Supramolecular-Structured Hydrogels Showing a Reversible Phase Transition by Inclusion Complexation between Poly(ethylene glycol) Grafted Dextran and α-Cyclodextrin

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ABSTRACT: Supramolecular-structured hydrogels were prepared on basis of the inclusion complexation between poly(ethylene glycol) grafted dextrans and α-cyclodextrins (α-CDs) in aqueous media. The inclusion complexes from the PEG grafted dextrans showed a unique gel−sol phase transition which cannot be obtained from usual polymer inclusion complexes that form crystalline precipitates. The gel−sol transition was based on the supramolecular assembly and dissociation, and the transition was reversible with hysteresis. The transition temperature was controllable by variation in the polymer concentration and the PEG content in the graft copolymers as well as the stoichiometric ratio between the guest and host molecules. The properties of the hydrogel were characterized by DSC, X-ray diffraction, and ^{13}C CP/MAS NMR. The X-ray diffraction data indicated that the gel contains a channel-type crystalline structure, demonstrated by a strong reflection at $2\theta = 20°$ ($d = 4.44$ Å). It was confirmed from the DSC and ^{13}C CP/MAS NMR measurements that all the PEG grafts participate in the complexation. A phase-separated structure consisting of hydrophobic and channel-type crystalline PEG inclusion complex domains and hydrated dextran matrices was suggested as the internal structure, which comprises the supramolecular-structured hydrogel.

Introduction

Various kinds of polymer inclusion complexes (PICs) formed by noncovalent host−guest interactions have been extensively reported and investigated as useful building blocks for constructing supramolecular structures.[1−3] Particularly, cyclodextrins (CDs) have been the most widely used host molecules, because they are water-soluble and capable of selectively including a wide range of guest molecules.[4] Harada et al. have introduced many PICs (or pseudo-polyrotaxanes) by a series of combinations between CDs, usually α-, *β*-, and *γ*-CD, which consist of 6, 7, and 8 glucose units, respectively, and the corresponding linear polymers.[5] Tonelli et al. have also studied several PICs and their unique properties from confined structures where each polymer chain is included and isolated.[6] They have fabricated polymer−polymer composites and blends with normally incompatible polymers using such a PIC formation.[7]

Over the past years, our group has tried to design various supramolecular-structured polymeric systems for biomedical applications such as drug carriers and tissue scaffolds.[8,9] We have reported characteristic drug release and degradation with desired patterns, which are induced by supramolecular dissociation. Recently, we have demonstrated a supramolecular network formation by the inclusion complexation between an α-CD-based molecular tube and poly(ethylene oxide) monocetyl ether-*graft*-dextran.[10]

Recently, hydrogels that can absorb a significant amount of water have attracted much attention for biomedical and pharmaceutical applications due to their high biocompatibility and other unique properties.[11−13] Chemical gels can be generally obtained by chemical cross-linking of hydrophilic polymers with appropriate cross-linking agents, which often cause some limitations to their biomedical applications.[14] On the other hand, physical gelation can be achieved by noncovalent cohesive interactions, such as hydrophobic interaction, stereocomplex formation, ionic complexation, and crystallization, and thus can avoid the use of such cross-linking agents and the related reactions.[15]

In this study, we demonstrate a new PIC structure that can introduce a novel type of gelation in aqueous media. It is hypothesized that IC formation of the polymers grafted to hydrophilic polymers, here represented as dextran, can induce crystalline PIC domains, which act as physical cross-linking. It is significant that the physical gelation is introduced by a specific host−guest interaction, providing supramolecular-structured hydrogels. Previously, Li et al. reported a gelation phenomenon using IC formation between the high molecular weight poly(ethylene oxide) and α-CD.[16] In that system, partial inclusion complexes, which formed at both ends of the PEO chains, introduced such gelation. Even though it has a distinct gelation mechanism and exhibits a sol−gel transition, the gel seems not suitable for use in biomedical fields because it needs a long gel induction time and a high temperature above 80 °C is required for gel melting. In contrast, such problems can be overcome with our gel system. The IC formation of the PEG grafted dextran with α-CD can induce a gelation with a short gel induction time. In addition, it is interesting that the obtained hydrogels exhibit a unique thermoreversible gel−sol transition based on supramolecular assembly and dissociation, and

