



Chang, Y., Jiao, Y., Symons, H., Xu, J., Faul, C. FJ., & Zhang, X. (2019). Molecular engineering of polymeric supra-amphiphiles. *Chemical Society Reviews*, 48(4), 989-1003. [DOI: 10.1039/c8cs00806j].  
<https://doi.org/10.1039/C8CS00806J>

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## Molecular Engineering of Polymeric Supra-amphiphiles

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Received 00th January 20xx,  
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Polymeric supra-amphiphiles are amphiphiles that are fabricated by linking polymeric segments, or small molecules and polymeric segments, by noncovalent interactions or dynamic covalent bonds. Compared with conventional amphiphilic polymers, polymeric supra-amphiphiles are advantageous in that they possess dynamic features and their preparation may be to some extent more facile. Moreover, polymeric supra-amphiphiles are endowed with richer structure and higher stability compared with small-molecule supra-amphiphiles. Owing to these properties, polymeric supra-amphiphiles have so far shown great promise as surfactants, nanocarriers and in therapies. In this tutorial review, recent work on polymeric supra-amphiphiles, from molecular architectures to functional assemblies, are presented and summarized. Different polymeric supra-amphiphile topologies and related applications are highlighted. By combining polymer chemistry with supramolecular chemistry and colloid science, we anticipate that the study of polymeric supra-amphiphiles will promote the continued development of the molecular engineering of functional supramolecular systems, and lead to practical applications, especially in drug delivery.

### Key learning points

1. Introduction to the concept of polymeric supra-amphiphiles.
2. Design strategies for constructing polymeric supra-amphiphiles with different topologies.
3. Structure-related applications of polymeric supra-amphiphiles such as surfactants, drug delivery and therapies.
4. Perspectives and potential future directions of polymeric supra-amphiphiles.

### 1. Introduction: From Supra-amphiphiles to Polymeric Supra-amphiphiles

Amphiphiles are molecules that contain both a hydrophobic component and a hydrophilic component connected by covalent bonds. Owing to the amphiphilic property, amphiphiles have been extensively employed in daily living and industry as detergents, emulsifiers and solubilizers, amongst others.<sup>1</sup> Moreover, these moieties can assemble into well-organised aggregates such as micelles, vesicles, lyotropic liquid crystals, 2D monolayers and 3D multilayers. This aspect has greatly enriched the supramolecular chemistry of amphiphiles, leading to the emerging development of functional assemblies. Different from conventional amphiphiles, supra-amphiphiles are amphiphiles that are connected through noncovalent interactions, such as electrostatic interactions,<sup>2-4</sup> host-guest interactions,<sup>5-7</sup> hydrogen bonds,<sup>8</sup> and others<sup>9</sup>. These constructs serve as a bridge between colloid science and supramolecular chemistry. Compared with conventional amphiphiles fabricated

by covalent bonds, the noncovalent approach may simplify the procedures for the preparation of supra-amphiphiles to some extent, depending on the type and complexity of the molecular design.<sup>10</sup> In addition, responsive and functional components can be linked to the supra-amphiphiles in a facile fashion. Supra-amphiphiles may therefore be endowed with stimuli-responsiveness, reversibility and adaptivity, the properties that are not easily achieved in conventional amphiphiles.

The initial construction of supra-amphiphiles can be regarded as the primary self-assembly step and the supra-amphiphiles can then be used as units to fabricate aggregates through so-called secondary self-assembly.<sup>11-14</sup> Supra-amphiphiles can be constructed to possess various structures through the design of their sub-components (e.g., volume and length of the hydrophobic tail section), which can further aggregate to form advanced architectures with tunable properties and diverse functions. For example, well-designed supra-amphiphiles may function as surfactants, nanocarriers or be applied in the fields of analysis, therapy, surface chemistry, catalysis and others. Noncovalent interactions with dynamic nature are the foundation of the above fascinating properties, and thus lead to an intertwined relationship between structure, function and application of supra-amphiphiles.

However, there are two sides to every coin. The dynamic properties of the supra-amphiphiles usually lead to fast equilibrium between complexation and decomplexation. In other words, the stability of supra-amphiphiles is not as high as

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

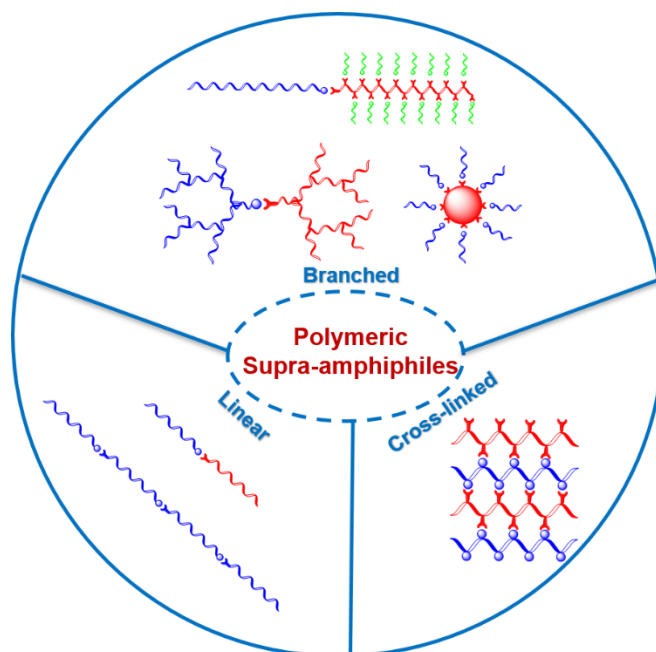
that of conventional amphiphiles. Changes in the concentration of building blocks are prone to affect the formation of supra-amphiphiles as well as their further assemblies. This drawback of supra-amphiphiles is a significant distinction from conventional amphiphiles, as the concentration of conventional amphiphiles influences their self-assemblies but has no effect on their covalently bonded intrinsic structures. Therefore, the relatively low stability may be the Achilles' heel for finding practical applications for supra-amphiphiles.

