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Cyclodextrin Inclusion Polymers Forming Hydrogels

Jun Li

Abstract This chapter reviews the advances in the developments of supramolecular hydrogels based on the polypseudorotaxanes and polyrotaxanes formed by inclusion complexes of cyclodextrins threading onto polymer chains. Both physical and chemical supramolecular hydrogels of many different types are discussed with respect to their preparation, structure, property, and gelation mechanism. A large number of physical supramolecular hydrogels were formed induced by self-assembly of densely packed cyclodextrin rings threaded on polymer or copolymer chains acting as physical crosslinking points. The thermo-reversible and thixotropic properties of these physical supramolecular hydrogels have inspired their applications as injectable drug delivery systems. Chemical supramolecular hydrogels synthesized from polypseudorotaxanes and polyrotaxanes were based on the chemical crosslinking of either the cyclodextrin molecules or the included polymer chains. The chemical supramolecular hydrogels were often made biodegradable through incorporation of hydrolyzable threading polymers, end caps, or crosslinkers, for their potential applications as biomaterials.

Keywords Biomaterials, Cyclodextrin, Drug delivery, Hydrogel, Inclusion complex, Polyrotaxane, Supramolecule

Contents

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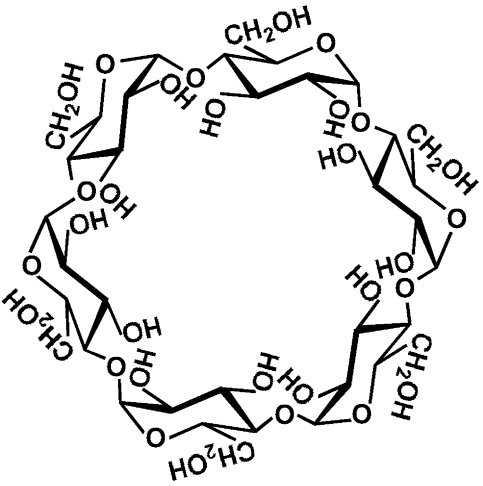
1 Introduction

Hydrogels are three-dimensional crosslinked macromolecular networks formed by hydrophilic polymers swollen in water. The three-dimensional networks can retain large volumes of water in the crosslinked structures. The extent of swelling and the content of water are largely dependant on the hydrophilicity of the polymer chains and the crosslinking density. The crosslinks can be formed by either covalent bonds or physical cohesion forces between the polymer segments such as ionic bonds, hydrogen bonds, van der Waals forces, and hydrophobic interactions [1–4]. Polymeric hydrogels have been of great interest relative to biomaterials applications because of their favorable biocompatibility [5, 6]. High in water content, they are attractive for delivery of delicate bioactive agents such as proteins [2, 7, 8]. For example, chemically crosslinked poly(ethylene oxide) (PEO) hydrogels have been extensively studied for this purpose [9–11].

Cyclodextrins (CDs) are a series of natural cyclic oligosaccharides composed of 6, 7, or 8 D(+)-glucose units linked by α-1,4-linkages, and named α-, β-, or γ-CD, respectively (Fig. 1). The geometry of CDs gives a hydrophobic inner cavity having a depth of ca. 8.0 Å, and an internal diameter of ca. 4.5, 7.0, and 8.5 Å for α-, β-, and γ-CD, respectively [12]. Various molecules fit into the cavity of CDs to form supramolecular inclusion complexes, which have been extensively studied as models for understanding the mechanism of molecular recognition [13–15].

The overwhelming interest on the developments of CD inclusion polymers arose since the discovery of α-CD inclusion complexes with PEO of different molecular weights [16] and the subsequent synthesis of the polyrotaxanes composed of multiple α-CD rings threaded and entrapped on a polymer chain (Fig. 2) [17,18]. So far, a large number of reports have been published on the CD-based polypseudorotaxanes and polyrotaxanes [12, 18–49] and their applications in biomaterials [50–58].

Fig. 1 Structure of α-CD



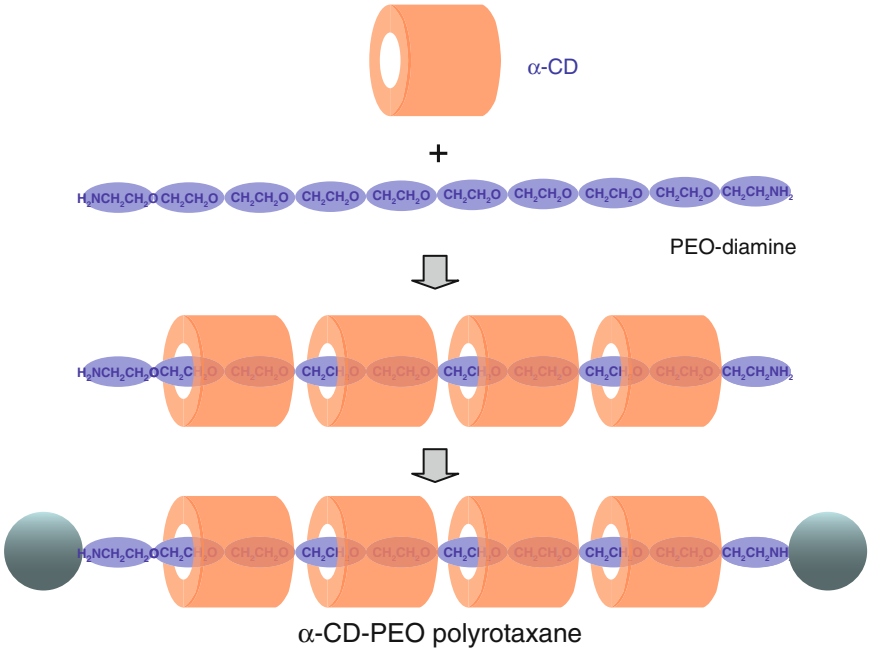


Fig. 2 The synthesis of polyrotaxane composed of multiple α-CD rings threaded and entrapped on a PEO chain [17]

The first report on a CD inclusion polymer forming hydrogels dates back to 1994, which describes the discovery of the sol–gel transition during the inclusion complex formation between α-CD and high molecular weight PEO in aqueous solution [59]. The gelation was induced by the partially formed α-CD–PEO inclusion complexes, which self-assembled into water-insoluble domains acting as a kind of

physical crosslinking. This review will update the developments of hydrogels based on the inclusion complexes, both polypseudorotaxanes and polyrotaxanes, formed between CDs and various polymers and copolymers. There are basically two classes of CD inclusion complex hydrogels: the physical hydrogels formed from polypseudorotaxanes induced by the self-assembly of inclusion complex domains acting as the physical crosslinks and the chemical hydrogels crosslinked through intermolecular covalent bonding either between CD molecules or between included polymers.

There are also physical hydrogels self-assembled from modified CDs in the absence of polymers [60], or physical hydrogels obtained by reversible inclusion compound formation between CD polymers and guest dimmers [61] or guest-containing copolymers [62–64], and between CD dimmers and thermosensitive guest-containing copolymers [65]. Another interesting thermosensitive pseudo-block copolymer system with controllable low critical solution temperature (LCST) based on CD-star polymer and guest-bearing PEO was reported recently [66]. These CD-based systems do not involve the inclusion complexation of polymer chains in CD cavities, and are out of the scope of this review. Readers can refer to the relevant literature for the details.

2 Physical Hydrogels Formed by Polypseudorotaxanes and Polypseudorotaxanes

2.1 Gelation Induced by Inclusion Complexation Between α-CD and PEO

2.1.1 Hydrogels of α-CD and PEO Homopolymer

The formation of inclusion complexes between α-CD and PEO of medium or low MW is accompanied by the precipitation of the formed polypseudorotaxanes from the aqueous solutions. The polypseudorotaxane precipitates are crystals that are self-assembled from the inclusion complexes. This phenomenon indicates that the formation of the polypseudorotaxanes altered the water solubility of their components, i.e., α-CD and PEO, which are both very hydrophilic and water-soluble. However, the α-CD–PEO polypseudorotaxanes are less water-soluble.

When high molecular PEO (MW higher than 3,500) is used to form polypseudorotaxanes with α-CD, the PEO chains thread into α-CD from the two ends to form inclusion complexes, which subsequently self-assemble into crystalline and water-insoluble domains, while the middle segments of PEO still remain uncomplexed and hydrophilic. As a result, the polypseudorotaxanes of α-CD and high molecular PEO form hydrogels (Fig. 3) [59]. This is an interesting class of supramolecular hydrogels in which only physical crosslinking is involved. The hydrogels of α-CD and high molecular PEO were further studied in terms of their structures, properties, and applications as an injectable drug delivery system [67]. Table 1 lists the α-CD–PEO

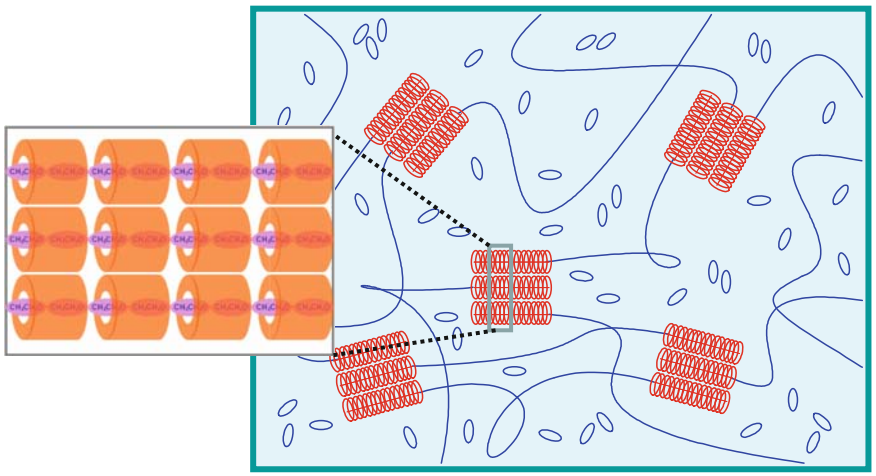


Fig. 3 Hydrogel formed between α-CD and high molecular weight PEO based on the partially formed self-assembled inclusion complex domains as physical crosslinks [59]

Table 1 Preparation of α-CD–PEO hydrogels [67]

α-CD–PEO hydrogel[a]	Average MW of PEO	Gel composition	
		α-CD (g mL^{-1})	PEO (g mL^{-1})
Gel-8K-60	8,000	0.0967	0.133
Gel-10K-60	10,000	0.0967	0.133
Gel-20K-60	20,000	0.0967	0.133
Gel-35K-20	35,000	0.0967	0.044
Gel-35K-40	35,000	0.0967	0.088
Gel-35K-60	35,000	0.0967	0.133
Gel-35K-80	35,000	0.0967	0.177
Gel-35K-100	35,000	0.0967	0.222
Gel-100K-60	100,000	0.0967	0.133

[a]The hydrogels were prepared by mixing 0.3 mL of α-CD aqueous solution (0.145 g mL^{-1}) with 0.15 mL of PEO solution. The first and second numbers denote the number–average MW of PEO and the amount of PEO used in the hydrogel preparation in mg, respectively. For example, Gel-10K-60 means 60 mg of PEO with number–average MW of 10,000 was used

hydrogels studied in that work, including the molecular weights of PEO and the gel compositions. Mixture of the PEO and α-CD solutions became opaque within minutes or hours of contact, depending on the concentrations of PEO and α-CD, as well as on the molecular weight of PEO. It may take even longer until the gel forms. For most compositions, the supramolecular hydrogels turned fluid upon heating at above 70 °C.