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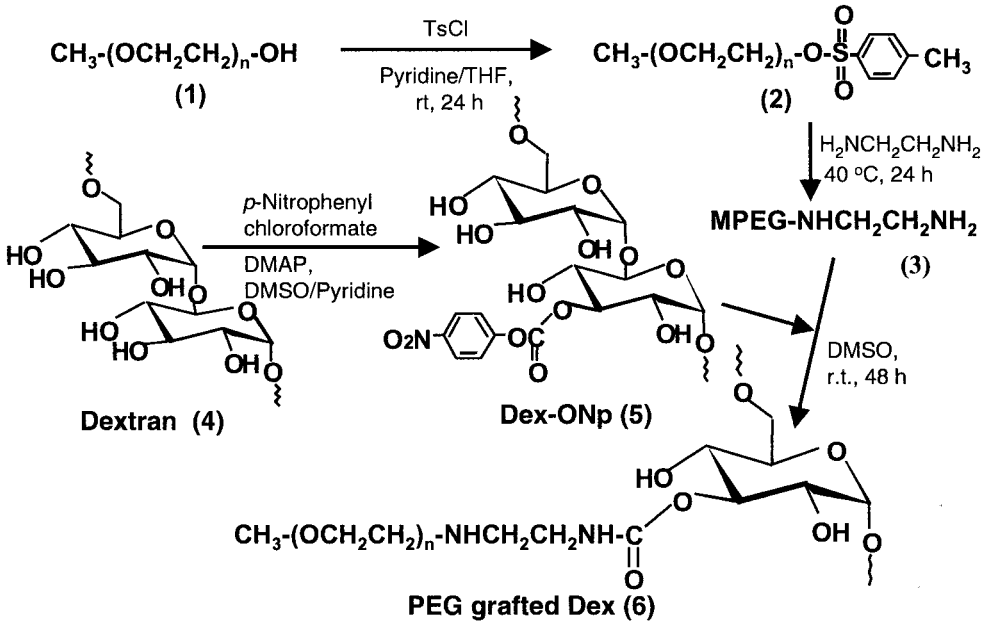
Scheme 1. Synthetic Route for PEG Graft Dextrans



the transition temperature is controllable from 20 to 55 °C. Such a hydrogel property may be useful in the field of biomedical applications, especially injectable drug delivery systems,[17] as well as for understanding the gel structure and gelation mechanism.

Experimental Section

Materials. Poly(ethylene glycol) methyl ethers (MPEG, Aldrich) with $\overline{M}_n$ = 750 and 2000 were used after drying in vacuo at 100 °C for 24 h. Dextran ($\overline{M}_n$ = 40 000) was purchased from Tokyo Chemical Industry Co., Tokyo, Japan. α-CD was purchased from Bio-Research Corporation, Yokohama, Japan. Dimethyl sulfoxide (DMSO, Wako), pyridine (Wako), and tetrahydrofuran (THF, Wako) were dried over CaH_2 and distilled. *p*-Toluenesulfonyl chloride (TsCl, Wako), ethylenediamine (EDA, Wako), *p*-nitrophenyl chloroformate (Aldrich), 4-*N*,*N*-(dimethylamino)pyridine (DMAP, Wako) and all other chemicals were used as received without further purification.

Synthesis of Amino-Terminated MPEG (MPEG-NH_2). MPEG of $\overline{M}_n$ = 750 (27 g, 36 mmol) was dissolved in 200 mL of a THF/pyridine mixture (1/1, v/v). TsCl (34.3 g, 180 mmol) was added to the solution, and the mixture was stirred for 12 h at room temperature. The product was precipitated from cold diethyl ether. The oily product was retrieved and recrystallized from ethanol. The product was filtered and dried under vacuum. Tosylated MPEG (**2**) was dissolved in EDA, and the solution was refluxed for 24 h. After evaporation of the EDA, the product was precipitated in cold diethyl ether. The precipitate was filtered, washed, and dried under vacuum. As a result of an acid−base titration of the amino end groups, more than 85% of the hydroxyl groups had been converted to amino end groups (yield: 60%). The MPEG-NH_2 of $\overline{M}_n$ = 2000 was obtained by the same procedures (yield: 80%).