Polymeric supra-amphiphiles, i.e., supra-amphiphiles containing one or more polymeric components, seem to have achieved a balance between dynamic features and practical stability. In contrast to conventional amphiphilic polymers, polymeric supra-amphiphiles are able to be constructed simply and possess dynamic properties owing to the noncovalent interactions. Compared with small-molecule supra-amphiphiles, polymeric supra-amphiphiles can achieve richer structures and higher stability owing to their slower dynamics. In the organized assemblies from polymeric supra-amphiphiles, molecular exchange is slowed down by multiple noncovalent interactions and entanglement between polymer chains. Thus, the ability of supra-amphiphiles to withstand the effects of dilution can be enhanced generally through the use of polymeric building blocks. Moreover, the long polymer chains give the aggregated supramolecular reservoirs a large loading capacity, which is an important factor for exploring the functions of these materials. Owing to these unique properties, polymeric supra-amphiphiles have found wide application in chemistry and biomedicine.

In this tutorial review we aim to introduce recent developments in polymeric supra-amphiphiles. We will place particular emphasis on the topologies of polymeric supra-amphiphiles, and highlight selected cases where polymeric supra-amphiphiles are applied as surfactants, and in drug delivery and therapies. We expect the study of polymeric supra-amphiphiles will promote the continued development of the molecular engineering of functional supramolecular systems through combining polymer chemistry with supramolecular chemistry and colloid science.

## 2. Construction and Topology of Polymeric Supra-amphiphiles

For conventional polymeric amphiphiles, the realization of amphiphilicity mainly depends on the covalent linking of hydrophilic and hydrophobic polymeric components, or the synthesis of block copolymers bearing both hydrophilic and hydrophobic regions.<sup>15</sup> Different from polymeric amphiphiles, polymeric supra-amphiphiles are fabricated by linking polymeric segments or small molecules and polymeric segments by noncovalent interactions or dynamic covalent bonds. Aside from the essential polymeric segments, a wide variety of building blocks including synthetic molecules and natural molecules, have been utilized for constructing polymeric supra-amphiphiles. Diverse noncovalent interactions including hydrogen bonding,  $\pi$  stacking (i.e., interactions



**Scheme 1.** Construction and topologies of polymeric supra-amphiphiles

between aromatic rings containing  $\pi$  orbitals), electrostatic interactions, charge-transfer interactions and host-guest interactions, have been utilized to fabricate polymeric supra-amphiphiles. In addition, polymeric supra-amphiphiles can also be prepared by dynamic covalent bonds such as imine bonds, disulfide bonds and diselenide bonds. These dynamic covalent bonds can undergo reversible formation, cleavage and metathesis under certain conditions, and are therefore considered here as part of the wider gamut of dynamic interactions forming supra-amphiphiles. Compared with conventional polymeric amphiphiles, the preparation of polymeric supra-amphiphiles simplifies the tedious chemical synthesis to some extent, whilst holding the potential to generate more diverse structures with dynamic properties.

Based on the binding sites of noncovalent interactions or dynamic covalent bonds, different topologies have been realized with polymeric supra-amphiphiles. So far, linear, branched and cross-linked topologies have been developed for polymeric supra-amphiphiles (Scheme 1). Comparable to conventional polymeric amphiphiles, the diverse topologies and structures of polymeric supra-amphiphiles have led to tunable physicochemical properties, which in turn give rise to fruitful and desirable emergent functions. In each of the following sections, we will introduce some examples of the corresponding structures. In this way, the general concepts and structure-property relationships of polymeric supra-amphiphiles will be discussed, with the aim to provide useful insight for the practical applications of polymeric supra-amphiphiles in the future.

### 2.1 Linear Polymeric Supra-amphiphiles

The linear topology is the simplest polymer architecture, with repeat units linked in a one-dimensional manner. In linear polymeric supra-amphiphiles, the noncovalent interactions or

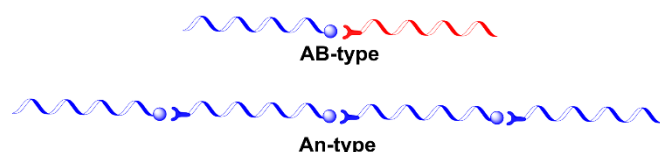


Fig. 1. The AB-type and An-type linear polymeric supra-amphiphile.

dynamic covalent bonds are usually introduced into the main chain, connecting two or more polymeric segments to form amphiphiles. Based on the configuration of the polymeric segments, the linear topology can be further classified into AB and  $A_n$ -type architectures for polymeric supra-amphiphiles (Fig. 1).

### 2.1.1 AB-type linear polymeric supra-amphiphiles

AB-type linear polymeric supra-amphiphiles refer to the polymeric supra-amphiphiles composed of one hydrophilic segment and one hydrophobic segment. Host–guest interactions have been frequently used to fabricate AB-type linear polymeric supra-amphiphiles. The nature of host–guest units influences the properties of the resultant polymeric supra-amphiphiles. Owing to the multitude of restrictions on the guests in terms of size, shape, charge, and polarity, the resultant polymeric supra-amphiphiles combine the characteristic features of traditional polymers with host–guest systems (e.g., stability, tunability, reversibility). Increasingly, linear polymeric supra-amphiphiles have been assembled in an ordered and directed fashion by molecular recognition of host–guest pairs.