The threading of α-CD on the PEO chains and formation of inclusion complexes and their supramolecular self-assembly in the hydrogels were confirmed

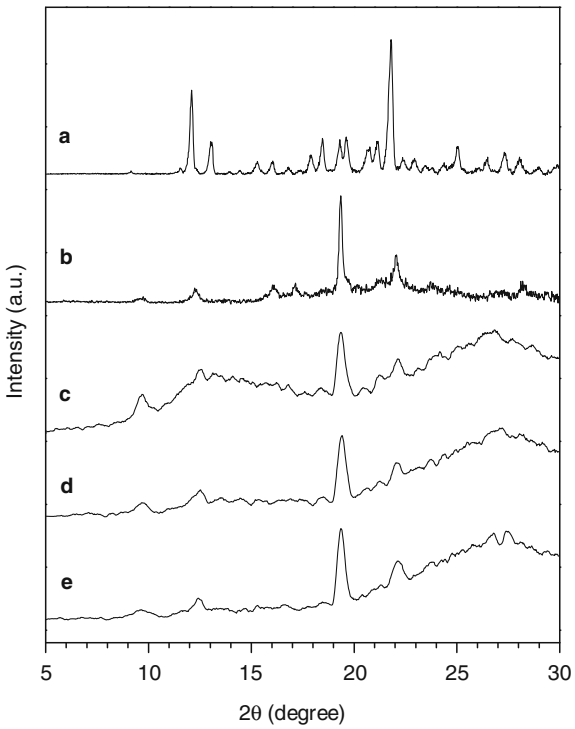


Fig. 4 a–e Wide-angle X-ray diffractograms for α-CD–propionic acid complex **a**, crystalline stoichiometric α-CD–PEO (MW 1,000) inclusion complex **b**, and α-CD–PEO supramolecular hydrogels Gel-10K-60 **c**, Gel-20K-60 (**d**), and Gel-35K-60 **e** [67]

with wide-angle X-ray diffraction studies of the hydrogels in comparison with other inclusion complexes of α-CD with propionic acid and PEO of low molecular weight (MW 1,000) (Fig. 4) [67]. In Fig. 4a, the pattern of α-CD–propionic acid complex represents a cage-type structure of α-CD inclusion complexes. In Fig. 4b, the pattern of crystalline α-CD–PEO (MW 1,000) complex with a number of sharp reflections represents the channel-type structure of necklace-like stoichiometric inclusion complex of α-CD and low molecular weight PEO, which is totally different from that of α-CD–propionic acid complex. In particular, the sharp reflection at $2\theta = 19.4^\circ$ ($d = 4.57$ Å) is a characteristic peak for the channel-type α-CD inclusion complexes. In Fig. 4c–e, the characteristic peak as well as a similar pattern to α-CD–PEO (MW 1,000) complex are observed, suggesting the gel system contains necklace-like inclusion complexes formed by α-CD densely threaded on parts of the PEO segments, and its self-assembling acts as physical cross-links and provides the primary driving force for the gelation of the solutions of α-CD and the high molecular weight PEOs. The patterns in Fig. 4c–e are quite broad as compared to that of the crystalline stoichiometric α-CD–PEO (MW 1,000) complex. This is in accordance with the fact that the crystalline domains within the hydrogel are rather small. The hydrogel contains large amorphous domains of PEO chains besides the crystalline ones. The amorphous domains are necessary for the hydrogel to retain large volumes of water in its supramolecular structure.

The gel formation can be confirmed visually [59], or be traced with the viscosity of the PEO/α-CD systems, which increased significantly during the gelation [67]. The gelation kinetics is dependent on the concentrations of the polymer and cyclodextrin, as well as on the molecular weight of the PEO used. Generally, the higher the molecular weight, the slower the gelation process, because the PEO must thread through α-CD at the two ends, and the concentration of the ends becomes lower with increasing molecular weight PEO [59].

2.1.2 Hydrogels of α-CD and PEO Block Copolymers

Since α-CD and high molecular weight PEO can form supramolecular hydrogels where the gelation is induced by inclusion complex domains formed by the partially complexed PEO segments, a block copolymer comprising a flanking PEO block is also possible to form a hydrogel with α-CD. A number of works on supramolecular hydrogel formation between α-CD and triblock or diblock copolymers comprising PEO block and other thermosensitive or biodegradable polymer blocks were reported [68–72].

Although PEO–PPO–PEO triblock copolymers (also known as Pluronics) form hydrogels at high concentrations and elevated temperatures, it was found that α-CD could aid the formation of hydrogels of PEO–PPO–PEO triblock copolymers with 25 wt% or more of PEO segment at much lower copolymer concentrations [68]. The hydrogel formation was traced by the changes in viscosity of the solutions. The viscosity of a solution containing 13 wt% of copolymer $EO_{10}PO_{44}EO_{10}$ and 9.7 wt% of α-CD reached up to 10^4 cP at 22 °C, while that of the same solution without a-CD remained at a level lower than a few hundred cP. The studies also tested the viscosities of the same copolymer $EO_{10}PO_{44}EO_{10}$ solution at 13 wt%, or the same solution with 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 a low level.

The inclusion complexes formed by α-CD and PEO blocks of Pluronics are thought to aggregate into microcrystals, which act as physical crosslinks 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 Pluronic 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. Therefore, the driving force for the gelation of Pluronic and α-CD solutions is a combination of the inclusion complexation between α-CD and PEO blocks and the micellization of the PPO block of Pluronic copolymer.

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 [68]. The effect of α-CD to aid the gelation of

PEO–PPO–PEO copolymer aqueous solutions was further evidenced by the phase diagrams of the mixtures of PEO–PPO–PEO copolymer and α-CD aqueous solution [70]. Figure 5 presents the temperature–polymer concentration phase diagrams of PEO–PPO–PEO copolymer $EO_{13}PO_{30}EO_{13}$ aqueous solutions at the absence and presence of α-CD with different α-CD concentrations. The regions marked with gel indicate that the formulations of $EO_{13}PO_{30}EO_{13}$ and α-CD aqueous solutions form a hydrogel, which remains intact when the tube is inverted upside down. The regions marked with sol indicate that the formulations are either a clear or turbid solution, or a mixture containing partially gel and fluid portions, which will flow when the tube is inverted. The region where the pure $EO_{13}PO_{30}EO_{13}$ can form a hydrogel is very small (α-CD 0%), while the concentration must be very high. With increase in α-CD concentration, the gelation regions become larger and larger, and the lowest concentration at which the copolymer can form hydrogel becomes much lower with higher α-CD concentrations. When plotting the lowest gelation concentrations of $EO_{13}PO_{30}EO_{13}$ as function of α-CD concentration at 31 °C, it was found that, with the increase in α-CD concentration, the lowest copolymer gelation concentration decreased from 50 to about 20%. It is clear that the partially formation of inclusion complexes between the EO blocks of $EO_{13}PO_{30}EO_{13}$ with α-CD largely changed the hydrophobicity of the PEO–PPO–PEO copolymer, and significantly lowered its gelation concentration.

A biodegradable poly(ethylene oxide)-poly[(*R*)-3-hydroxybutyrate]-poly (ethylene oxide) (PEO–PHB–PEO) triblock copolymer was synthesized [73] and used to form supramolecular hydrogel with α-CD (Fig. 6) [71]. It was found that the preferential inclusion complexation of α-CD with the PEO block together with the hydrophobic interaction between the middle PHB blocks cooperatively result in a self-assembly system that induces a strong macromolecular network. The strong intermolecular hydrophobic interaction between the middle PHB blocks of PEO–PHB–PEO triblock copolymer was proved by their very low critical micellization concentration (cmc) values (Table 2) [74, 75]. Although the two copolymers were water-soluble, they formed micelles in aqueous solution at very low concentrations. The cmc values of PEO–PHB–PEO triblock copolymers were found to be significantly smaller than their counterparts of Pluronic PEO–PPO–PEO or PEO–PLLA–PEO triblock copolymers with similar compositions [71, 74–76].

Despite the formation of micelles, 13 wt% of aqueous solution of both polymers did not form hydrogels. However, aqueous solutions containing 13 wt% of either PEO–PHB–PEO copolymers and 9.7 wt% of α-CD formed hydrogels at room temperature. In other words, α-CD aided the gel formation for PEO–PHB–PEO triblock copolymers at a low copolymer concentration. Here the inclusion complexes formed by α-CD and PEO blocks of PEO–PHB–PEO triblock copolymers are thought to aggregate into microcrystals, which act as physical crosslinks and induce formation of a supramolecular polymer network, consequently resulting in the gelation of the solutions. The micellization of the PHB block is also important in the gelation process. The hydrophobic interactions between the PHB blocks facilitate the formation of the polymer network. Therefore, the gelation of the aqueous solutions of PEO–PHB–PEO triblock copolymers and α-CD is the result of a cooperation of the

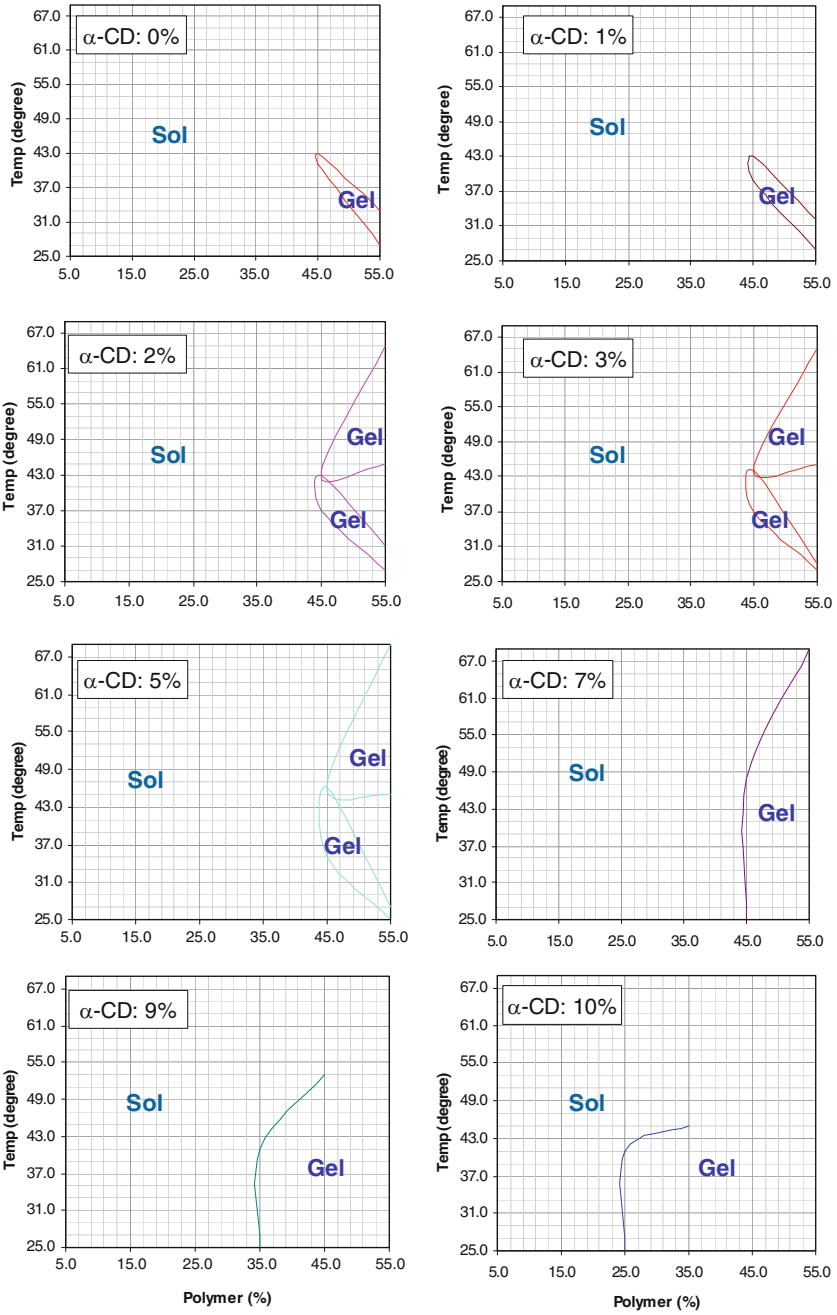


Fig. 5 The temperature–polymer concentration phase diagrams of PEO–PPO–PEO copolymer $EO_{13}PO_{30}EO_{13}$ aqueous solutions at the absence and presence of α-CD with different α-CD concentrations [70]