Synthesis of PEG Grafted Dextrans. The hydroxyl groups of dextran were activated with *p*-nitrophenyl chloroformate in the presence of DMAP. Dextran (4 g, 0.1 mmol), *p*-nitrophenyl chloroformate (4.35 g, 21. 6 mmol), and a small amount of DMAP as a catalyst were dissolved in 250 mL of a mixture of DMSO and pyridine (1/1 in volume ratio) and kept at 0 °C for 8 h. The product was precipitated in ethyl alcohol and filtered. The final product was washed two times with ethyl alcohol and dried in vacuo for 24 h. The *p*-nitrophenyl groups in the activated dextran were confirmed by ^{1}H NMR characterization. The number of *p*-nitrophenyl groups in the activated dextran was 20 per 100 glucose units by comparing the integration values from four aromatic protons in the *p*-nitrophenyl groups (δ = 7.54 and 8.30 ppm) and anomeric protons of the glucose units in dextran (δ = 4.66 ppm).

Finally, PEG grafted dextrans were synthesized by a series of coupling reactions between the *p*-nitrophenyl chloroformate-activated dextran (Dex-ONp) and MPEG-NH_2, as shown in Scheme 1. A variation in the feed ratio introduced a different number of PEG grafts in the graft copolymers. As an example, 2 g of the activated dextran (0.04 mmol) and 1.2 g of MPEG-NH_2 (1.5 mmol) were dissolved in 60 mL of DMSO. After reaction at room temperature for 48 h, the solution was diluted with distilled water. The diluted solution was dialyzed (MWCO = 15 000) against water for 3 days to remove the unreacted MPEG-NH_2 and then lyophilized. The product was dissolved in an 0.01 M NaOH aqueous solution to hydrolyze the residual *p*-nitrophenyl groups in the graft copolymers, and dialysis/lyophilization was performed again (yield: 75%). The number-average molecular weight and the PEG graft number in the graft copolymers were calculated from the integration of two characteristic peaks from the methylene units in PEG and the anomeric proton of the glucose units in dextran.

Preparation of Inclusion Complexes Consisting of PEG Grafted Dextran and α-CD. For the preparation of the inclusion complexes, 2 mL of an aqueous solution saturated with α-CD (0.29 g) was added to glass vials containing a predetermined amount of the graft copolymers. The feed molar ratio between the PEG repeating unit (EG) and α-CD was varied in the range of 4:1−1:1 (EG:α-CD). The vials were mechanically shaken and kept for inclusion complexation at room temperature for a day. In a similar manner, an inclusion complex from PEG and α-CD was prepared as a reference for the graft copolymers. In this case, the solution mixture became opaque and PEG IC instantaneously formed as a crystalline precipitate after adding the α-CD solution. The precipitated PEG IC was separated by centrifugation and washed with distilled water, followed by drying in vacuo for 24 h.

Characterization. The ^{1}H NMR spectra of the graft copolymers were recorded using a 300 MHz NMR spectrometer (Varian, Unity plus). X-ray diffraction measurements were performed with a powder diffractometer (RINT2000, Rigaku) and two-dimensional image-plate photography using graphite-monochromatized Cu Kα radiation (λ = 1.542 Å). The X-ray diffraction patterns of the hydrogels were obtained for the samples sealed in glass capillary tubes. A differential scanning calorimeter (DSC) (DSC821^e, METTLER TOLEDO) was used to measure the thermal properties of the polymers. The DSC thermograms covered the temperature range of −30 to 130

Table 1. Synthetic Results of PEG Grafted Dextrans

sample	Dex-ONp (mmol)	MPEG-NH_2 (mmol)	$\overline{M_n}$ of MPEG (g/mol)	no. of grafts[a]	$\overline{M_n}$ (g/mol)[b]
GC-1	0.08	0.68	750	7.5	45 600
GC-2	0.04	0.63	750	13.5	50 100
GC-3	0.04	1.50	750	27.0	60 250
GC-4	0.05	0.25	2000	4.2	48 400
GC-5	0.05	0.50	2000	9.0	58 000

[a] The average number of grafts per dextran calculated by integral ratio of ^{1}H NMR spectra. [b] The number-average molecular weight of PEG grafted dextran determined by the peak integration of ^{1}H NMR spectra.

