Formation of Supramolecular Hydrogels Induced by Inclusion Complexation between Pluronics and α-Cyclodextrin

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Received April 30, 2001
Revised Manuscript Received July 17, 2001

Introduction. Polymer hydrogels are attractive for different biomedical applications because of their favorable biocompatibility.[1] Hydrogels, for example, play an important role in controlled drug delivery because of their pertinence in delivering delicate bioactive agents such as proteins. Recently, physical hydrogels formed with temperature- or pH-sensitive copolymers or based on stereocomplexation of enantiomeric polymers have attracted much attention and been studied potentially as injectable drug delivery matrix.[2]

Cyclodextrins (CDs) are a series of cyclic oligosaccharides composed of 6, 7, and 8 D(+)-glucose units linked by α-1,4-linkages and named α-, *β*-, and *γ*-CD, respectively. They have been extensively studied in supramolecular chemistry as host molecules capable of including guest molecules ranging from small organic/inorganic compounds to polymers.[3] It was reported that linear polymers such as poly(ethylene oxide) (PEO) can penetrate the inner cavity of cyclodextrins to form inclusion complexes with necklace-like supramolecular structure.[4] Previously, we studied the sol−gel transition during inclusion complexation between α-CD and high molecular weight PEOs.[5] Pluronics are the triblock copolymers of poly(ethylene oxide)−poly(propylene oxide)−poly(ethylene oxide) (PEO−PPO−PEO), which were extensively studied as a nonionic surfactant.[6] Here we have found the gel formation of pluronic and α-CD when PEO blocks of the copolymers form inclusion complexes with α-CD in aqueous solution. This is the first report that a block copolymer forms hydrogels with a cyclodextrin.

Results and Discussion. Table 1 shows the Pluronic PEO−PPO−PEO triblock copolymers used in this study and the results of the gelation of the Pluronic copolymers with and without α-CD in aqueous solution. It was reported that aqueous solutions of certain Pluronics form gels at high concentrations and elevated temperatures.[7] We tested the gel formation of Pluronics at concentrations of 40 and 13 wt %, respectively, at 22 °C. Of all the copolymers we tested, Pluronic copolymers 5, 6, and 9 formed hydrogels at 40 wt %, while none of the copolymers gelled at 13 wt % concentration. However, aqueous solutions containing 13 wt % of Pluronic copolymers 4, 5, 6, 7, 8, 9, or 10 and 9.7 wt % of α-CD turned into viscous gels at 22 °C (Table 1). In other words, α-CD can aid the gel formation at room temperature for Pluronics with 25 wt % or more of PEO segment even at a low polymer concentration. Interestingly, we found that the same solutions of Pluronics and α-CD which gelled at 22 °C did not form hydrogels at 4 °C (Table 1). The solutions of copolymers 4, 5, 6, 7, 8, 9, or 10 and α-CD became turbid, and white suspensions formed instead of the hydrogels at 4 °C.

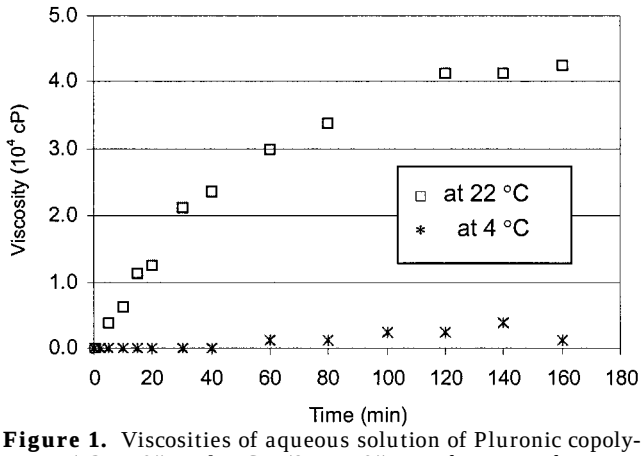

Figure 1. Viscosities of aqueous solution of Pluronic copolymer 4 (13 wt %) and α-CD (9.7 wt %) as a function of time at 22 and 4 °C.

The gel formation was traced by the changes in viscosity of the solutions, using a Brookfield HADV-III+ digital viscometer coupled with a small sample adapter SSA 15/7R and a temperature controlling unit. As shown in Figure 1, the viscosity of a solution containing 13 wt % of copolymer 4 and 9.7 wt % of α-CD increased up to 10^4 cP at 22 °C, while that of the same solution remained almost unchanged at a level lower than a few hundred cP. We also tested the viscosities of a copolymer 4 solution at 13 wt % or an aqueous solution containing 13 wt % of copolymer 4 and 9.7 wt % of D(+)-glucose at 4 and 22 °C, respectively. The viscosities of the two solutions at both temperatures were found to remain unchanged with time at about 20 cP, which is the lowest reading of the equipment.

It is known that α-CD will form crystalline inclusion complexes with low molecular weight PEO in aqueous solution.[8] The inclusion complexes formed by α-CD and PEO blocks of Pluronic are thought to aggregate into microcrystals, which act as physical cross-links and induce formation of a supramolecualr polymer network, consequently resulting in the gelation of the solutions. The micellization of the PPO block is also important in the gelation of the copolymer and α-CD solutions. At the elevated temperatures, the hydrophobic interaction between the PPO segments of Pluronics facilitates the formation of the polymer network. This is why a solution of Pluronic and α-CD could not form hydrogels at 4 °C, at which temperature the interaction between PPO segments of Pluronic is weak and the micelles tend to dissociate.[9] Therefore, the driving force for the gelation of Pluronic and α-CD solutions is a combination of the inclusion complxation between α-CD and PEO blocks and the micellization of the PPO block of Pluronics.