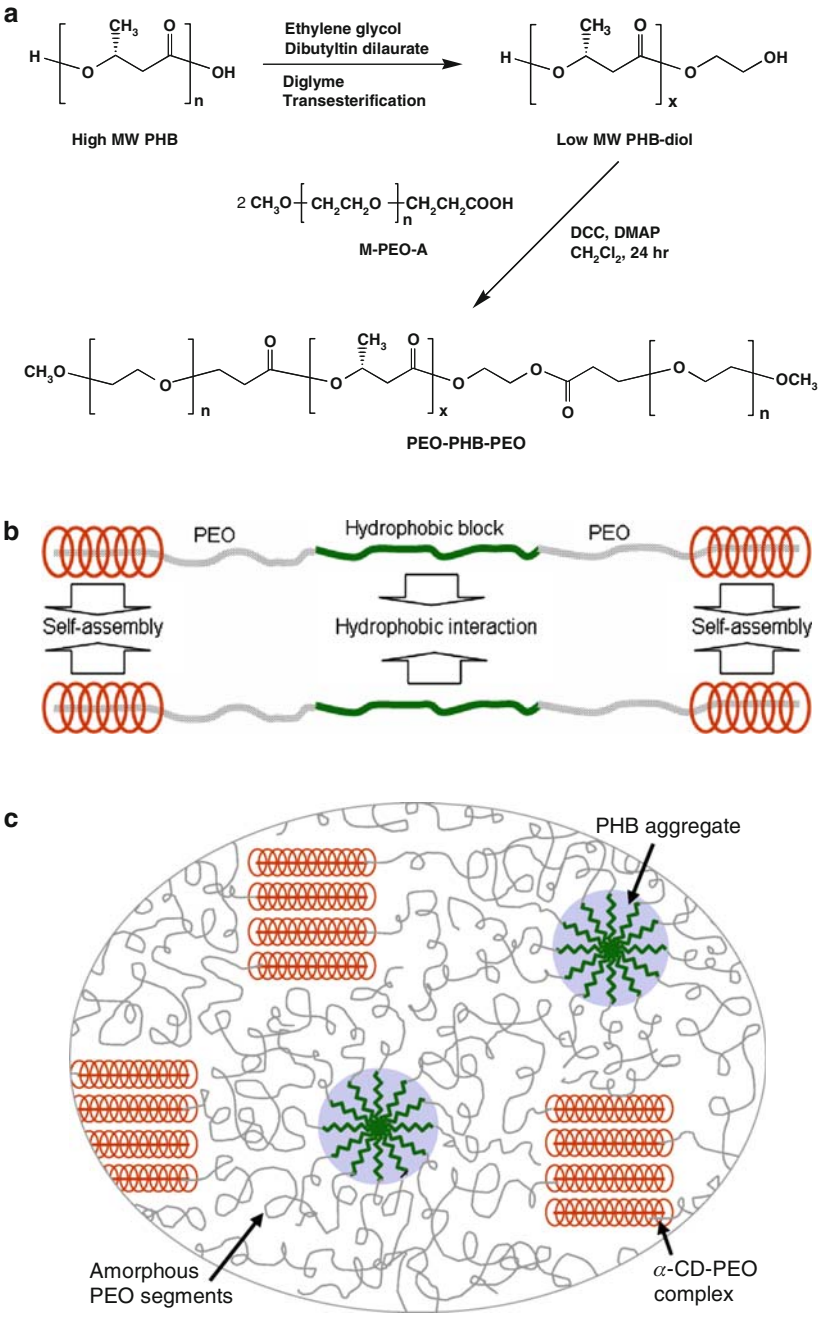


Fig. 6 a–c The synthesis of PEO–PHB–PEO triblock copolymer **a**, and the schematic illustrations of the proposed structures of a-CD–PEO–PHB–PEO inclusion complex **b**, and a-CD–PEO–PHB–PEO supramolecular hydrogel **c** [71]

Table 2 PEO–PHB–PEO triblock copolymers used for preparation of hydrogels with α-CD [71]

Triblock copolymer[a]	M_n	Block length (M_n)		cmc[b] (g L^{-1})
		PEO	PHB	
PEO–PHB–PEO(5000–1750–5000)	11,270	4,830	1,750	5.7×10^{-2}
PEO–PHB–PEO(5000-3140-5000)	12,160	4,830	3,140	2.7×10^{-2}

[a]The numbers in the parentheses show the indicative block length of each block in g mol^{-1}

[b]Critical micellization concentration (cmc) determined by dye absorption experiments for PEO–PHB–PEO copolymers at 23 °C

inclusion complexation between α-CD and PEO blocks and the micellization of the PHB block of the triblock copolymers.

Based on the results of the X-ray diffraction studies, the structure of the α-CDPEO–PHB–PEO supramolecular hydrogels was proposed (Fig. 6c). In the α-CD–PEO–PHB–PEO complexes (Fig. 6b), PEO chains penetrate α-CD rings from both ends, and then form necklace-like inclusion complexes. The molecular weight of each PEO block is ca. 5,000 Da in the supramolecular hydrogels. Only a length of PEO segments of about molecular weight 2,000 Da or less from each end of the copolymers could be included by α-CD rings based on the studies on complex formation between α-CD and PEO–PHB–PEO triblock copolymers with PEO length of 2,000 Da, where only crystalline solid complexes formed [30, 37]. The hypothesis was also supported by the number of α-CD rings threaded on a PEO chain and capped by bulky groups at the two ends, as described in the study on synthesis of α-CD–PEO polyrotaxanes [17]. In the courses of preparation of polyrotaxanes, a maximum average number of 23 α-CD rings, corresponding to a length of PEO molecular weight 2,000 Da, were trapped over a PEO chain, even if the molecular weight of PEO used was more than 3,000 Da. In the cases of PEO–PHB–PEO block copolymers with PEO block length of 5,000 Da, the PEO segments covered by α-CD rings should be shorter than 2,000 Da from each end because the cooperative gelation process may hinder α-CD further threading over the PEO blocks. The partial inclusion complexation of α-CD with PEO block together with the hydrophobic interaction between the middle PHB blocks cooperatively result in a self-assembly system that induces a strong network and gives a novel supramolecular hydrogel.

Another supramolecular hydrogel was formed between α-CD and biodegradable amphiphilic poly(ethylene oxide)-*b*-poly(ε-caprolactone) (PEO–PCL) diblock copolymer [72]. In this study, a PEO–PCL diblock copolymer of molecular weight of 5,000 for PEO and 5,000 for PCL was used. A turbid solution was obtained after dispersing this diblock copolymer into water under sonicating and stirring, and no gelation was observed. However, a viscous mixture was obtained when α-CD aqueous solution was employed instead of the pure water. The viscous mixture could further transfer to homogeneous hydrogel in a few minutes. It was assumed that the gelation is induced by the supramolecular self-assembly of the PEO–PCL diblock polymer chains partially included by α-CD. It was proposed that the PEO block is preferentially complexed by α-CD, while the complexed hydrophobic PCL block forms aggregates due to the hydrophobic interaction.

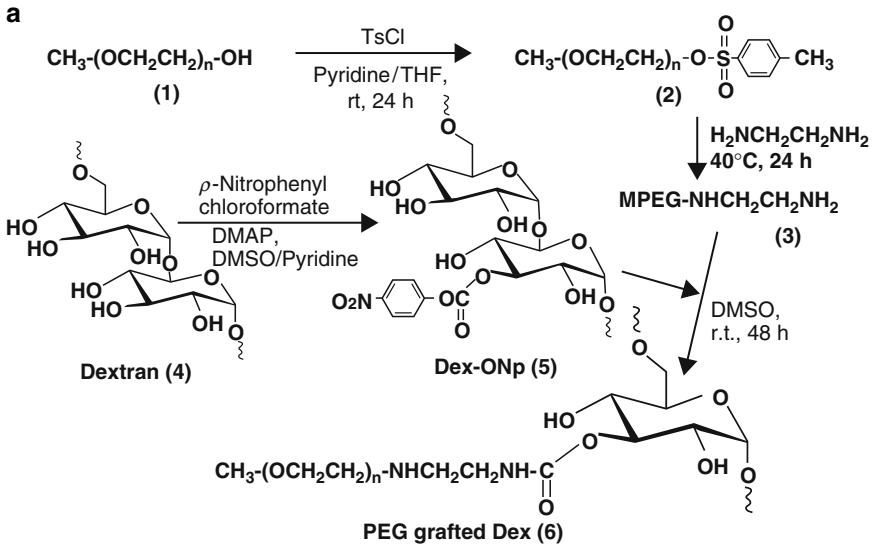
2.1.3 Hydrogels of α-CD and PEO-Grafted Copolymers

Based on similar principles to the hydrogels formation between α-CD and various block copolymers comprising a PEO block, there were a few reports on hydrogel formation between α-CD and PEO-grafted hydrophilic polymers CD [77–80].

Supramolecular hydrogels were prepared based on the inclusion complexation between PEO-grafted dextrans and α-CD in aqueous media (Fig. 7) [77]. The gel–sol transition was reversible with hysteresis. The transition temperature was controllable by variation in the polymer concentration and the PEO content in the graft copolymers as well as the stoichiometric ratio between the guest and host molecules. The X-ray diffraction data indicated that the hydrogel contains a channel-type crystalline structure, demonstrated by a strong reflection at $2\theta = 20^\circ$ ($d = 4.44$ Å). The authors suggested that the supramolecular hydrogels comprise a mico-phase separated structure consisting of hydrophobic and channel-type crystalline PEO inclusion complex domains and hydrated dextran matrices.

In a similar way, supramolecular hydrogels were prepared on the basis of inclusion complex formation between PEO-grafted chitosans and α-CD [78]. A series of PEO-grafted chitosans were synthesized by coupling reactions between chitosan and monocarboxylated PEO using water-soluble carbodiimide as coupling agent. The PEO side-chains on the chitosan backbones were found to form inclusion complexes with α-CD, resulting in the formation of channel type crystalline micro-domains, which play a role of physical crosslinking for the hydrated chitosan chains. The gelation property was affected by several factors including the PEO content in the polymers, the solution concentration, the mixing ratio of host and guest molecules, temperature, pH, etc. All the hydrogels in acidic conditions exhibited thermo-reversible gel–sol transitions. The authors proposed that the supramolecular hydrogels comprise a phase-separated structure that consists of hydrophobic crystalline inclusion complexes domains formed by the α-CD and the grafted PEO segments, and the hydrated chitosan matrices below the *pK*a.