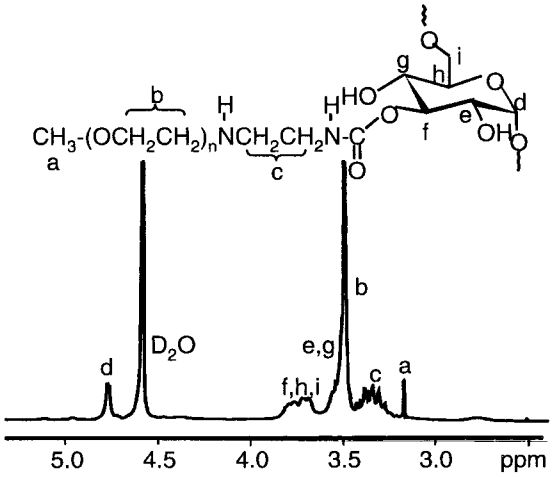


Figure 1. ^{1}H NMR spectrum of a PEG grafted dextran in D_2O.

°C at a scanning rate of 5 °C/min. The solid-state ^{13}C CP/MAS NMR spectrum was measured at 100.4 MHz on a JNM-GSX 400 NMR spectrometer with a sample spinning rate of 6 kHz at 19 °C. The amount of sample used was 100 mg. CP spectra were acquired with a 5 ms contact time, a 12 s repetition time, and 18 000 accumulations.

The gelation and gel melting were determined by a vial inversion method with a monotonic temperature increase or decrease of 1 °C per step. The sample vials were immersed in a water bath at each temperature for 10 min. The gelation temperature ($T_{gelation}$) was visually monitored with decreasing temperature when the polymer solutions did not flow any more by inverting the vials. The gels became mobile as the temperature increased. The point where the gels started to flow was taken as the gel-melting temperature ($T_{gel-melting}$).

Results and Discussion

Various kinds of PEG grafted dextrans with different graft numbers were successfully synthesized through a coupling reaction between the activated dextran and amino-terminated MPEG (**3**). The synthetic results of the graft copolymers are summarized in Table 1. For the graft copolymers obtained in this experiment, the average number of grafts per dextran ranged from 4 to 27, which was calculated from the ^{1}H NMR peak integration. The representative ^{1}H NMR spectrum shown in Figure 1 ascertains the chemical composition of the graft copolymers.

It is well-known that low molecular weight PEGs form inclusion complexes with α-CD by a stoichiometry of 2:1 (EG unit:α-CD) in aqueous solutions.[18] The stoichiometry (1.6:1 to 1.9:1) of our obtained PEG IC, which was calculated from the ^{1}H NMR peak integration, was almost consistent with the previously reported value. PEG grafted dextrans were also expected to form inclusion complexes with α-CD molecules due to the existence of the PEG grafts although dextran itself can not participate in the complexation. When the graft copolymers were added to aqueous solutions saturated with α-CD, the solutions became opaque within several minutes and finally changed to a gel. The induction time for gelation ranged from several minutes to several hours depending on the concentration and the PEG content of the graft copolymers. Usually, it takes a longer time for gelation with a low concentration and low PEG content of the graft copolymers.

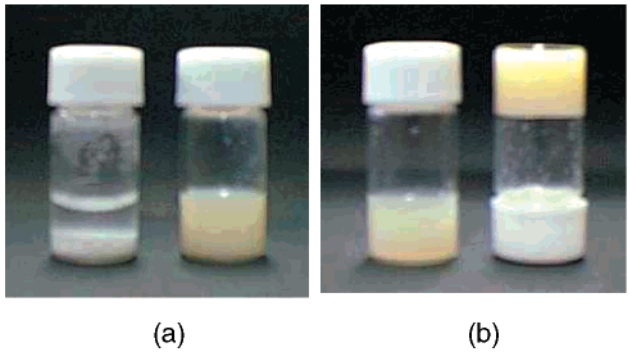


Figure 2. Photographs for comparing PEG IC with GC IC (a) and GC IC gel in upright and inverted glass vials (b).

