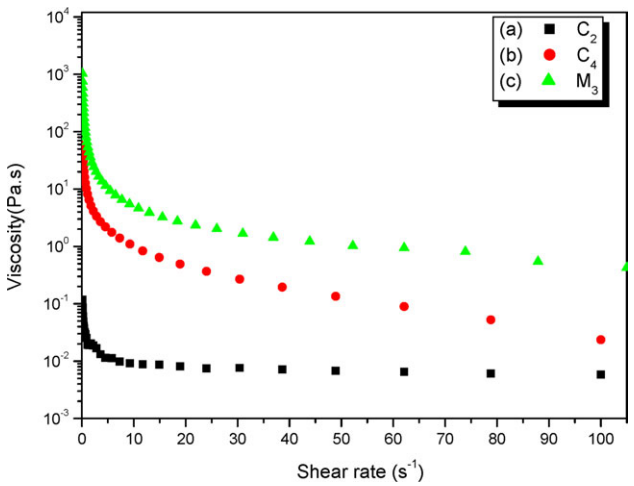


Figure 3. Relationship between the apparent viscosity and shear rate of the inclusion complexes: (a) C_2, (b) C_4, and (c) M_3. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

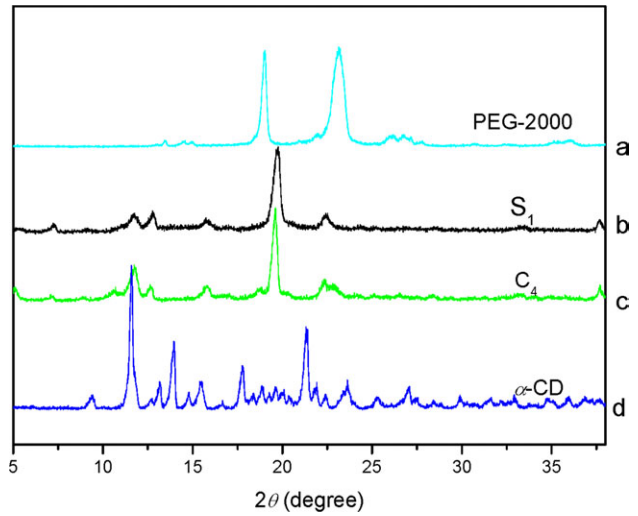


Figure 4. XRD powder patterns for PEG-2000, α-CD, and freeze-dried inclusion complexes with different polymer concentrations: (a) PEG-2000, (b) S_1 (R = 1.6/1, $C_{PEG\text{-}2000}$ = 10 mg/mL), (c) C_4 (R = 6.3/1, $C_{PEG\text{-}2000}$ = 40 mg/mL), and (d) α-CD. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The concentration of α-CD is important for the formation of hydrophobic polypseudorotaxanes through crosslinking. We carried out additional experiments on the effects of the PEG concentration on polypseudorotaxane formation with the concentration of α-CD kept at 102 mg/mL. The data are shown in Table III. We observed that the obtained hydrogels were all unstable and were gradually destroyed. The results show that a low PEG-2000 concentration (T_1 and T_2) or high R (T_3 and T_4) was disadvantageous to the formation of hydrogels. Taking into account the previous results, we concluded that the better experimental method investigating the effect of $C_{PEG\text{-}2000}$ on the ability of gelation was to keep R at a suitable value.

The formation of the stable C_4 hydrogel was traced by rheological measurement. As shown in Figure 2(a–d) and Figure 3(a,b), the modulus and viscosity values of C_4 outclassed those of C_2, and the storage modulus (G') value of C_4 was greater than its its loss modulus (G'') over the entire range of frequency; this suggested that C_4 formed stable hydrogel. At the same time, the viscosity of the C_4 hydrogel greatly decreased as it was sheared; this showed that it retained the basic characteristic of supramolecular physical hydrogels.