α-CD inclusion complex formation of highly densely PEO-grafted polymer brushes and resulting hydrogel formation were reported (Fig. 8) [79]. The polymers grafted with PEO macromonomers were prepared through the "grafting from" approach by atom transfer radical polymerization (ATRP) of poly(ethylene glycol) methyl ether methacrylate, PEOMA, from a well-defined poly(macroinitiator), poly(2-(2-bromoisobutyryloxy)ethyl methacrylate) (PBIEM). The inclusion complexation and hydrogel formation of this type of polymer brush with α-CD were studied. The column-type crystalline structures of the hydrogels were confirmed by XRD measurement. The mechanism for the hydrogel formation was proposed by the authors as follows. The polymer brush PBIEM-g-P(PEOMA) with very higher densely grafted PEO chains formed hydrogels with α-CD due to the density of grafted PEO segments. The PEO segments that located at the outer end of the side chains could be threaded relatively easily and formed column inclusion complex aggregates to give a physical crosslinking point. The formed inclusion complex columns are parallel to the main chain, and the orientation of the inclusion complex columns for the polymer brush may promote the physical crosslinking for the



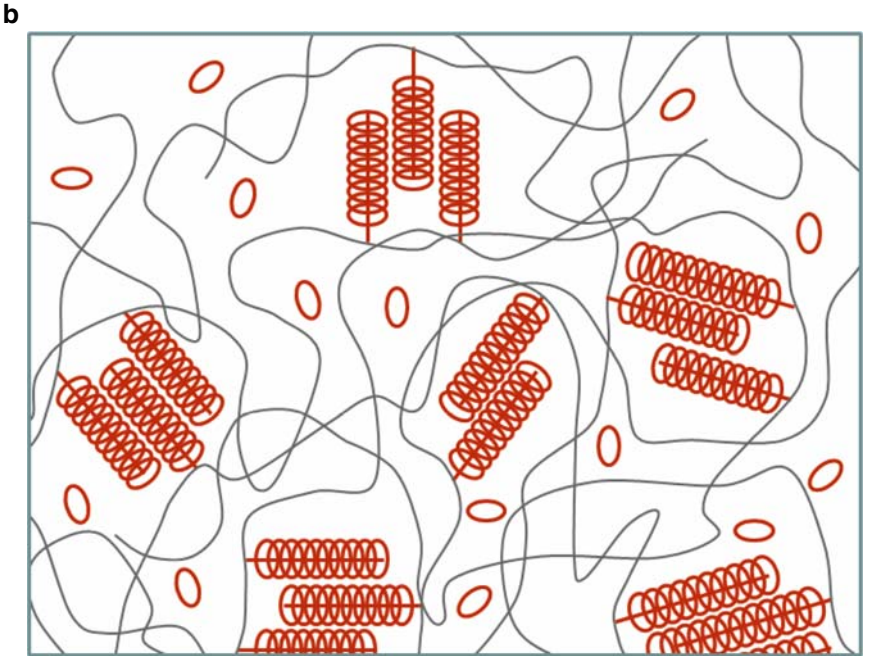


Fig. 7 The synthesis route for PEO-grafted dextran **a** and the schematic illustration of proposed structure of supramolecular hydrogel by inclusion complexation between PEO-grafted dextran and α-CD **b** [77]

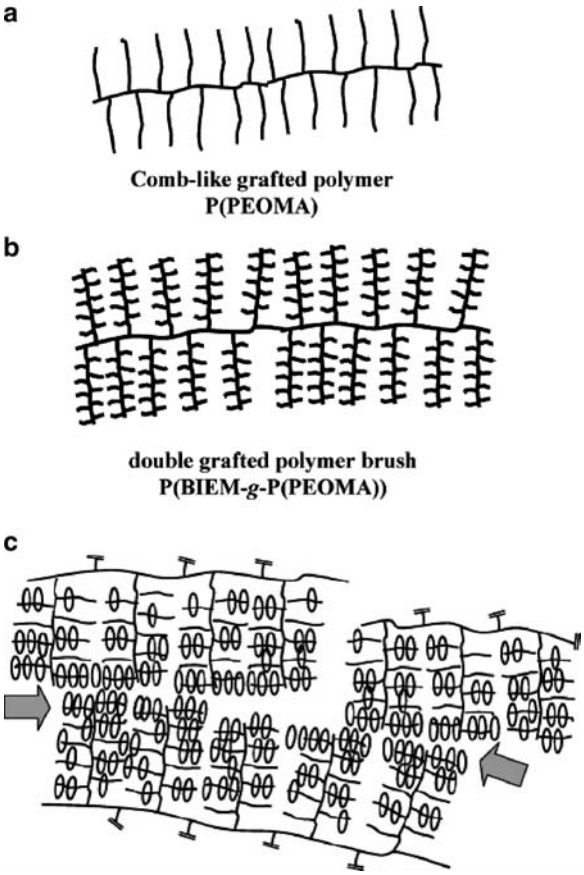


Fig. 8 a–c The schematic illustrations of comb-like PEO-grafted polymer P(PEOMA) **a**, double grafted polymer brush P(BIEM-g-P(PEOMA)) **b**, and structure of hydrogel formed from polymer brush P(BIEM-g-P(PEOMA)) and α-CD **c**. *Arrows* indicate the crosslinking points [79]

gelation (Fig. 8c, arrows). On the other hand, owing to the steric hindrance, the PEO segments attached close to the backbone were very crowded and difficult to be threaded by α-CD. Therefore, some PEO segments were free of complexation and were swollen by water. The combination of above two factors induced formation supramolecular networks of the hydrogels.

The preparation of supramolecular hydrogels formed between α-CD and Pluronic copolymers hybridized with single-walled carbon nanotubes (SWNTs) was reported as well (Fig. 9) [80]. Such hydrogel hybridized with SWNTs was prepared by mixing an aqueous solution of α-CD with an aqueous dispersion of SWNTs stabilized by Pluronic copolymer. In the hydrogels, the SWNTs were well dispersed through interaction of their walls with the PPO blocks of Pluronic copolymer. In other words, the PPO blocks are aggregated to the SWNTs while the PEO blocks look like grafted chains of the SWNTs. Therefore, the

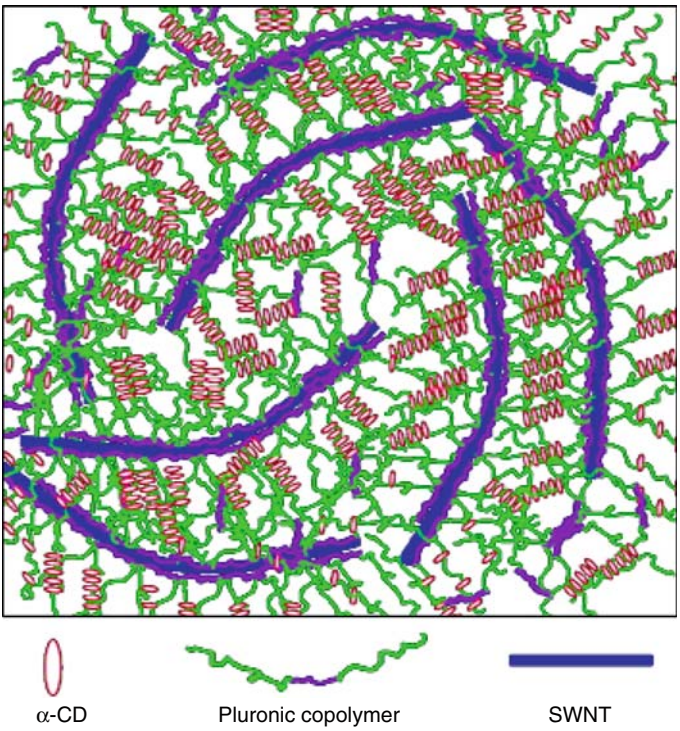


Fig. 9 Proposed structure of the supramolecular hydrogel formed between α-CD and Pluronic copolymer in the presence of well-dispersed single-walled carbon nanotubes (SWNTs) [80]

Pluronic copolymer plays dual roles in dispersing SWNTs as well as forming inclusion complexes with α-CD in the hydrogels. Although the introduction of well-dispersed SWNTs changed the gelation mechanism as compared to that of the native hydrogels between Pluronic copolymers and α-CD, the study showed that there was no obvious influence on the structure and morphology. The resultant hybrid hydrogel retained the basic characteristics of the supramolecular hydrogels, especially the shear-thinning and reversible temperature-responsive properties.

2.2 Gelation Induced by Inclusion Complexation Between α-CD and PEI

It was reported that a series of linear polyethylenimines (PEIs) with various molecular weights were synthesized and used to prepare polypseudorotaxanes with α-CD [81]. The PEIs were found to form stable polypseudorotaxanes at suitable pH and/or temperature, because PEIs have ionizable secondary amino groups ($pK\mathrm{a} = 8.9$), which play a role of an energy barrier for the polypseudorotaxane formation.

Some of the polypseudorotaxanes with 40–55% of α-CD coverage could form hydrogels, similar to that of the gelation of the polypseudorotaxanes of α-CD and PEO of high molecular weight where a PEO chain is partially included by α-CD [59].

To decrease the energy barrier for polypseudorotaxane formation, the PEIs and α-CD solutions were mixed at 60 °C. After adjusting the pH to 11.0, the mixture was cooled down gradually. At a certain temperature (the gelation temperature), the solutions became turbid and formed a gel-like network. It was found to be interesting that the hydrogels could undergo a transition from gel state to crystalline precipitate state during a repeated heating and cooling processes (Fig. 10) [81].

On slow heating up to the gel-melting temperature, the formed hydrogels became soft and transparent. Stirring at this temperature led to further threading of α-CD onto the PEI chains. With a decrease in temperature after this process, the solutions did not form hydrogels but became turbid. Repeated heating and cooling processes resulted in crystalline precipitates after several cycles. It was found that the coverage of the PEI chains by α-CD was significantly increased in the crystalline precipitates [81].

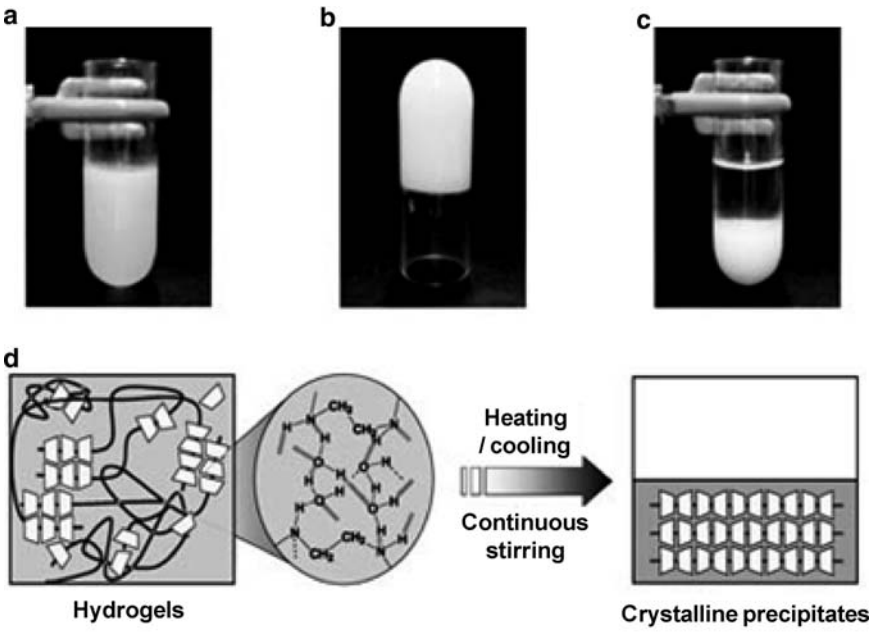


Fig. 10 a–d Optical images of polypseudorotaxane formed by α-CD and PEI: gel-like network formed at gelation temperature **a**, equilibrated hydrogel at gelation temperature **b**, and crystalline precipitate formed by thermal process **c**; and the schematic illustration of the transition process from the hydrogels to the crystalline precipitates **d** [81]

2.3 Gelation Induced by Inclusion Complexation Between α-CD and Grafted PL

A pH-sensitive and thermo-reversible supramolecular hydrogel system formed between α-CD and poly(ε-lysine) (PL)-grafted dextran was reported [82]. The PL grafting chains could form inclusion complexes with α-CD. The gelation was induced from a phase-separated structure comprising hydrated dextrans and hydrophobically aggregated inclusion complexes in buffer solution at pH 10.0. A rapid phase transition from gel to sol was observed upon decreasing the pH value to 4.0, which resulted from the dissociation of the inclusion complexes because of the protonation of the guest PL polymer chains.