Table 2. X-ray Interplanar Spacing Data of GC IC Hydrogel and PEG IC

	d_0/Å		
indices	hydrogel (hydrated)	hydrogel (freeze-dried)	PEG IC
001		16.40	15.80
100	11.90	11.80	11.80
002	8.90	8.11	7.86
110	6.90	6.83	6.80
210	4.50	4.46	4.44
300	3.97	3.94	3.92

The resulting graft copolymer ICs (GC ICs) exhibited a very different physical property from the typical PICs. Figure 2 shows the IC formation of PEG ($\overline{M_n}$ = 750) and a PEG grafted dextran (GC-3) with α-CD molecules in glass vials. Both polymer ICs were prepared from the same feed composition (EO:α-CD = 2:1). PEG IC was obtained as a crystalline precipitate, because the α-CD molecules became hydrophobic during inclusion complexation due to the formation of intermolecular hydrogen bonding among the α-CDs threaded along the polymer chain. On the other hand, for GC-3 IC, it did not show any flow even when the glass vial was inverted as shown in Figure 2b. The IC formation of the PEG grafted dextrans did not give any crystalline precipitates but led to gelation. This particular phenomenon is closely related to the inclusion complex formation between the PEG grafts and α-CD molecules, followed by a subsequent aggregation of PEG ICs to make physical junctions.

To characterize the crystalline structure of aggregations in the hydrogels, we measured the X-ray diffraction patterns of a hydrogel (GC-3 IC) in the freeze-dried and hydrated states and compared them with those from dextran and well-dried PEG IC. The X-ray reflection data from GC-3 IC and PEG IC are summarized in Table 2, and their diffraction patterns are compared in Figure 3. As shown in Figure 3a, a diffuse halo observed for dextran indicates that it exists in an amorphous state. In contrast, the diffraction pattern of PEG IC exhibits a number of sharp reflections including strong

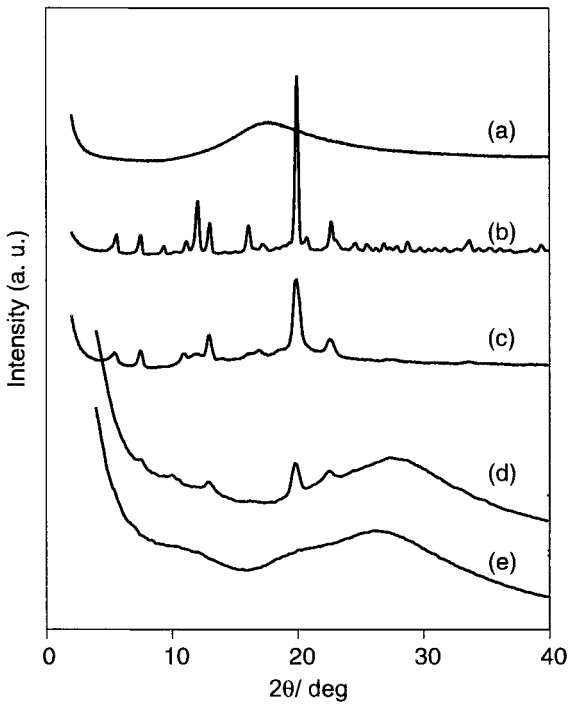


Figure 3. X-ray diffraction patterns for dextran (a), PEG IC (b), GC-3 IC in freeze-dried state (c), GC-3 IC in hydrated state (d), and GC-3 IC above $T_{gel-melting}$ (sol state) (e), measured with graphite-monochromatized Cu Kα radiation.

ones at $2\theta = 20.0°$ ($d = 4.44$ Å) and 22.6° ($d = 3.96$ Å). These are assigned to the 210 and 300 reflections from the hexagonal lattice with $a = 13.6$ Å. The strong {210} reflection is a typical peak observed for PICs with α-CD,[5,6,19] suggesting the electron density distribution of the core of the α-CD molecules with a radius of ∼5 Å. It is a well-known fact that PICs have a channel-type crystalline structure due to the long-chain nature of the guest molecules. These characteristic reflections also appeared in the profiles of both the freeze-dried and hydrated gels from GC-3 IC. These results indicate that the GC ICs contain the channel-type crystalline structure like the other PICs not only in the dried state but also in the hydrated state, although the broader reflection profiles suggest some disorder in the aggregation. From the spacings of the rather sharp equatorial reflections, the lateral distance between the hexagonally packed complexed chains expanded in the hydrated state ($a = 13.8$ Å) and freeze-dried state ($a = 13.65$ Å) as compared with that of PEG IC ($a = 13.6$ Å). The nonequatorial reflections of PEG IC suggested the 3D crystalline order with the axial repeat distance of 15.8 Å corresponding to the dimerized sequence of α-CD. On the other hand, the hydrogel exhibited only two non-equatorials, 001 (5.4°) and 002 (10.9°), which indicated the axial period of 16.3 Å, but with displacement disorder in the axial direction. The longer axial spacing is attributable to the water molecules bound in the α-CD sequence of the hydrogel. Such crystalline aggregations induced by IC formation can be considered to play an important role in the gelation.