XRD powder patterns were used to characterize the crystalline structure of the inclusion complexes (Figure 4). α-CD alone formed crystal with a cage structure characterized by a strong reflection around $2\theta = 12°$ [Figure 4(d)], whereas two characteristic diffraction peaks at $2\theta = 19$ and 23° [Figure 4(a)] were found in the XRD pattern of PEG. However, a new sharp and strong diffraction peak at $2\theta = 20°$[Figure 4(c)], identical with the channel structure of α-CD beside the small characteristic peaks of PEG, appeared in the XRD pattern of sample C_4; this indicated that α-CD threaded onto the PEG chains could stack

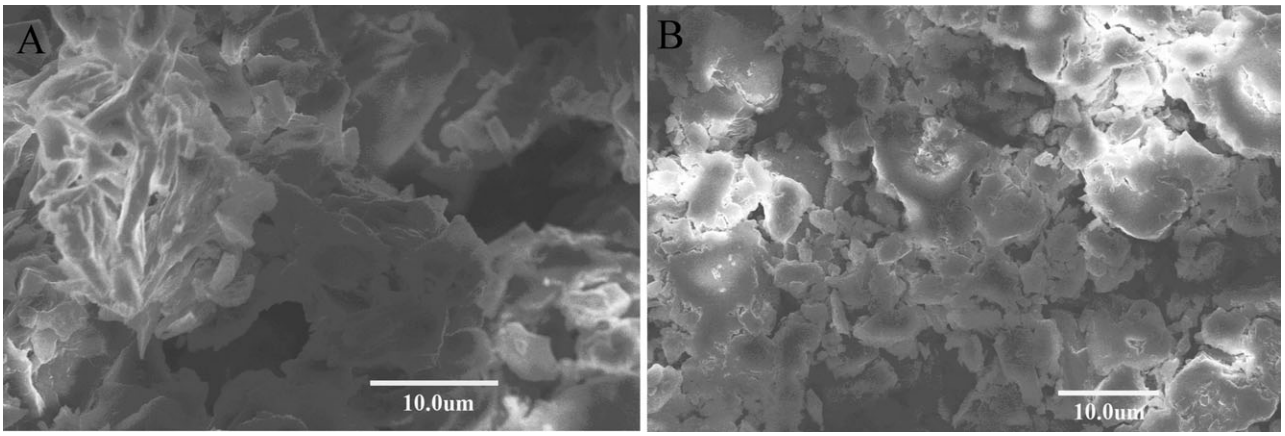


Figure 5. SEM images of the freeze-dried inclusion complexes: (A) precipitate S_1 from PEG-2000 and α-CD and (B) stable hydrogel C_4 from PEG-2000 and α-CD.

on top of each other in the crystal lattice to form cylindrical channels in which the guest molecules resided.[11] Both PEG-2000 and α-CD were soluble in aqueous solution. The resulting channel-type crystalline domains were hydrophobic and could act as physical crosslinking points. At the same time, the remaining uncovered PEG was hydrophilic and could act as network chains. Both of them constructed the previous supramolecular hydrogel.

Furthermore, the microstructure of the complexes was observed by SEM. Generally speaking, the crystals of the inclusion complexes of the α-CDs and linear polymeric guests appeared as a well-edged flakelike lamellar structure. As shown in Figure 5(A), the precipitated complex S_1, in which PEG-2000 with a low concentration was fully included into α-CDs, presented a large flakelike structure with an average size of 6 μm; the flake in the space was loose, and the accumulation was random. The hydrogel complex C_4 also presented a lamellar structure, but the layer assembled to a domain with a small size of about 4 μm, and the domain further aggregated into networks with porous structures [Figure 5(B)].

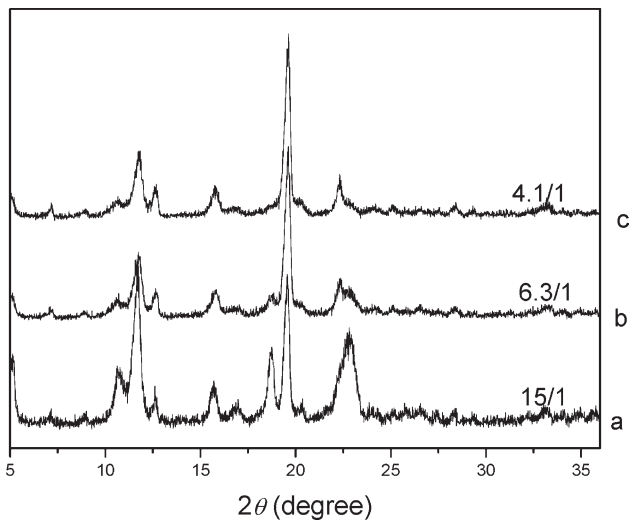


Figure 6. XRD powder patterns for the freeze-dried inclusion complexes with different *R* values: (a) M_1 (15 : 1), (b) M_2 (6.3 : 1), and (c) M_3 (4.1 : 1).