2.4 Gelation Induced by Inclusion Complexation Between β-CD and Grafted PPO

Poly(propylene oxide) (PPO)-grafted dextran was synthesized and used to form inclusion complexes and supramolecular hydrogels with β-CD [83]. In this work, the average number of grafted PPO per dextran was in the range of 1.1–38.5 per polymer chain. The supramolecular hydrogels were formed induced by the formation of inclusion complexes between the grafted PPO and β-CD. Similar to the hydrogels formed by α-CD and PEO-grafted dextran [77], the supramolecular hydrogels between β-CD and PPO-grafted dextran comprise a microphase separated structure consisting of the hydrophobic and channel-type crystalline inclusion complex domains as the physical crosslinks and the hydrated dextran matrices which contain a large amount of water in the structure. The significance of this β-CD inclusion complex hydrogel system is that the gelation process is very fast.

2.5 Gelation Induced by Double Chain Inclusion Complexation between γ-CD and Grafted PEI

It was found that the large γ-CD molecule can include two chains of PEO into its cavity to form double-strand polypseudorotaxanes [22]. For developing a supramolecular network which can lead to formation of hydrogels, a PEO–PEI-grafted dextran (PEO–PEI–dex) was synthesized and used to form supramolecular hydrogels with γ-CD based on the double-strand inclusion complexation (Fig. 11) [84]. When adding γ-CD to the aqueous solution of PEO–PEI–dex, double strands of the PEG–PEI chains grafted on dextran backbones can intrude into the inner cavity of γ-CD, in either the same or opposite directions, which leads to formation of double-strand inclusion complexes with either a parallel or antiparallel direction. Therefore, the whole hydrogel system consists of a phase separated structure of the double-strand inclusion complex domains and the hydrated dextran

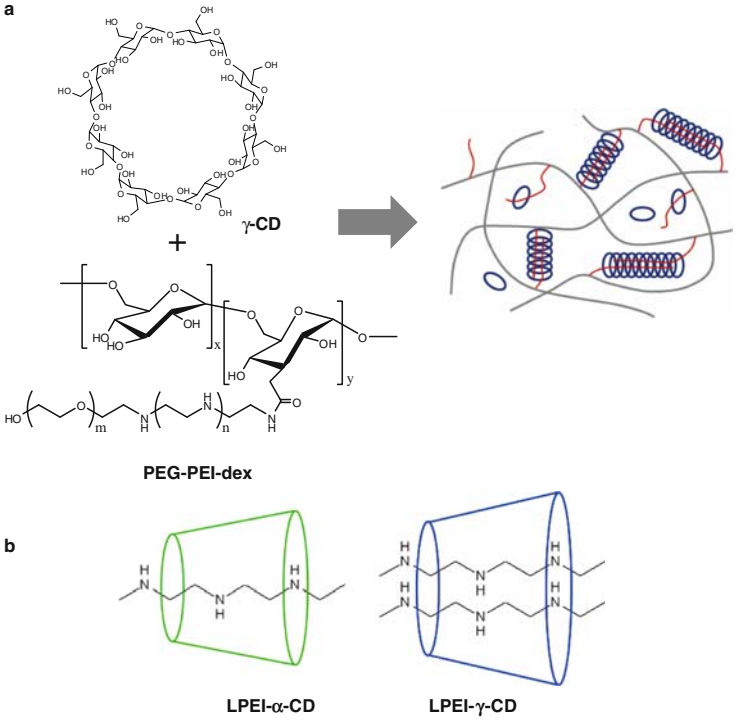


Fig. 11 a,b Schematic representation for the formation of PEO–PEI–dex·γ-CD networks. **a** A supramolecular network is formed via the double-strand complex between γ-CD and double strands of the PEO–PEI chains. The double-strand complexes are either of the parallel or antiparallel type. **b** α-CD and γ-CD include single and double strands of PEI, respectively. Stoichiometric ratios of α-CD or γ-CD to the repeating unit of PEI are 1:2 and 1:4, respectively [84]

matrices. The PEI segments can be protonated at low pH, which increases their hydrophilicity and leads to dissociation of the inclusion complexes. Therefore, the supramolecular hydrogels formed between PEO–PEI–dex and γ-CD are pH-sensitive. Their viscosity changes depending on the pH as shown in Fig. 12 [84]. It is commented that, although PEO–PEI–dex and α-CD will not form double-strand inclusion complexes, the single-strand inclusion complex may still form self-assembled crystalline domains, which can play a role of physical crosslinking and lead to the formation of a hydrogel as reported elsewhere [77, 78, 82].

2.6 Supramolecular Hydrogels as Injectable Drug Delivery Systems

Polymeric hydrogels have been attractive biomaterials for drug delivery, particularly for controlled release of delicate bioactive agents such as proteins and peptides. However, chemically crosslinked hydrogels can be applied only as implantables,

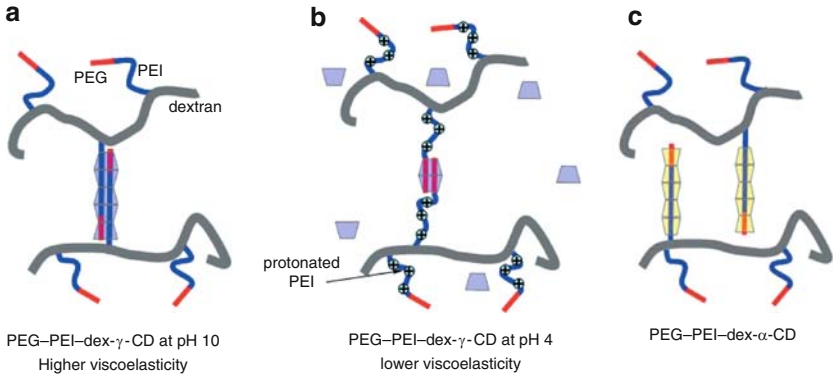


Fig. 12 a–c Proposed structures of supramolecular networks under different conditions. **a** PEO–PEI–dex·γ-CD network is formed with a full double-strand complex at pH 10. **b** The full double-stand complex of PEO–PEI–dex·γ-CD network is transformed to a partial double-stand complex at pH 4 owing to protonation of the PEI chains. **c** PEO–PEI–dex·α-CD networks do not form any double-strand complex at pH 10 [84]

and the incorporation of drugs by sorption may be time-consuming and limiting in the loading level. In addition, the cross-linking reaction may conjugate the drug to the hydrogel or impair the chemical integrity of the drug. Therefore, a delivery system where gelation and drug loading can be achieved simultaneously, taking place in an aqueous environment and without covalent crosslinking, would be attractive. Since both PEO and CDs are known to be biocompatible and bioabsorbable, the supramolecular hydrogels formed between CDs and PEO or its copolymers could be excellent candidates a new class of bioabsorbable physical hydrogels for controlled drug delivery [67].

Generally, the supramolecular hydrogels of CDs and polymers based on the formation of inclusion complexes which play the role of physical crosslinking are thermo-reversible. [59, 67, 68, 77–79]. The supramolecular hydrogels were also found to be thixotropic and reversible. For example, the viscosity of the hydrogel form between α-CD and PEO greatly diminished as it was agitated (Fig. 13a). This property renders the hydrogel formulation injectable even through a fine needle. The diminished viscosity of the hydrogels eventually restored towards its original value, in most cases within hours, when there was no more agitation (Fig. 13b). The thixotropic and thermo-reversible properties of the gel afforded us with a unique injectable hydrogel drug delivery system. One can first incorporate bioactive agents, such as drugs, proteins, vaccines, or plasmid DNA, into the hydrogel in a syringe at room temperature without any contact with organic solvents. The drug-loaded hydrogel formulation can then be injected into the tissue under pressure because of the thixotropic property. After restoration of the gelation in situ, the hydrogel serves as a depot for controlled release (Fig. 14) [50]. As compared to implantable hydrogels, the injectable hydrogel will be much more attractive.

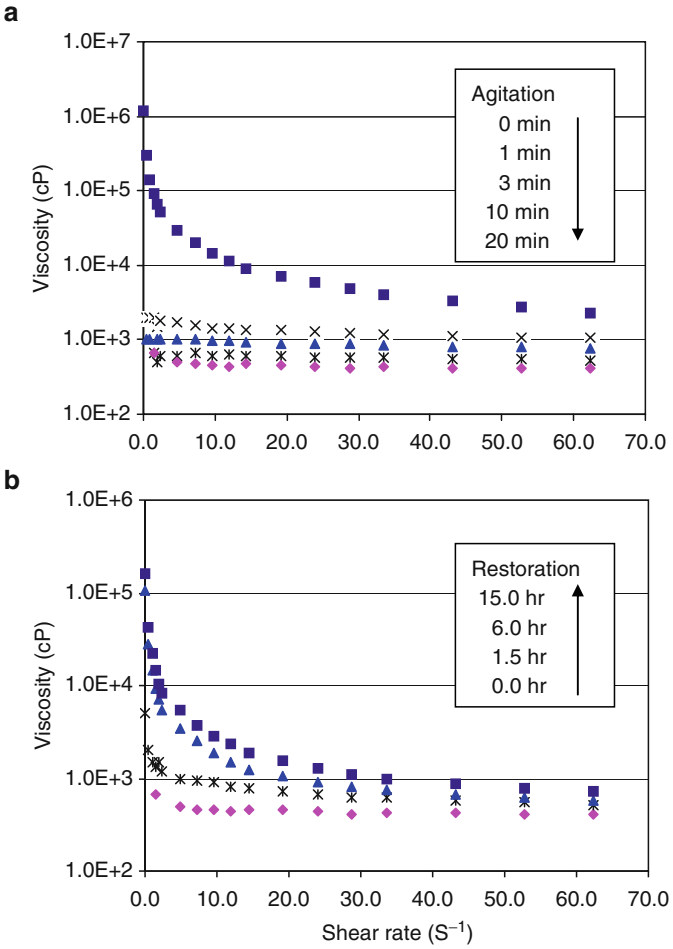


Fig. 13 a, b Changes of the viscosities of Gel-20K-60 as a function of agitation time at a shear rate of $120\,s^{-1}$ **a**, and restoration of the viscosities of the gel after 20 min agitation at a shear rate of $120\,s^{-1}$ **b** [67]

The effect of the injection through needles on the viscosity of the hydrogels was studied (Table 3) [67]. The viscosity dropped significantly after injection from the syringes. Inducing a higher shear rate, the finer needle caused a steeper decrease in viscosity of the hydrogel. The maximum speeds at which the hydrogels can be injected through a syringe of different needle sizes were also reported [67]. The hydrogels formed from PEOs of higher molecular weights were more difficult to be injected though fine needles. Injection of Gel-35K-60 through a 27G needle was limited to only $0.09\,mL\ min^{-1}$.