The thermal properties of the GC ICs were observed by differential scanning calorimetry (DSC) and compared with their constituent polymers, as shown in Figure 4. While dextran did not show any melting behavior over our experimental temperature range, a small melting peak was observed around 45 or 50 °C for the graft copolymers, resulting from the melting of

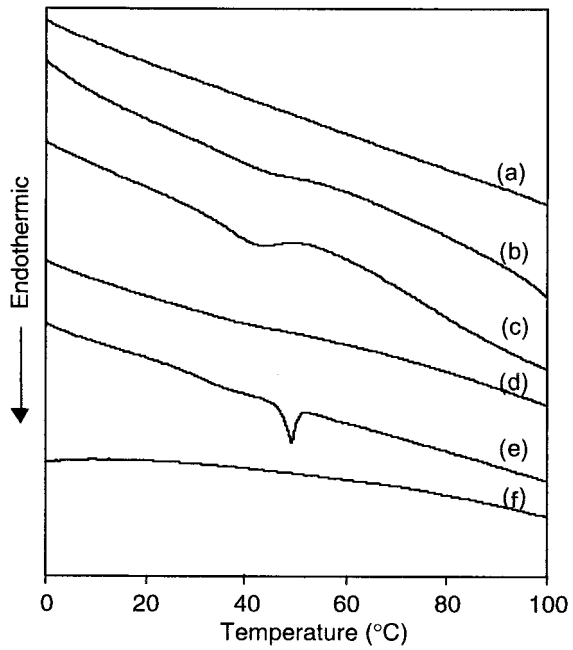


Figure 4. DSC thermograms of dextran (a), GC-1 (b), GC-3 (c), GC-3 IC (d), GC-5 (e), and GC-5 IC (f) in freeze-dried state.

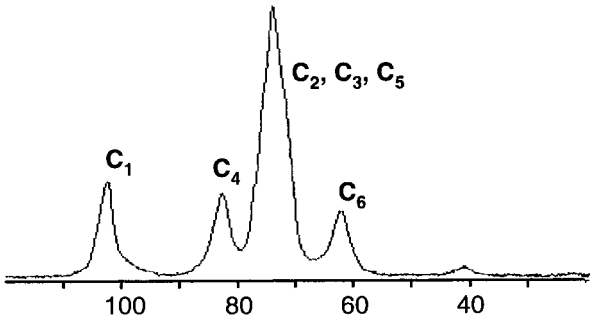


Figure 5. ^{13}C CP/MAS NMR spectrum of GC IC.

the PEG chains. The PEG melting peak became larger and clearer with the PEG content and length increasing in the graft copolymers. However, for the GC ICs there is no observed melting peak, corresponding to the melting of PEG because as long as the PEG chains are included are isolated in the CD molecules, they do not show any more melting behavior. These results may indicate that all the PEG chains participate in the formation of a new channel-typed crystalline structure together with the α-CD molecules. They are well coincident with those from usual previously reported PICs.[6]

Another strong evidence for the inclusion complexation of the PEG grafts with α-CD molecules can be obtained by observing the ^{13}C CP/MAS NMR spectra of the GC ICs. CD molecules retain a less symmetrical cyclic conformation when crystallized in a cage structure with water as the guest molecules and are represented by multiple resolved C_1 and C_4 resonances of the glucose units of the α-CD.[6,19] When polymer guest molecules are introduced into the internal cavity of the α-CD and are crystallized in a channel structure, they acquire a symmetrical cyclic conformation, resulting in single C_1 and C_4 resonances. In Figure 5, each carbon of the glucose is observed as a single peak, indicating that the α-CD molecules include PEG chains in a channel structure IC.