Effect of *R* on Gelation

We observed that the previous gel C_3 was not stable and became sol after 48 h when *R* was 6.3 and $C_{PEG\text{-}2000}$ was 30 mg/mL [Figure 1(3,4)]. One of the possible reasons is that the physical crosslinking points of hydrophobic channel-type crystal domains were unstable. So the effect of *R* on the gelation was further studied, keeping $C_{PEG\text{-}2000}$ as 30 mg/mL. As shown in Table II and Figure 1, the time that it took for the gel network to be disrupted was prolonged with increased *R*, and a stable hydrogel, M_3, was obtained when *R* reached 4.1 [Figure 1(8)]. The formation of the stable M_3 hydrogel was also traced by rheological measurement. As shown in Figure 2(e,f) and Figure 3(c), the modulus and viscosity of M_3 was larger than that of C_4, and the G' value of M_3 was greater than its G'' over the entire range of frequency; this suggested that M_3 formed a stable hydrogel. At the same time, the viscosity of the hydrogel M_3 greatly decreased as it was sheared; this showed that it retained the basic characteristics of a supramolecular physical hydrogel.

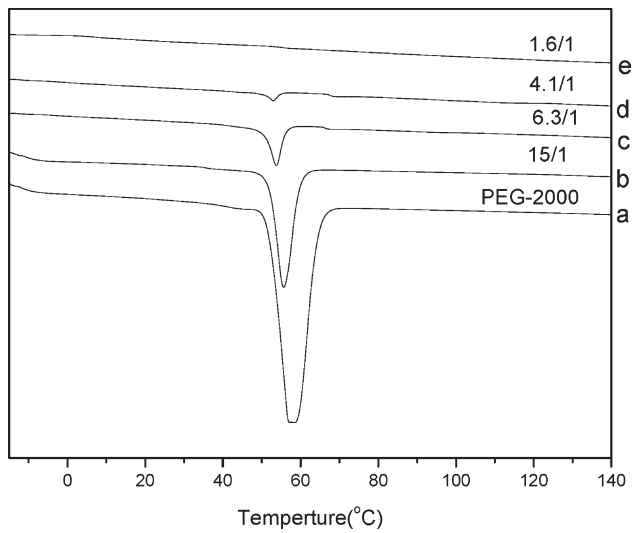


Figure 7. Second heating curves of differential scanning calorimetry for PEG-2000 and freeze-dried inclusion complexes with different *R* values: (a) PEG-2000, (b) M_1 (15 : 1), (c) C_3 (or M_2, 6.3 : 1), (d) M_3 (4.1 : 1), and (e) S_1 (1.6 : 1).

Table IV. Thermal Properties of the Inclusion Complexes of PEG-2000 and α-CD

Sample	T_c (°C)	T_m (°C)		ΔT (°C)	ΔH_c (J/g)	ΔH_m (J/g)	
		T_{m1}	T_{m2}			ΔH_{m1}	ΔH_{m2}
PEG-2000	40.57	57.56	58.47	16.99	152.53	−170.36	−159.66
S_1	—	—	—	—	—	—	—
C_2	28.78	51.99	53.89	23.21	12.74	−14.84	−13.75
C_4	23.70	53.24	53.55	29.54	9.42	−12.74	−9.48
M_1	31.75	53.42	55.59	21.67	55.19	−58.00	−56.58
M_2 (or C_3)	28.22	52.45	53.84	24.23	15.26	−19.61	−15.88
M_3	19.13	49.48	52.94	9.02	3.90	−7.26	−2.78