Since the formation of the hydrogels is induced by the supramolecular self-assembling in aqueous solution, and there is no any chemical crosslinking reagents,

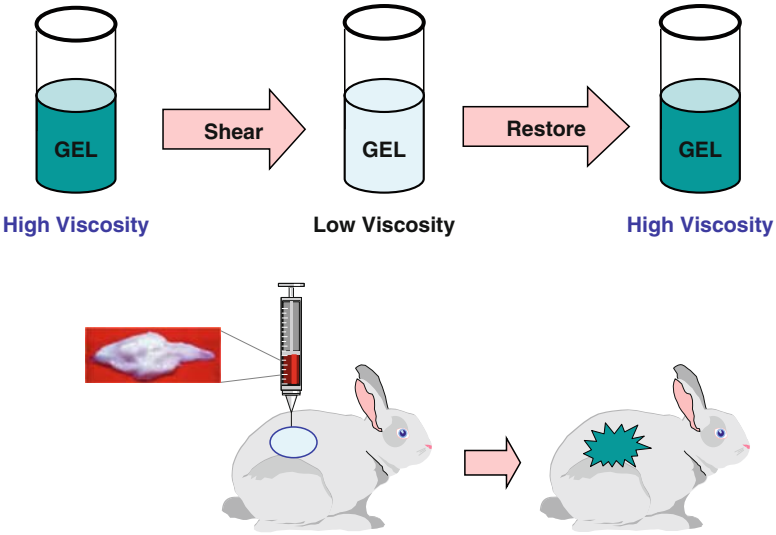


Fig. 14 Injectable drug delivery system based on supramolecular hydrogels formed by α-CD and PEO [50]

Table 3 Maximum speeds at which the hydrogels can be injected though needles of different sizes [67]

Needle size[a]	Maximum injection speed of hydrogel (mL min^{-1})			
	Gel-8K-60	Gel-10K-60	Gel-20K-60	Gel-35K-60
18G × 1.5 in	–[b]	75.1	32.8	8.93
19G × 1.5 in	–[b]	47.5	15.3	3.15
21G × 1.5 in	33.9	13.8	5.72	1.66
22G × 1.5 in	22.6	4.35	3.41	0.72
27G × 0.5 in	2.61	1.01	0.36	0.09

[a]Terumo 6-mL syringes were used for the experiments
[b]The injection speed is higher than 100 mL min^{-1}

bioactive agents, the drugs, can be incorporated into the hydrogel in situ at room temperature without any contact with organic solvents. The drug carrier properties of the supramolecular hydrogels were evaluated in vitro using a model system [67]. Fluorescein isothiocyanate labeled dextran (dextran-FITC) was physically entrapped in the hydrogels and their in vitro release properties were characterized. Figure 15 shows the in vitro release profiles of dextran-FITC from the hydrogels with PEO of different molecular weights or different PEO concentrations. The release rate decreases sharply with an increase in the molecular weight of PEO up to 35,000, presumably because of the chain entanglement effect and different complex stability (Fig. 15a). The release rate is quite steady with time for gels formed with PEO 35,000 (Gel-35K-60) and 100,000 (Gel-100K-60). Although Gel-100K-60 shows the most sustained release kinetics, it was studied here mostly for

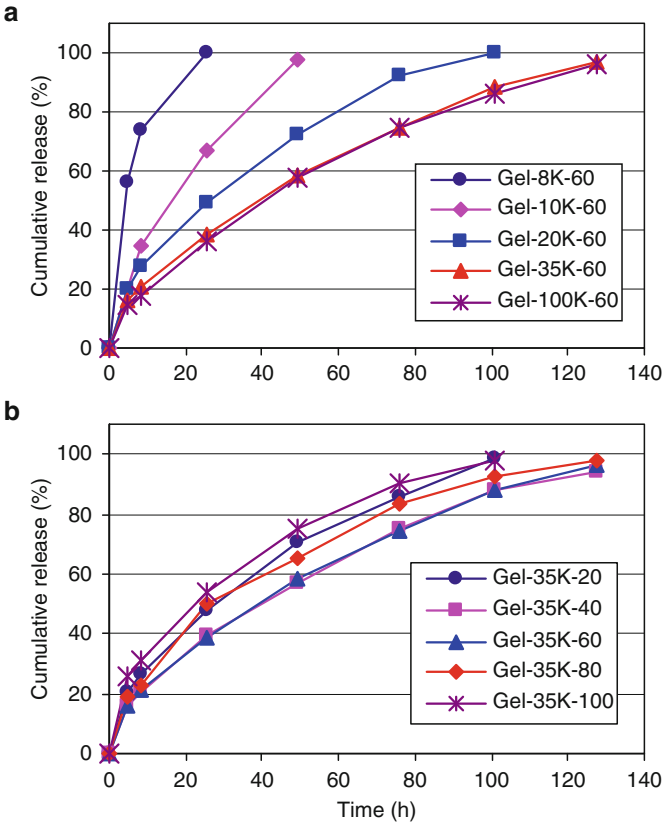


Fig. 15 a,b In vitro release profiles for dextran-FITC (MW 20,000) released from α-CD–PEO hydrogels formed from PEO of different molecular weights **a** and different concentrations **b**. Refer to Table 1 for the compositions of the hydrogels [67]

understanding of the structure–property relationship as PEO at this large would be undesirable for in *vivo* applications due to the difficulty of its clearance from the body. When α-CD used was fixed at 0.0967 g mL^{-1}, hydrogel compositions with PEO of 0.133–0.177 g mL^{-1} (Gel-35K-60 and Gel-35K-80) gave the most sustained release profiles (Fig. 15b). Compositions with PEG contents outside this range resulted in more rapid release. Therefore, the optimal formulations of the α-CD–PEO hydrogels for sustained release of drugs may be those of Gel-20K-60 and Gel-35K-60.

Hydrogels formed by PEO block copolymers have previously been proposed as sustained release matrix [85, 86]. The α-CD–PEO hydrogel delivery system differs in that the gelation relies on the formation of a polymer inclusion complex induced by the PEO-threaded CDs. The properties of the supramolecular hydrogel can be fine-tuned with the composition, molecular weight and chemical structure of the polymer or copolymers.

Although the α-CD–PEO hydrogels were demonstrated as a potential injectable drug delivery system, we are facing some challenges in applying the hydrogels in clinical applications. Generally, the release kinetics is too fast, and only suitable for short-term drug release with a time span of less than 1 week, because the dissociation of the hydrogel in aqueous environment is rapid due to the hydrophilic nature of PEO. In addition, the use of high molecular weight PEO of more than 10,000 in *vivo* will be problematic, because PEO is not biodegradable, and the high molecular weigh PEO is not suitable for filtration through human kidney membrane due to the large hydrodynamic radius.

To overcome the above mentioned problems, the supramolecular hydrogels self-assembled between α-CD and the biodegradable PEO–PHB–PEO triblock copolymers were studied for controlled drug delivery applications. It was found that the preferential inclusion complexation of α-CD with PEO block together with the hydrophobic interaction between the middle PHB blocks cooperatively result in a self-assembly system that induces a strong macromolecular network to give a supramolecular hydrogel system which is suitable for long-term sustained release of drugs [71].

The in vitro controlled release properties of the α-CD–PEO–PHB–PEO hydrogels were studied using fluorescein isothiocyanate labeled dextran (dextran-FITC) as a model macromolecular drug. Table 4 lists the dextran-FITC encapsulated α-CD–PEO–PHB–PEO hydrogels with different compositions that were used for the in vitro release kinetics studies. The α-CD–PEO (35,000 Da) hydrogel formulation was used as a comparison. Figure 16 shows the in vitro release profiles for dextran-FITC released from the supramolecular hydrogels. Both PEO–PHB–PEO triblock copolymers at 13 wt% in water were solutions, and could not sustain release of dextran-FITC because they dispersed in large quantity of water or PBS buffer in seconds. The α-CD–PEO homopolymer hydrogel even with very high PEO molecular weight (35,000 Da) dissociated and dissolved in PBS within 5 days (Fig. 16a, Gel-1) [67]. However, the α-CD–PEO–PHB–PEO (5000–3140–5000) hydrogels with reasonably high α-CD concentration (9.7 wt%, Fig. 16e, Gel-5) showed excellent controlled release property, sustaining the release of dextran-FITC for more than 1 month. The hydrogels with lower α-CD concentrations resulted in much faster release kinetics (Fig. 16c, Gel-3, and Fig. 4d, Gel-4), indicating

Table 4 α-CD-PEO–PHB–PEO supramolecular hydrogel formulations used for in vitro controlled release studies [71]

Hydrogel formulation	Polymer used	Gel composition (wt%)			
		α-CD	Polymer	Dextran–FITC	H_2O
Gel-1	PEO(35000)	9.7	13.3	0.66	76.3
Gel-2	PEO–PHB–PEO(5000-1750-5000)	9.7	13.3	0.66	76.3
Gel-3	PEO–PHB–PEO(5000-3140-5000)	5.4	13.3	0.66	80.6
Gel-4	PEO–PHB–PEO(5000-3140-5000)	7.9	13.3	0.66	78.1
Gel-5	PEO–PHB–PEO(5000-3140-5000)	9.7	13.3	0.66	76.3

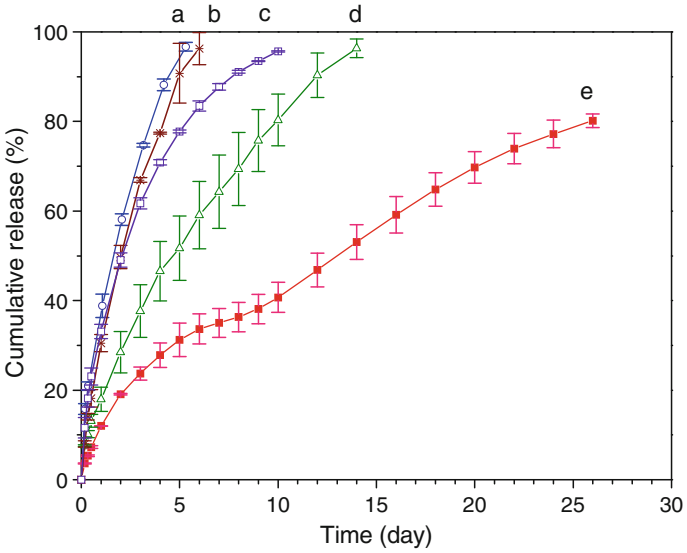


Fig. 16 a–e In vitro release profiles for dextran-FITC released from α-CD–PEO–PHB–PEO hydrogels with different compositions in comparison with α-CD–PEO hydrogel: **a** Gel-1; **b** Gel-2; **c** Gel-3; **d** Gel-4; **e** Gel-5 [71]. The compositions of the hydrogels are listed in Table 4

that the complexation between α-CD and the PEO blocks play a key role in formation of a stable supramolecular hydrogel. Interestingly, α-CD–PEO–PHB–PEO (5000–1750–5000) hydrogel with shorter PHB block only sustained the release of dextran-FITC for 6 days (Figs. 16 and 2b, Gel-2), although its α-CD concentration was high (9.7 wt%). The results indicate that the PHB block length is also critical for the stability of the supramolecular hydrogels, which further support the hypothesis that the cooperation effect of both α-CD complexation with PEO segments and the hydrophobic interaction between PHB blocks results in the formation of hydrogels with strong supramolecular networks as well as the long-term sustained release property that many simple triblock copolymer delivery systems could not achieve. These findings implicate that, the properties of the supramolecular hydrogels can be fine-tuned not only with different lengths of PHB block, but also with different copolymers, which may open up a wide range of possible biomedical applications. Although there were supramolecular hydrogel formation between α-CD with homo-PEO [59, 67], the α-CD–PEO–PHB–PEO hydrogels were different because there was the cooperative effect of the self-assembly of inclusion complexes of α-CD with PEO segments and the hydrophobic interaction between the PHB segments, which led to the formation of a strong hydrogel network. Not only are lower molecular weights of the copolymer needed in the α-CD–PEO–PHB–PEO hydrogels for sustained release, but also the biodegradable PEO–PHB–PEO copolymers will have the advantage that the hydrogel formulations will be bioabsorbable after the drug delivery and dissociation of the hydrogels into their components [71].