The inclusion complex formation between PEO blocks of the Pluronic copolymers and α-CD in the hydrogels was confirmed with wide-angle X-ray diffraction studies of the hydrogels. Figure 2 shows the X-ray diffractograms for the hydrogels and other inclusion complexes of α-CD with propionic acid and PEO of molecular

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10.1021/ma010742s CCC: $20.00
Published on Web 09/12/2001

Table 1. Pluronic PEO−PPO−PEO Triblock Copolymers and Their Gelation with and without α-CD in Aqueous Solutions[a]

				gelation of Pluronics at 22 °C		α-CD-induced gelation of Pluronics[e]	
copolymer[b]	composition	av MW	PEO (wt %)	high conc[c]	low conc[d]	22 °C	4 °C
1	$EO_1PO_{17}EO_1$	1100	10	−	−	−	−
2	$EO_2PO_{31}EO_2$	2000	10	−	−	−	−
3	$EO_3PO_{43}EO_3$	2800	10	−	−	−	−
4	$EO_{10}PO_{44}EO_{10}$	3400	25	−	−	+	−
5	$EO_{15}PO_{53}EO_{15}$	4400	30	+	−	+	−
6	$EO_{20}PO_{70}EO_{20}$	5800	30	+	−	+	−
7	$EO_{13}PO_{30}EO_{13}$	2900	40	−	−	+	−
8	$EO_{11}PO_{16}EO_{11}$	1900	50	−	−	+	−
9	$EO_{113}PO_{57}EO_{113}$	13300	75	+	−	+	−
10	$EO_{76}PO_{30}EO_{76}$	8400	80	−	−	+	−

[a] "+" means a gel was formed, and "−" means no gel was formed. [b] Copolymers 4 and 9 were purchased from Polysciences, Inc., and the others from Aldrich. [c] Pluronic concentration 40 wt %. [d] Pluronic concentration 13 wt %. [e] Concentrations of Pluronic and α-CD were 13 and 9.7 wt %, respectively.

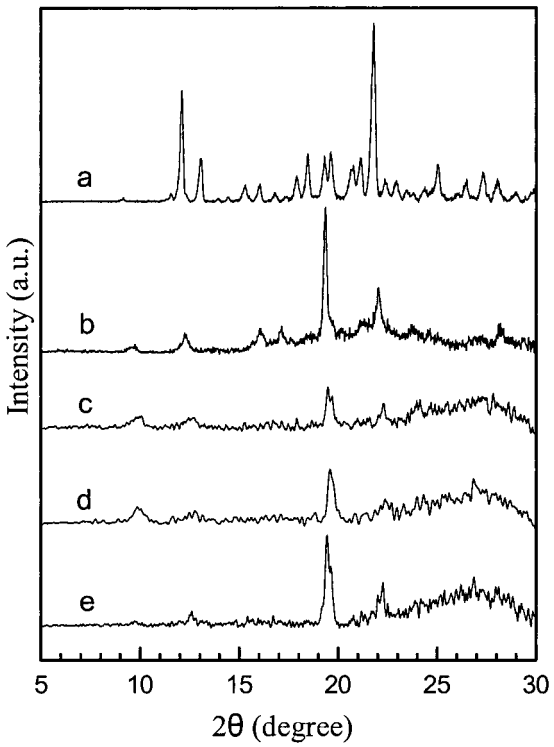

Figure 2. X-ray diffractograms for α-CD−propionic acid complex (a), α-CD−PEO (MW 1000) complex (b), and hydrogels formed with α-CD and Pluronic copolymers 4 (c), 6 (d), and 10 (e).

weight 1000. In Figure 2a, the pattern of α-CD-propionic acid complex represents a cage type structure of α-CD inclusion complexes.[10] In Figure 2b, the pattern of α-CD-PEO complex with a number of sharp reflections and the main one at $2\theta = 19.4°$ ($d = 4.57$ Å) represents the channel type structure of crystalline necklace-like complex of α-CD and PEO,[8,10] which is totally different from that of α-CD−propionic acid complex. The pattern for the α-CD−PEO complex also appears in Figure 1c−e, suggesting the existence of the inclusion complex of α-CD and the PEO blocks of Pluronics, which provides the primary driving force for the gelation of the solutions of pluronic copolymers and α-CD.

The supramolecular hydrogels may be used as a controlled release matrix in protein delivery. A preliminary in vitro study revealed that the hydrogels formed with different Pluronics and α-CD showed a wide range of release kinetics (results will be published elsewhere). A study of the rheological properties of the gels showed that the gels are thixotropic; i.e., the viscosity of the hydrogels greatly diminishes as they are sheared, rendering the controlled release formulations injectable through fine needles.

In conclusion, Pluronic copolymers containing more than 25 wt % PEO segments can form hydrogels with α-CD at room temperature and low copolymer concentrations. This work has demonstrated a new class of supramolecular hydrogels formed with a triblock copolymer and cyclodextrin. Now the detailed studies on the gel formation and their applications as biomaterials are in progress.

Acknowledgment. This work was financially supported by the Institute of Materials Research and Engineering.

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MA010742S