The physical hydrogel obtained here can be discriminated from the typical physical gels reported so far. The

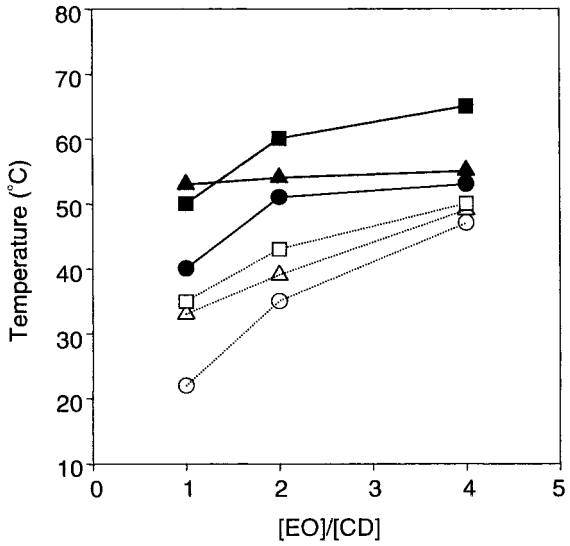


Figure 6. Gel-melting and gelation behavior of GC ICs as a function of the ratio of [EO]/[CD] (▲, $T_{gel-melting}$ of GC-1 IC; △, $T_{gelation}$ of GC-1 IC; ●, $T_{gel-melting}$ of GC-3 IC; ○, $T_{gelation}$ of GC-3 IC; ■, $T_{gel-melting}$ of GC-5 IC; □, $T_{gelation}$ of GC-5 IC).

gelation is based on supramolecular assembly between the host and guest molecules while associative forces for physical cross-linking in the typical physical gels include hydrogen bonding, ionic association, hydrophobic interaction, stereocomplexation and cross-linking by crystalline segments, and solvent complexation.[21] Furthermore, our gel was found to easily and nonelastically deform when a mechanical shear stress was applied.

It is very attractive that the gel exhibits a transition from gel to sol with increasing temperature. It becomes mobile (sol phase) above a certain temperature, here defined as $T_{gel-melting}$. The GC IC hydrogels containing PEG grafts of $\overline{M}_n$ = 750 exhibited three kinds of phases. When the GC ICs were formed, the solutions became opaque and immobile (opaque gel). As the temperature increased, they were still opaque but mobile (opaque solution). With further increased temperature, they became clear solutions. On the other hand, if the temperature decreased below any temperature, represented as the gelation temperature ($T_{gelation}$), they returned to the opaque gel phase again. However, for GC-4 IC and GC-5 IC with long PEG grafts ($\overline{M}_n$ = 2000), they did not exhibit a change from an opaque to clear solution even with further heating to temperatures that are 5 °C higher than their gel-melting temperature. This means that they do not completely dissociate and retain their complexation to some degree even above $T_{gel-melting}$.

All the hydrogels showed reversibility in the gel−sol transition with temperature fluctuation, and there exists a significant difference between $T_{gel-melting}$ and $T_{gelation}$ (hysteresis). Figure 6 shows the results of measuring the gel-melting and gelation temperatures of GC-1 IC, GC-3 IC, and GC-5 IC. The gel property could be controlled by several parameters, for example, solution concentration, feed ratio of [EO]/[CD], and PEG content of the graft copolymers. For GC-3 IC, with an increasing content of EO from [EO]/[CD] = 1 to 2 in the feed, $T_{gel-melting}$ dramatically increased, but a further increase over [EO]/[CD] = 2 was not observed. The increase in $T_{gel-melting}$ as well as $T_{gelation}$ with the increasing ratio of [EO]/[CD] may be attributed to an enhanced physical cross-linking in the hydrogel, resulting from an increase in the amount of IC formation between the PEG chains and α-CD molecules. The stoichiometry of [EO]/[CD] is known to be 2.[18] Above the stoichiometric ratio such an increase is not so large because almost all the PEG grafts and α-CD molecules have already participated in the inclusion complexation. As a result, the feed ratio was found to significantly affect the gel properties. However, GC-1 IC with a relatively low PEG content showed less dependence of $T_{gel-melting}$ on the feed ratio, and its $T_{gel-melting}$ was observed at higher temperatures than GC-3 IC. A high polymer concentration might contribute to the gel stability, resulting in a higher $T_{gel-melting}$. GC-5 IC showed a relatively higher $T_{gel-melting}$ and $T_{gelation}$ due to the long nature of the PEG grafts, resulting in more stable ICs which were not easily dissociable even at temperatures higher than its $T_{gel-melting}$.