Recently, another supramolecular hydrogel formed between α-CD and biodegradable and amphiphilic PEO–PCL diblock copolymer was also studied for controlled drug delivery. The hydrogel was found to have significantly improved sustained release property compared to α-CD–PEO supramolecular hydrogels. The release of dextran-FITC from α-CD–PEO–PCL hydrogels could be lasted for 1 month even though the molecular weight of PEO block is only 5,000, which is attributed to the strong hydrophobic interaction between uncovered PCL blocks. Thus, the requirement of high molecular weight PEO for long term delivery system is avoided [72].

It was found that the α-CD–PEO–PCL hydrogel showed similar performance to those formed by PEO–PHB–PEO triblock copolymers and α-CD in controlled release of macromolecular drugs [71]. So, the α-CD–PEO–PCL hydrogel can be an alternative to achieve the sustained release using different copolymers. Particularly, PEO–PCL diblock copolymer is easier to synthesize and commercially available, thus it is attractive for further application studies using the α-CD–PEO–PCL hydrogels.

2.7 *Gelation Induced by Physical Interaction of Threaded Methylated CDs in Polyrotaxanes*

Recently a polyrotaxane composed of multiple methylated α-CD rings threaded on a high molecular weight PEO chain and end-capped by bulky adamantyl groups was synthesized (Fig. 17) and investigated in terms of its thermo-reversible sol–gel transition and hydrogel formation [87].

The aqueous solutions of the polyrotaxane of methylated α-CD (MePR), where the degree of substitution (DS) of the methylated α-CD, the number of modified

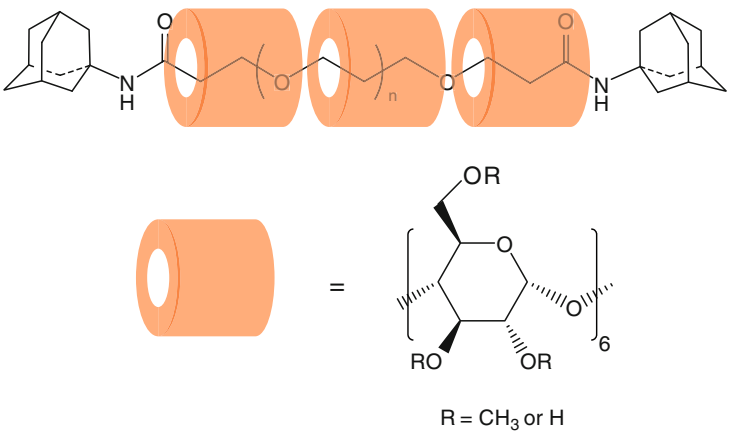


Fig. 17 Molecular structure of polyrotaxane formed by methylated α-CD (MePR) [87]

hydroxyl groups per glucose unit, was 2.8, showed a lower critical solution temperature (LCST) and form an elastic hydrogel with increasing temperature. When the concentrations of the MePR was 2 wt%, the solution became turbid at 40 °C. The MePR solution of 4 wt% formed a hydrogel at 20 °C, and became a sol at lower temperature. The X-ray diffraction investigation revealed that the localization and highly ordered arrangement of methylated α-CD along the PEG chain in the gel increased with increasing temperature. The arrangement of methylated α-CD was also reflected by the changes in elasticity and long relaxation behavior of the solution around the sol–gel transition.

Based on the investigations by the authors using X-ray diffraction, microdifferential scanning calorimetry, and rheometry, they proposed a mechanism for the sol–gel transition of the MePR/water system (Fig. 18) [87]. The crystal-like crosslinks of MePR in water are originated from the regularly ordered structure of methylated α-CDs along a PEG chain. The thermal gelation of MePR solution is induced not merely by the hydrophobic association among methylated α-CD, but also by the strong crystal-like aggregation as proved by the X-ray diffraction study.

3 Chemical Hydrogels Formed by Polypseudorotaxanes and Polyrotaxanes

3.1 Gelation Induced by Chemical Crosslinking of CDs

Through chemically crosslinking the α-CD molecules in polyrotaxanes, a class of supramolecular networks which are also called "sliding gels" has been developed (Fig. 19) [88], where cyanuric chloride, divinyl-sulfone, and bifunctional PEO were used as the chemical crosslinking agents [88–95].

Okumura and Ito reported the synthesis of sliding gels by chemically crosslinking α-CD molecules in the polyrotaxanes formed by multiple α-CD rings threaded on a PEO chain and end-capped by 2,4-dinitro-phenyl groups, using cyanuric chloride as the crosslinking agent. The crosslinking points are also described as figure-of-eight crosslinks (Fig. 20) [89]. The resultant sliding gels are transparent gels with good tensility, low viscosity, and large swellability in water. It is interesting that the threading PEO polymer chains in the gels are neither covalently crosslinked like in a chemical gel, nor physically crosslinked by weak cohesion forces like in a physical gel. Instead, they are topologically interlocked by the figure-of-eight cross-links. It is expected that this kind of special crosslink can pass along the polymer chains freely to equalize the 'tension' of the threading polymer chains like a pulley. Therefore, the nanoscale heterogeneity in structure and stress may be automatically equalized in the gel. Another example of sliding gels was reported by Hadzziioannou and coworkers, where the α-CD molecules in the polyrotaxanes were crosslinked by using divinyl-sulfone as the crosslinking agent (Fig. 21) [88].

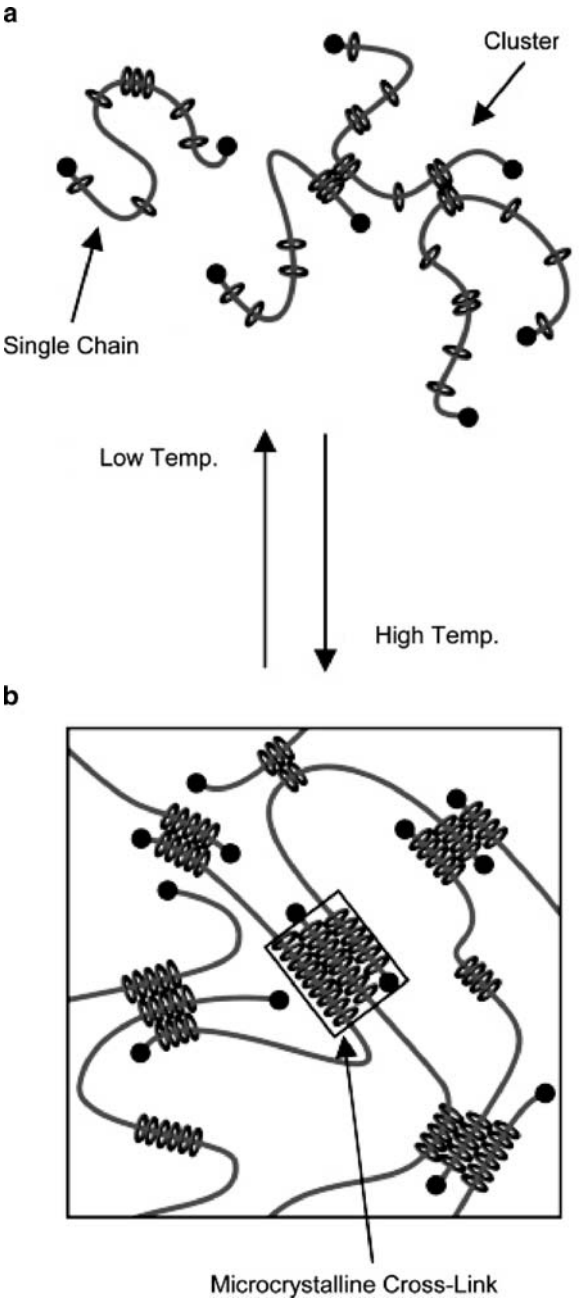


Fig. 18 a, b Schematic illustration of the sol–gel transition of the polyrotaxane of methylated α-CD in Water. There are isolated chains and only limited clusters of polyrotaxane in the solution at lower temperature **a** and large number of crosslinks consisting of crystal-like aggregates among localized methylated CDs in the gel at higher temperatures **b** [87]

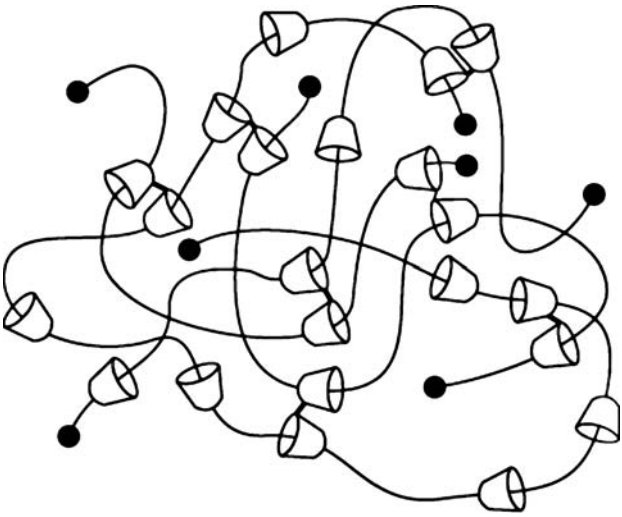


Fig. 19 Schematic illustration of the sliding gel [88]

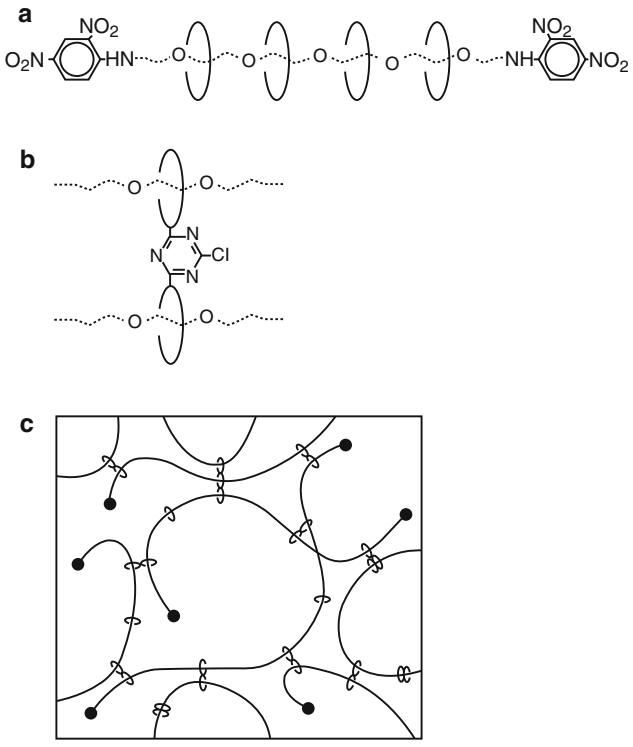


Fig. 20 **a** The polyrotaxane formed by α-CD and PEO with 2,4-dinitro-phenyl end caps. **b** The figure-of-eight cross-link: covalently cross-linked cyclodextrins. **c** Schematic diagram of the polyrotaxane gel prepared from the sparse polyrotaxane by covalently cross-linking cyclodextrins using cyanuric chloride as crosslinking agent [89]