Crown ethers are the first-generation artificial macrocyclic host. The interactions between crown ethers and suitable guest molecules are widely used to construct new materials mimicking natural systems.<sup>16</sup> Owing to the moderate molecular recognition based on crown ethers, stimuli-responsive polymeric supra-amphiphiles can be fabricated when hydrophobic and hydrophilic components are linked through such host–guest interactions. For example, based on the molecular recognition between a hydrophilic poly(ethylene oxide) (PEO) modified by a crown ether host and a derivative of

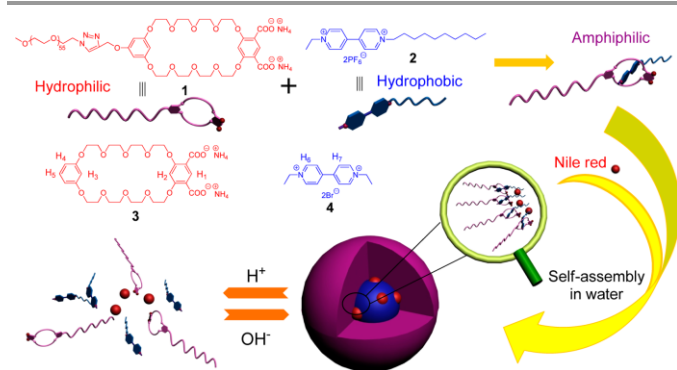


Fig. 2. The AB-type linear polymeric supra-amphiphile driven by host–guest interaction of crown-ether and its controllable assembly and disassembly in water. Reprinted from ref. 17 with permission from the American Chemical Society.

viologen containing one hydrophobic alkyl chain, Huang and co-workers prepared a polymeric supra-amphiphile with AB-type linear topology (Fig. 2).<sup>17</sup> In water, supramolecular micelles with a core–shell structure and an average diameter of 50 nm were assembled from this supra-amphiphile. When acid was added, the carboxylate groups in the crown ether changed to the corresponding neutral carboxylic acid. As a result, the host–guest interactions were weakened, leading to the disassembly of the polymeric supra-amphiphile and thus the micellar structure. The process was reversible on the addition of base, demonstrating that a change in pH could reversibly control the assembly and disassembly. By utilizing this transition, loaded small molecules could be released in a controlled fashion, displaying great potential as controllable drug carriers.

Cyclodextrins (CDs), cyclic oligomers formed by six ( $\alpha$ ), seven ( $\beta$ ) or eight ( $\gamma$ ) glucopyranose units, have been extensively explored in host–guest chemistry. In aqueous solution, hydrophobic guests such as stilbene, ferrocene (Fc), azobenzene, and others with appropriate sizes are readily encapsulated into the hydrophobic interior of CD macrocycles.<sup>18</sup> Using CD-based host–guest interactions, AB-type linear polymeric supra-amphiphiles can be prepared easily. Through the combination of click chemistry and atom transfer radical polymerization (ATRP), Liu and co-workers synthesized well-defined  $\beta$ -CD-terminated poly(*N*-isopropylacrylamide) ( $\beta$ -CD-PNIPAM) and adamantyl-terminated poly(2-(diethylamino)ethyl methacrylate) (Ad-PDEA) (Fig. 3).<sup>19</sup> Linked by the host–guest interactions of adamantyl moieties and  $\beta$ -CD, an AB-type linear polymeric supra-amphiphile (DHBC) was fabricated from Ad-PDEA and  $\beta$ -CD-PNIPAM. Ad-PDEA acted as the pH-responsive component while  $\beta$ -CD-PNIPAM acted as the thermo-responsive component. With pH or temperature stimuli, the obtained aggregates could reversibly transform from micelles to vesicles in water.

Another well-known group of macrocyclic components, also widely utilized to construct polymeric supra-amphiphiles, are

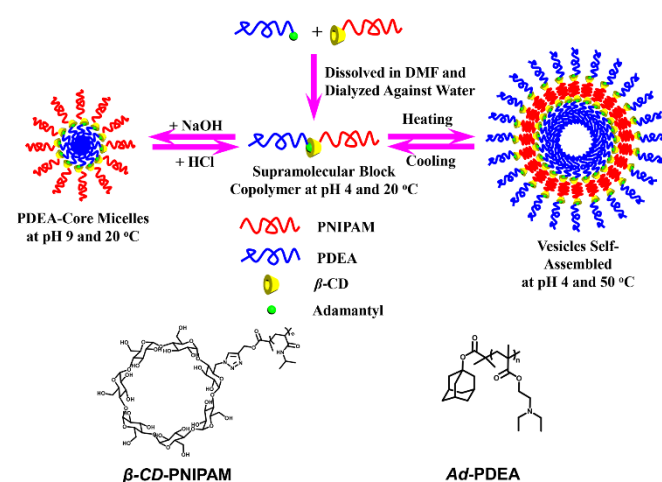


Fig. 3. The AB-type linear polymeric supra-amphiphile driven by the host–guest interactions of adamantyl moieties and  $\beta$ -CD, and its pH and temperature responsiveness. Reprinted from ref. 19 with permission from John Wiley & Sons, Inc..