The properties of the hydrogels, gel melting, and gelation are closely related to supramolecular assembly and dissociation, corresponding to a threading−dethreading process of the α-CD molecules along the PEG grafts. This fact could be confirmed from X-ray diffraction measurements of the hydrogels. Parts d and e of Figure 3 represent the diffraction patterns from GC-3 IC in the gel and sol phases, respectively. All the characteristic peaks from the crystalline structure in the gel disappeared in the sol phase, indicating the dissociation of the PIC structure. Since the inclusion complexation of a polymer chain into the CDs is entropically unfavorable and prompted by attractive interactions such as hydrogen-bonding and hydrophobic interactions, the temperature increase can induce dissociation of the polymer chains from the CDs with a restoration of its intrinsic entropy from random conformations in solution, and vice versa.[22]

The hydrogel structure of GC ICs is schematically represented in Figure 7. Figure 7a shows the presence of the graft copolymers and α-CD molecules before the complexation process. It also stands for the sol state of the GC ICs above $T_{gel-melting}$, where the α-CD molecules are dethreaded from the PEG grafts, resulting in the dissociation of the supramolecular assembly. On the other hand, Figure 7b represents the GC IC formation in aqueous media, where the α-CD molecules are threaded on the PEG grafts by hydrogen-bond formation among adjacent CDs, resulting in hydrophobically aggregated crystalline domains. Such PEG IC domains can act as physical cross-links that hold together the hydrated dextran chains, introducing a phase-separated gel phase as shown in Figure 7b.

Conclusion

A novel thermoreversible hydrogel network with a supramolecular structure that consisted of biodegradable and biocompatible components, PEG grafted dextrans and CD molecules, was developed using host−guest interactions. PEG grafts were found to form inclusion complexes with α-CD molecules, resulting in physical junctions. The thermoreversible gelation is based on supramolecular assembly and dissociation. Considering that most polymeric systems showing a phase-transition lack biodegradability and involve organic reactions, such a gel system would be very useful in many biomedical applications, including injectable drug delivery and tissue engineering due to biocompatibility, biodegradability, and supramolecular functionality. The physical properties needed for specific applica-

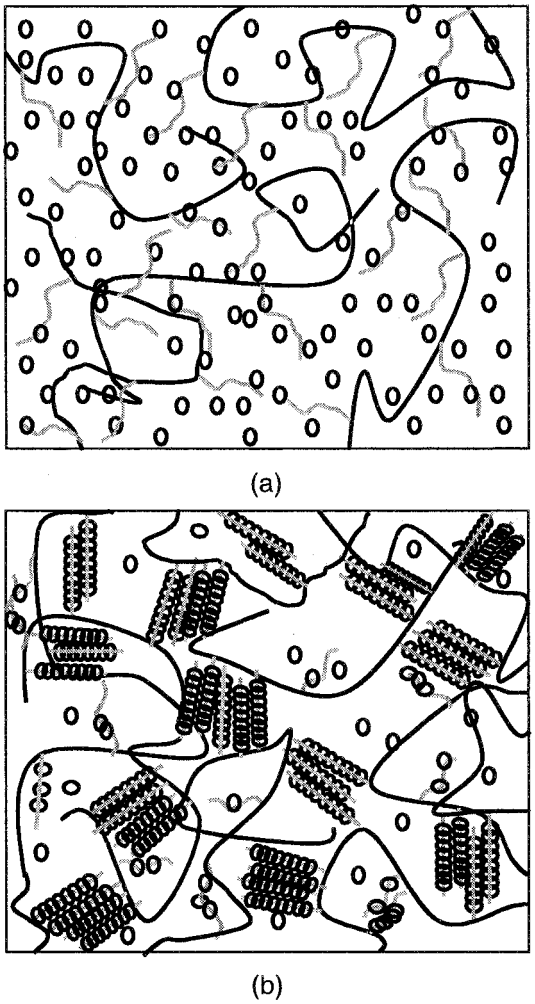


Figure 7. Schematic illustration of proposed structure of supramolecular-structured gel by inclusion complexation between PEG grafted dextran and α-CD: (a) uncomplexed or dissociated state corresponding to the initial stage before inclusion complexation between PEG grafts and α-CD molecules and above the gel-melting temperature, respectively (sol phase); (b) complexed state corresponding to the stage where inclusion complexation was partially or completely achieved or below the gelation temperature (gel phase).

tions could be improved by structural variation in the graft copolymers or changing the combination of polymer grafts and CD molecules.

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