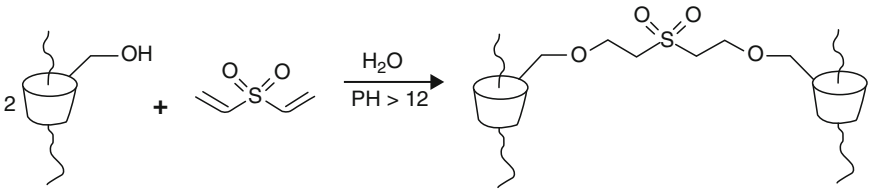


Fig. 21 General scheme for chemically crosslinking α-CD molecules in a polyrotaxane formed by α-CD and PEO with 2,4-dinitro-phenyl end caps by divinyl-sulfone as crosslinking agent [88]

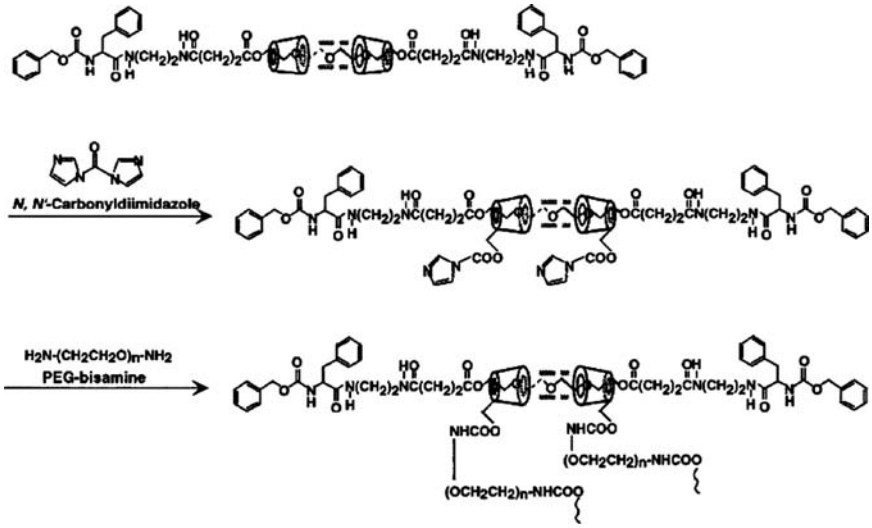


Fig. 22 Schematic illustration for the preparation of polyrotaxane hydrogels by chemically crosslinking α-CD molecules in the polyrotaxane with hydrolyzable end caps, using PEO-bisamine as the crosslinking agent [92]

Yui's lab prepared hydrogels by chemically crosslinking α-CD molecules in the polyrotaxanes using bifunctional PEO as the crosslinking agent (Fig. 22) [92–95]. In this design, a polyrotaxane with hydrolyzable end caps was used in order to obtain a biodegradable hydrogel. In addition, PEO is also a popularly used biocompatible polymer in biomaterials, therefore, the polyrotaxane hydrogels crosslinked PEO may be of interest in biomedical applications.

A series of polyrotaxane hydrogels crosslinked by PEO was prepared and their hydrolytic erosion behavior was studied [92–95]. Because of the interlocked supramolecular structure, the hydrogel degradation in a physiological condition followed a bulk mechanism. This characteristic may be useful for a biodegradable polymer hydrogel scaffold for tissue engineering application. The control of the gel erosion time with bulk mechanism can allow the scaffold to maintain its structures and properties during the tissue regeneration, and then rapidly decompose and disappear by the bulk erosion after the tissue regeneration has completed.

From the result of the erosion study, the time to reach complete gel erosion was found to be prolonged by increasing the PEO/α-CD ratio, the number of PEO chains per one α-CD molecule in the hydrogels. These results indicate the enhanced stability of ester hydrolysis in the hydrogels with highly water swollen state. The erosion profile of the hydrogels can be controlled by the molecular weight of the PEO-bisamine used, in addition to the PEO/α-CD ratio [93]. The fibroblast adhesion and proliferation on the polyrotaxane hydrogels were also studied [94].

3.2 Gelation Induced by Chemical Crosslinking of Threading Polymers

A class of supramolecular hydrogels was developed by Feng's group through chemically crosslinking the threading polymers in the polypseudorotaxane hydrogels [96–99]. Basically, polypseudorotaxanes were prepared from α-CD and photopolymerizable PEO copolymers bearing acrylate terminals. Since the PEO block has large molecular weight, the polypseudorotaxanes formed physical hydrogels as described in Sect. 2.1. The chemically crosslinked supramolecular hydrogels were prepared from the polypseudorotaxane hydrogels in a mixed solvent of water and dimethyl sulfoxide via in situ photopolymerization under UV irradiation using 2,2-dimethoxy-2-phenyl acetophenone as the photoinitiator. In the resultant chemical hydrogels, multiple α-CD rings are threaded and immobilized onto the network chains with the crosslinking junctions as topological stoppers to prevent the dethreading of the α-CD rings, forming permanent supramolecular hydrogels (Fig. 23) [96, 97].

The threading acrylate-terminated PEO copolymers used in these hydrogels preparation include PCL–PEO–PCL triblock polymer [96], PLA–PEO–PLA triblock polymer [97], 4-arm PEO star polymer [98], and PCL–Pluronic–PCL block polymer [100]. Particularly for those formed from biodegradable block copolymers as the threading polymers, the hydrogels may be of interest in biomaterials applications because of their potential biodegradability.

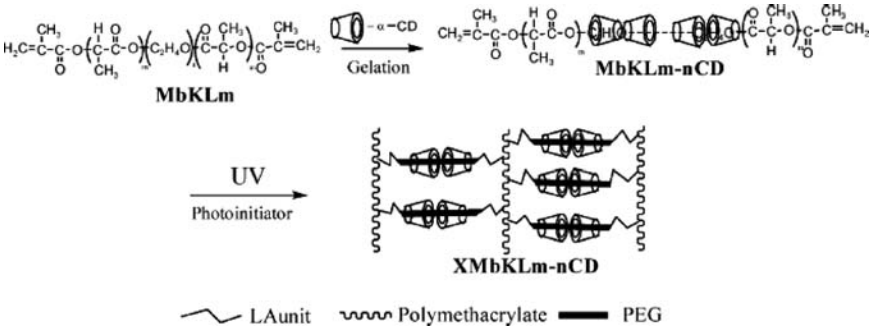


Fig. 23 Schematic illustration of the preparation of chemically crosslinked polyrotaxane hydrogels through crosslinking the ends of the threading polymers via UV photopolymerization [97]

Thermosensitive supramolecular hydrogels of this type were synthesized via copolymerization of *N*-isopropylacrylamide (NIPA) with photocurable and biodegradable polypseudorotaxanes as crosslinkers under UV irradiation, where the polypseudorotaxane precursors were prepared by α-CD and amphiphilic PLA–PEO–PLA copolymers end-capped with methacryloyl groups [99]. It was reported that the crosslinked hydrogel made of only the macromer guest shows also thermosensitive. However, this stimuliresponsive property disappears when α-CD rings are threaded onto the PLA–PEO–PLA polymeric backbone and reappears when PNIPA segments are introduced. The thermosensitivity of these hydrogels could be modulated by changing the PNIPA content as well as the α-CD to macromer ratio.

Most recently, three-dimensional crosslinked networks based on the α-CD polypseudorotaxane hydrogels formed from thiolated 4-arm PEO were prepared by thiol-disulfide interchange reaction using a three-step oxidation (Fig. 24) [101]. The channel-type crystalline structure of inclusion complexes is still maintained after the oxidation processes. The hydrogels may undergo a reversible gelation–decomposition transition through the oxidation and reduction processes because of the disulfide crosslinks. The swelling behaviors and degradation properties can be readily regulated by tuning the feed compositions of α-CD and PEO-thiolated prepolymer.

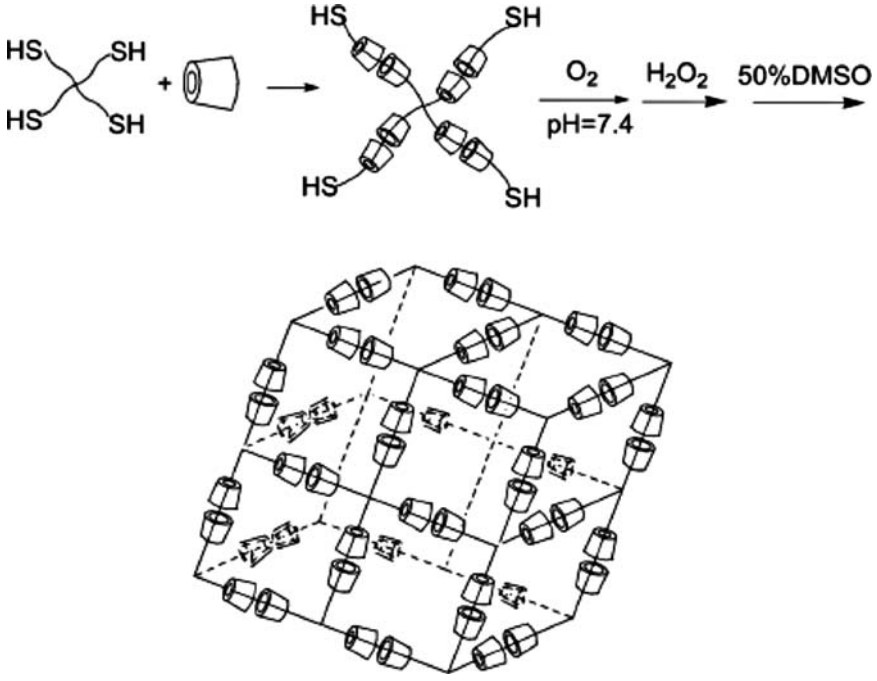


Fig. 24 Schematic illustration of the preparation of chemically crosslinked polyrotaxane hydrogels through crosslinking the ends of the threading polymers via oxidation crosslinking processes [101]

4 Concluding Remarks

The advances in the studies on the inclusion complexes of CDs threading onto polymer chains have led to interesting development of supramolecular hydrogels with many different molecular and supramolecular structures. Both physical and chemical hydrogels of many different types were developed based on the CD-based polypseudorotaxanes and polyrotaxanes.

Physical hydrogels were formed induced by self-assembled water-insoluble and crystalline polypseudorotaxane domains which act as physical crosslinking points. Such physical hydrogels include the polypseudorotaxane systems of α-CD threading on PEO or its copolymers, α-CD threaded on PEI, PL, or their copolymers, and even β-CD or γ-CD threaded PPO or PEI copolymers. The thermo-reversible and thixotropic properties of these supramolecular hydrogels have inspired their applications as injectable drug delivery systems. Physical hydrogels induced by physical interaction of threaded CD molecules in polyrotaxanes were also developed.

Chemical hydrogels formed from polypseudorotaxanes and polyrotaxanes were based on the chemical crosslinking of either CD molecules or the threading polymer chains. Polyrotaxane hydrogels with chemically crosslinked CD rings are also called sliding gels. A number of different crosslinking agents including PEO and small molecules were used for the crosslinking. Photopolymerizable or oxidative crosslinkable threading copolymers were used to form polypseudorotaxane hydrogels followed by chemical crosslinking. Such processes resulted in formation of another type of supramolecular chemical hydrogels. Notably, the chemical hydrogels formed from polypseudorotaxanes and polyrotaxanes were often made biodegradable through incorporation of hydrolyzable threading polymers, end caps, or crosslinkers, for their potential applications as biomaterials.

The hydrogels based on CD-based polypseudorotaxanes and polyrotaxanes will continue to be a hot topic because of the tremendous possibility of the different properties and functionalities induced by the supramolecular structures.

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