the cucurbit[n]urils (CB[n],  $n = 5-8, 10$ ).<sup>20</sup> Owing to their structural resemblance, CB[n] are named after a genus of herbaceous vines, the *cucurbita*. They are macrocyclic oligomers of glycoluril possessing a hydrophobic cavity, with the portals surrounded by carbonyl groups. Based on the discrimination originating from different portal and cavity sizes, specific host–guest complexation is achieved between CB[n] and different guests. Particularly, stable ternary complex can be formed when an electron-rich group (for example, 2,6-dihydroxynaphthalene) and an electron-deficient aromatic group (for example, methyl viologen) are mixed with CB[8]. Different linear polymeric supra-amphiphiles with well-organised composition and interesting functions have been fabricated using this unique host–guest molecular recognition. For example, through the host–guest interaction of CB[8], indole and methyl viologen (MV), Ji and co-workers constructed an AB-type linear polymeric supra-amphiphile, in which the PLA chain was the hydrophobic part and the PEO chain was the hydrophilic part.<sup>6</sup> In water, the polymeric supra-amphiphiles aggregated into solid nanoparticles. Doxorubicin, an anticancer drug, could be encapsulated into the nanoparticles through hydrophobic interactions. Moreover, because of the redox responsiveness of the MV group, the supra-amphiphile dissociated under treatment with a reducing agent ( $\text{Na}_2\text{S}_2\text{O}_4$ ). This stimulus induced the disassembly of the nanoparticles and resulted in controllable drug release (Fig. 4). When used for biomedical applications, the hydrophobic polymeric segments PLA can be degraded into lactic acid by the enzymes of the biological system.

The ratio of hydrophilic to hydrophobic blocks will influence the shapes and sizes of the aggregates assembled from amphiphiles greatly. For traditional amphiphilic polymers, it remains difficult to regulate the respective chain lengths and thus adjust the hydrophilic/hydrophobic ratio, as the monomers are covalently linked. On the contrary, in polymeric supra-amphiphiles, where the hydrophilic and hydrophobic components are held together by noncovalent interactions, modulation of amphiphilicity (and thus assembled aggregate

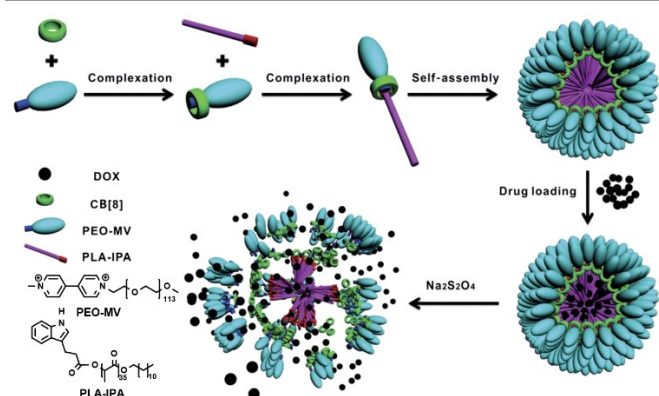


Fig. 4. The CB[8]-based AB-type linear polymeric supra-amphiphile for reduction-responsive drug delivery. Reprinted from ref. 6 with permission from the Royal Society of Chemistry.

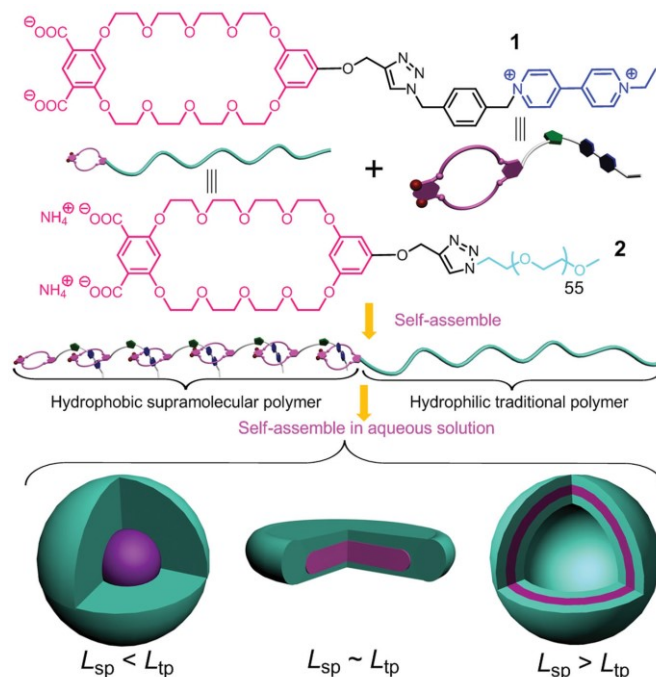


Fig. 5. The polymeric supra-amphiphiles prepared through host–guest interaction of crown ether/paraquat and their tunable aggregation behavior in aqueous solution. Reprinted from ref. 21 with permission from John Wiley & Sons, Inc..

structure) is much easier owing to the dynamic properties of supramolecular systems. Specifically, the hydrophilic/hydrophobic ratio can be regulated through changing the amount of monomer noncovalently bound to the main chain. Therefore, the preparation of polymeric supra-amphiphiles has proved to be an effective strategy for controllable self-assembly. For example, Huang and co-workers fabricated a polymeric supra-amphiphile through host–guest recognition between crown ethers and paraquats. The hydrophobic part comprised a supramolecular polymer, while a covalent polymer comprised the hydrophilic segment (Fig. 5).<sup>21</sup> The supramolecular polymer length could be modulated by changing the concentration of **1**. After the covalent polymer **2** was introduced into the system, the polymeric supra-amphiphile formed. The supramolecular polymer length could be adjusted through controlling the ratio between **1** and **2**, which produced a drastic influence on the hydrophobic/hydrophilic ratio of the supra-amphiphile. Consequently, different aggregates (including vesicles, micelles and disk-like micelles), could be assembled in a controlled fashion.