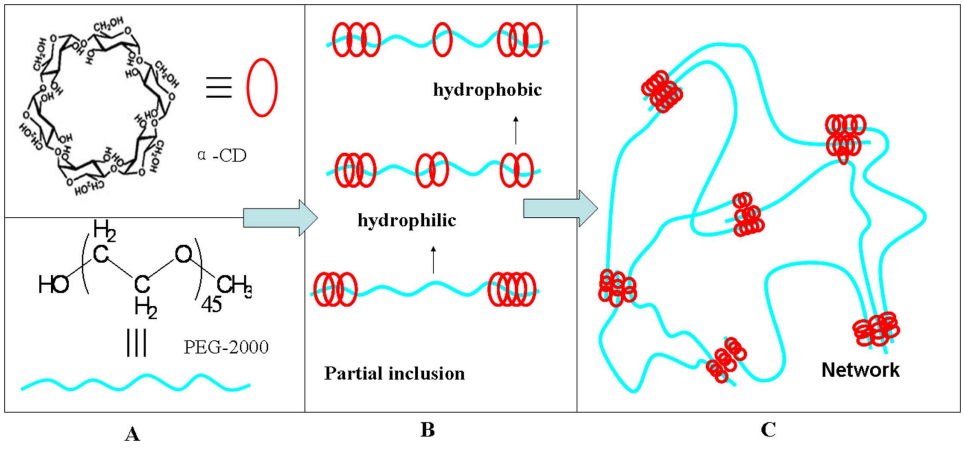
ΔHm_1, The change of melting enthalpy of inclusion complex during the first heating process; ΔHm_2, The change of melting enthalpy of inclusion complex during the second heating process; ΔH_C, The change of crystalline enthalpy of inclusion complex during the first cooling process.

The XRD analysis validated the previous results (Figure 6). Both the characteristic diffraction peak of the channel-type α-CD (20°) and that of the cage-type α-CD (12°) were observed in the complexes with different *R* values [Figure 4(c) and 6(a)]. With the decrease of *R*, the peak intensity at 20° increased, and that at 12° decreased. The results show that not all the feeding α-CDs could thread onto the PEG chains, and the length of channel-type structure was shorter at higher *R* so that the obtained hydrogel M_1 and M_2 is unstable [Figure 1(3–6)]. When *R* decreased to 4.1, the length of channel-type structure was longer, the size of the microcrystal was larger, and the obtained M_3 gel was stable [Figure 1(8)]. Although this have reduced the naked parts of the PEG chains, a stable hydrogel could be obtained because of the high concentration of PEG in aqueous solution.

The thermal properties of the inclusion complexes of PEG-2000 and α-CD were investigated by DSC (Figure 7 and Table IV). PEG is a crystalline polymer, and the T_m and enthalpy of PEG-2000 (ΔH_{m1}) are 58°C and 170 J/g, respectively. However, the PEG chain included in the cavity of α-CD could not array into the lattice to form crystals [Figure 7(e)]. Only the remaining uncovered PEG segments could crystallize, and this resulted in the decrease in T_m and enthalpy change of inclusion complex during the heating and cooling processes (ΔH). As shown in Figure 7 and Table IV, the T_m and ΔH values of the inclusion complexes were lower than those of pure PEG-2000. The lower *R* was, the lower T_m and ΔH of inclusion complex were.

Mechanism for the Gelation of PEG-2000 and α-CD

Scheme 1 shows a proposed mechanism for the gelation of PEG-2000 and α-CD. In the aqueous solution, the threading, dethreading, and sliding of the α-CD ring onto the PEG chain were in dynamic equilibrium. The α-CD ring could be located at any position of the PEG chain, especially for the low-MW PEG, which could nearly form stoichiometric complexes with the α-CD rings [Scheme 1(B)]. So the polypseudorotaxanes with necklacelike structure were thought to be multifunctional molecular chains, and the channel-type crystal structure, as crosslinking points of gelation, happened to self-assemble at any position of PEG chain and not just at the end of PEG chain [(Scheme 1(B)]. The resulting channel-type crystalline domains were hydrophobic and could act as physical crosslinking points. At the same time, the remaining uncovered PEG was hydrophilic and could act as network chains. Both of them constructed the supramolecular hydrogel [Scheme 1(C)].



Scheme 1. Schematic representation of supramolecular hydrogels based on inclusion complexes between PEG-2000 and α-CD. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

CONCLUSIONS

In this study, the inclusion complexation between α-CD and linear low-MW PEG (M_n = 2000) was thoroughly investigated. A kind of stable supramolecular hydrogel was obtained through the variation of $C_{PEG\text{-}2000}$ and R. The resulting hydrogel retained the basic characteristics of a supramolecular physical hydrogel, especially the property of shear thinning. The research was not only helpful to clearly determine the inclusion complexation between α-CD and low-MW PEG but also to provide a new idea of building biocompatible supramolecular hydrogels that should be useful as functional biomaterials for drug delivery.

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