Conventional polymeric amphiphiles are fabricated by covalent linkages and polymeric supra-amphiphiles are linked by noncovalent interactions. The combination of covalent linkages and noncovalent interactions can endow linear polymeric supra-amphiphiles with more structural tunability and diverse functions. Yuan and co-workers synthesized  $\beta$ -CD-modified poly(*N,N*-dimethylaminoethyl methacrylate) (PDMAEMA) using ATRP.<sup>22</sup> Furthermore, they prepared poly( $\epsilon$ -caprolactone) (PCL) capped with an adamantane (Ada) group at

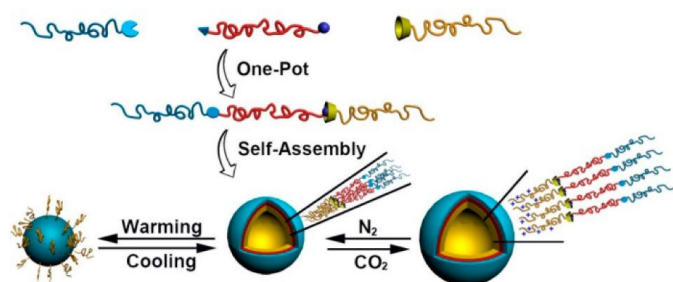


Fig. 6. AB-type linear polymeric supra-amphiphile PNIPAM-*b*-PCL-*b*-PDMAEMA with dual-responsiveness to temperature and CO<sub>2</sub> gas. Reprinted from ref. 22 with permission from the American Chemical Society.

one end and a  $-C=C-$  moiety at the other end through ring-opening polymerization (ROP) (Fig. 6). PNIPAM with a  $-S-C(S)-S-$  segment was prepared through reversible addition-fragmentation chain transfer polymerization (RAFT), and then converted into a thiol-capped polymer. When these three polymers were mixed in one pot, an AB-type linear polymeric supra-amphiphile was constructed through the host-guest complexations ( $\beta$ -CD and Ada) and thiol-ene Michael additions. With PNIPAM and PDMAEMA as the hydrophilic parts and PCL as the hydrophobic parts, vesicles were obtained through assembly of the AB linear polymeric supra-amphiphile in aqueous solution. The three components endowed the supra-amphiphile with good biocompatibility. Moreover, the supra-amphiphile was responsive to temperature owing to the introduction of PNIPAM, and responsive to carbon dioxide (CO<sub>2</sub>) gas owing to the presence of PDMAEMA. Specifically, the vesicles would be enlarged with the treatment of CO<sub>2</sub>, while the vesicles could be converted to micelles with a temperature change from 25°C to 40°C. The dual stimuli responsiveness deriving from the three components of this linear polymeric supra-amphiphile may provide wide applications in biomedical fields.

### 2.1.2 A<sub>n</sub>-type linear polymeric supra-amphiphiles

Linear polymeric supra-amphiphiles have simple architectures with repeating units linked together in a one-dimensional manner. Owing to their selectivity and specificity, host-guest interactions are usually incorporated into the main chain, driving two or more polymeric segments to form AB-type linear polymeric supra-amphiphiles, respectively. In addition, electrostatic interactions have also been explored as the driving force for AB-type linear polymeric supra-amphiphiles owing to the facile preparation of charged groups. In an alternative approach, quadruple hydrogen bonds were used to fabricate A<sub>n</sub>-type linear polymeric supra-amphiphiles, which exhibited unique properties in formation, disassociation, and self-healing. A<sub>n</sub>-type linear polymeric supra-amphiphiles (i.e., homopolymeric supramolecular polymer) present another important topology. Based on the ureidopyrimidinone (UPy), a quadruple hydrogen bonds binding unit, a series of A<sub>n</sub>-type linear polymeric supra-amphiphiles were constructed as supramolecular materials by Meijer and co-workers (Fig. 7).<sup>23</sup> Polymeric supra-amphiphiles with the general formula UPy-X-

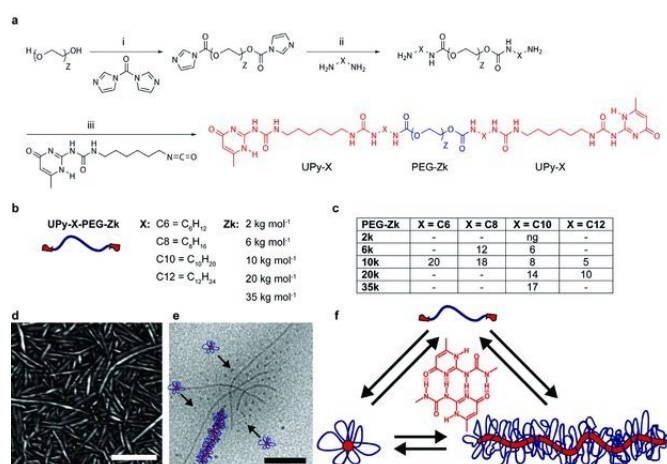


Fig. 7. An-type linear polymeric supra-amphiphile based on the quadruple hydrogen bonds for protein delivery. Scale bars represent 100 nm. Reprinted from ref. 23 with permission from John Wiley & Sons, Inc..

PEG-Zk were fabricated by the reaction of linear alkyldiamine with 1,1-carbonyldiimidazole-activated hydroxy-telechelic PEGs. Based largely on the strong interactions between the quadruple hydrogen bond UPy groups, micrometer-long hydrophilic nanofibers were fabricated. In addition, the macroscopic properties of this system could be regulated by controlling the ability to associate and disassociate through molecular design. Owing to the formation of a transient supramolecular network, the polymeric supra-amphiphile exhibited hydrogel-like properties. However, the exchange dynamics of the supramolecular network were tunable and could be controlled over different length-scales. In this way, unique characteristics were introduced into the transient supramolecular network not observed in typical hydrogels. Moreover, proteins, as model cargo, were loaded into the polymeric supra-amphiphile through a thermal encapsulation method. Owing to the non-linearity in formation, disassociation, and self-healing, the supramolecular network achieved controllable incorporation of proteins with maintained bioactivity. Therefore, this novel kind of polymeric supra-amphiphile shows great potential in protein delivery.

Aside from host-guest interactions and hydrogen bonds, linear polymeric supra-amphiphiles fabricated by other noncovalent interactions such as electrostatic interactions, charge transfer interaction, metal coordination and  $\pi$  stacking, may also present promising opportunities for further research towards new properties and functions.

### 2.2 Branched Polymeric Supra-amphiphiles

Another important topology of polymeric supra-amphiphiles are branched structures, which include side-chain polymeric supra-amphiphiles, hyperbranched polymeric supra-amphiphiles and star-type polymeric supra-amphiphiles. Side-chain polymeric supra-amphiphiles often have a number of branching sites, which are constructed by noncovalent interactions. Polymeric supra-amphiphiles with side chains have usually been obtained by introducing multiple chains on the

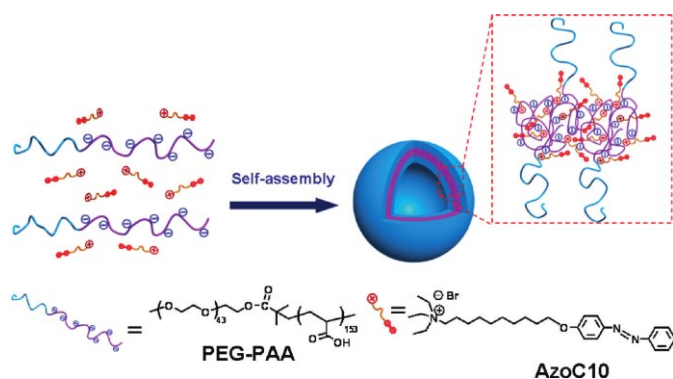


Fig. 8. The side-chain polymeric supra-amphiphile and light-responsive vesicles assembled from it. Reprinted from ref. 25 with permission from the American Chemical Society.

branching sites of covalent polymers, which can be also termed as graft-type polymeric supra-amphiphiles. As the branching sites are present in the covalent polymer chains, the density and number of branching points can be controlled through altering the covalent polymerization conditions. More importantly, different structural and functional side groups can be linked to the main chain by reversible noncovalent interactions, leading to opportunities to tune both assembled structures and function in a facile way. This approach has proved to be an effective strategy to achieve a variety of functional side-chain polymeric supra-amphiphiles.

### 2.2.1 Side-chain polymeric supra-amphiphiles

Electrostatic interactions have been frequently explored as the driving force for the formation of side-chain polymeric supra-amphiphiles, owing to the good water solubility and facile preparation of charged groups.<sup>24</sup> One common way to fabricate side-chain polymeric supra-amphiphiles is using an charged amphiphilic copolymer and small organic molecules with opposite charges. In this way, functional groups can be easily incorporated into the small molecules and further into the supra-amphiphiles. For example, using the interaction of poly(ethylene glycol)-block-polyacrylic acid (PEG-b-PAA) with small-molecule amphiphiles (AzoC10) composed of an azobenzene tail and a positively charged head group, Zhang and co-workers fabricated a light-responsive polymeric supra-amphiphile (Fig. 8).<sup>25</sup> This light-responsive system aggregated to form vesicles in water. Under UV irradiation, the vesicles were destroyed with the azobenzene groups of AzoC10 switching from the *trans*- to the *cis*- form, resulting in the release of loaded molecules. Utilizing this strategy, polymeric supra-amphiphiles with other types of stimuli-responsiveness, such as redox or enzyme responsiveness, have also been prepared.<sup>26,27</sup>

Owing to their promising use in drug loading and release, redox-responsive assemblies have attracted wide interest.<sup>28</sup> When treated by reductants or oxidants, organic selenium compounds exhibit strong redox activity and are therefore good candidates for redox-responsive materials.<sup>3</sup> Through the electrostatic interactions of selenium-containing surfactant and PEG-b-PAA, a side-chain polymeric supra-amphiphile was

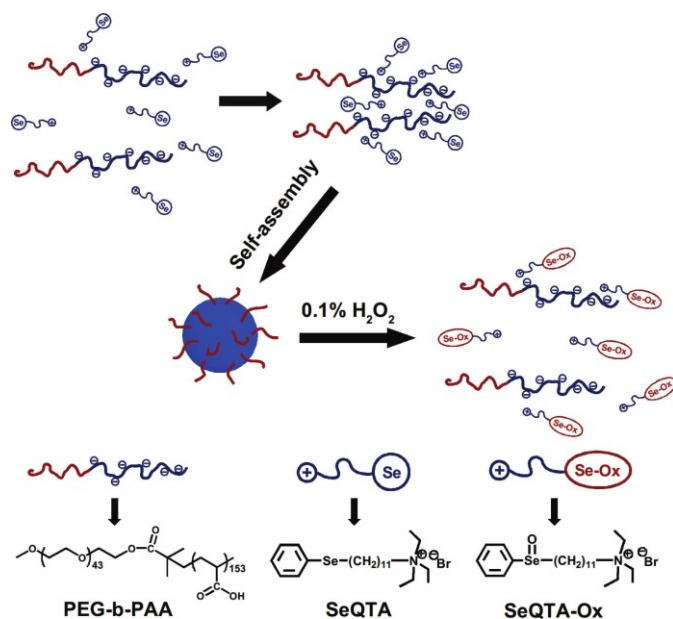


Fig. 9. The side-chain polymeric supra-amphiphile for the controllable drug release under mild oxidative conditions. Reprinted from ref. 29 with permission from the American Chemical Society.

prepared by Xu and Wang, which further assembled into micelles in water (Fig. 9).<sup>29</sup> For supramolecular amphiphiles based on mono-valent electrostatic interactions or hydrogen bonding, it is highly important to balance the degree of hydrophobicity to allow these interactions to be stable in the aqueous environment, which competes for both hydrogen bonding as well as solvation of ions. The selenide group of SeQTA could be oxidized to selenoxide by 0.1% H<sub>2</sub>O<sub>2</sub>. Oxidation changed the hydrophilicity of the supra-amphiphile, which

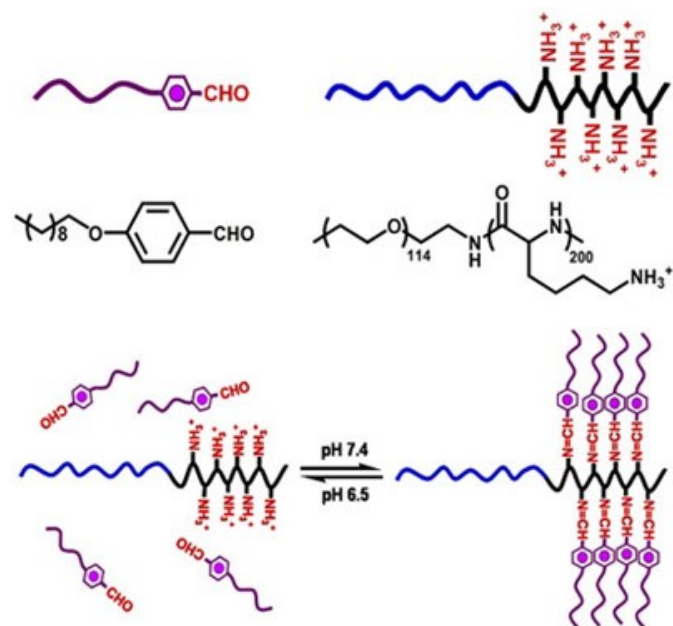


Fig. 10. The side-chain polymeric supra-amphiphile based on dynamic benzoic imine bonds with pH-responsiveness. Reprinted from ref. 30 with permission from John Wiley & Sons, Inc..

resulted in the disassembly of the aggregates. In this way, the guest molecules loaded in the micelles, such as fluorescein sodium, could be controllably released under mild oxidative conditions.

In many aspects, dynamic covalent bonds behave like noncovalent interactions owing to their dynamic nature, so they have already been utilized to prepare responsive polymeric supra-amphiphiles. Based on dynamic imine bonds, Zhang and co-workers fabricated a polymeric supra-amphiphile by using a building block containing benzoic aldehyde groups (DBA) and an amphiphilic block polymer (PEG-*b*-PLKC) containing amine groups (Fig. 10).<sup>30</sup> When pH = 7.4, the polymeric supra-amphiphile was formed by the formation of imine bonds, which led to aggregation into spherical assemblies. Moreover, the imine bond was cleaved in response to a pH change from 7.4 to 6.5, inducing the disassembly of the aggregates. Considering that this pH change occurs in the physiologically accessible range, this polymeric supra-amphiphile has great potential for application in nanomedicine.

Based on side-chain polymeric supra-amphiphiles, a variety of vesicles and micelles have been assembled with light-, redox- and enzyme responsiveness. The components of side-chain polymeric supra-amphiphiles range from synthetic building blocks to natural molecules and polymers, providing abundant choices for function and applications. Furthermore, the ability to precisely tailor the properties of these structures is vital for drug/gene delivery systems in which controlled circulation to specific pathological sites and release into target cells are highly desirable; the facile adjustment of the side chains by noncovalent interactions enables convenient balancing of the stability and dynamic properties of the self-assembled constructs.

### 2.2.2 Hyperbranched polymeric supra-amphiphiles

Contrary to side-chain polymeric supra-amphiphiles, hyperbranched polymeric supra-amphiphiles possess three-

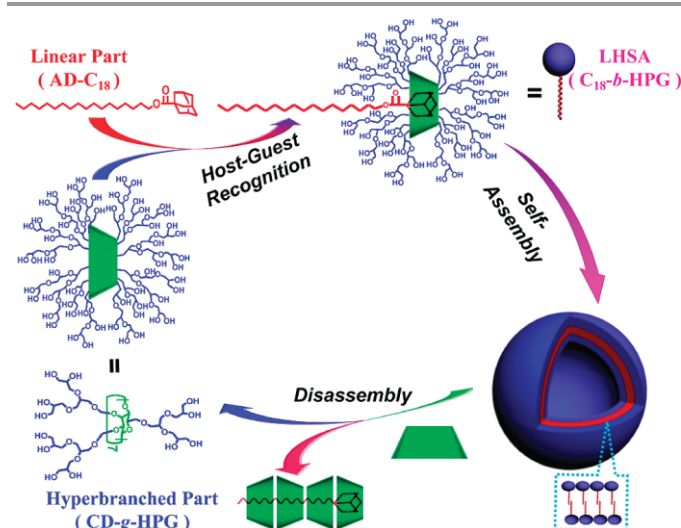


Fig. 11. The construction of hyperbranched polymeric supra-amphiphile based on host-guest complexation of Ada and  $\beta$ -CD. Reprinted from ref. 31 with permission from the American Chemical Society.

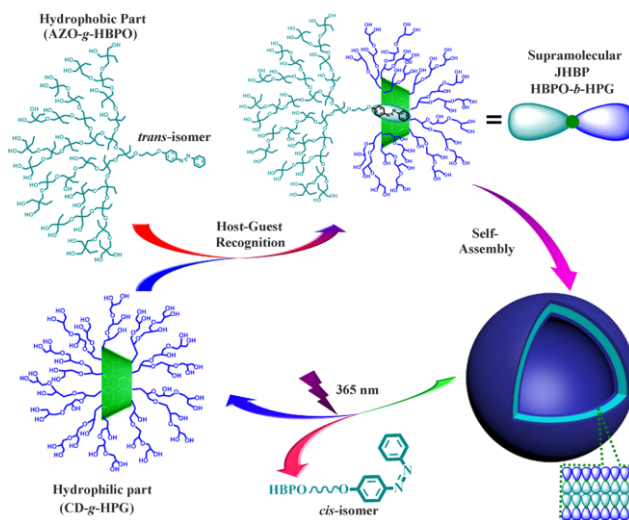


Fig. 12. The construction of hyperbranched polymeric supra-amphiphile based on the AZO/ $\beta$ -CD host-guest complexation and its UV light responsive assemblies. Reprinted from ref. 32 with permission from the American Chemical Society.

dimensional structure, low entanglement, low viscosity and a large number of end groups, potentially with multifunctional properties. Using specific host-guest interactions, Zhou and co-workers successfully fabricated a hyperbranched polymeric supra-amphiphile by combining an Ada-modified long alkyl chain and hyperbranched polyglycerol grafted from  $\beta$ -CD (Fig. 11).<sup>31</sup> In water, unilamellar vesicles with diameters ranging from 60 to 600 nm were formed by this supra-amphiphile. The obtained vesicles showed great ductility and disassembled with treatment of  $\beta$ -CD.

Along the same lines as this research, a hyperbranched polyglycerol-modified  $\beta$ -CD was synthesized as the hydrophilic part. A hyperbranched poly(3-ethyl-3-oxetanemethanol) modified azobenzene (AZO) was synthesized as the hydrophobic part. Driven by AZO/ $\beta$ -CD host-guest complexations, they were coupled to form a hyperbranched polymeric supra-amphiphile (Fig. 12).<sup>32</sup> Unilamellar bilayer vesicles with an average hydrodynamic diameter of 220 nm were obtained from this hyperbranched polymeric supra-amphiphile. Owing to the *trans*-to-*cis* isomerization of the AZO groups, the vesicles were UV light responsive. Once freeze-dried, crystal-like close-packed arrays were obtained through further aggregation of vesicles.

### 2.2.3 Star-type polymeric supra-amphiphiles

Star-type polymeric supra-amphiphiles with three-dimensional structures have also been prepared. Based on electrostatic interactions, Gauthier and co-workers designed a novel star-type polymeric supra-amphiphile (Fig. 13).<sup>33</sup> The shell of poly(acrylic acid)-block-poly(2-hydroxyethyl acrylate) was bound to the core of a polystyrene-graft-poly(2-vinylpyridine) copolymer. In water, they were dispersed as polyioncomplex (PIC) micelles whose diameter ranged from 42 to 67 nm. The concentration, pH and mixing molar ratio (*f*) all had an influence on the properties of the PIC micelles, including the weight average molar mass, hydrodynamic radius and radius of gyration of the scattering centers. Changes in the morphology



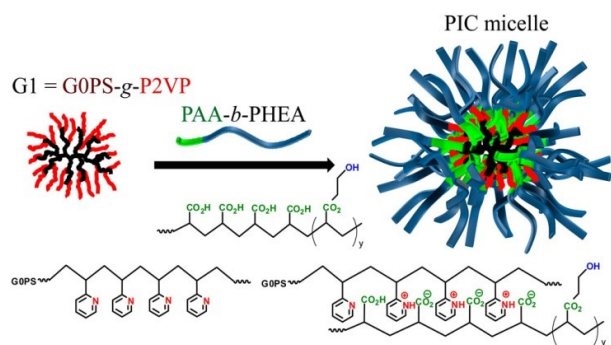


Fig. 13. The star-type polymeric supra-amphiphile that was dispersed as polyion complex (PIC) micelles. Reprinted from ref. 33 with permission from the American Chemical Society.

were studied by atomic force microscopy (AFM). The star-like structure of the PIC micelles could be observed through changing the force applied on the AFM tip. Moreover, no significant cytotoxicity was observed in this system, indicating good biocompatibility of the PIC micelles. More importantly, the fluorescently labeled PIC micelles were able to be adsorbed by negatively charged cancer cells (L929 cells), indicating the potential for application in biomedicine.

Another important topology, branched polymeric supra-amphiphiles include side-chain, hyperbranched and star-type polymeric supra-amphiphiles. Various noncovalent interactions and dynamic covalent bonds have been applied to construct branched polymeric supra-amphiphiles. The rich branching sites of such branched polymeric supra-amphiphiles provide the ability to link various functional groups, which contribute to establishing three-dimensional assembled structures and multifunctional properties.

### 2.3 Cross-linked polymeric supra-amphiphiles

Compared with linear or branched polymeric supra-amphiphiles, cross-linked polymeric supra-amphiphiles have more binding sites and more dense molecular entanglements, thus exhibiting better stability. Such cross-linked polymeric supra-amphiphiles can be obtained through mixing two kinds of multiple functionalized polymer blocks. Through the introduction of flexible connections, random cross-linked network can be fabricated. For example, by employing the interactions between Ada and  $\beta$ -CD as a driving force, Jiang and co-workers fabricated a cross-linked polymeric supra-amphiphile (PGMA-CD/PtBA-Ada) (Fig. 14).<sup>34</sup> The hydrophilic copolymer PGMA-CD was synthesized by free radical copolymerization, while the hydrophobic copolymer PtBA-Ada was produced by ATRP. In water, PGMA-CD/PtBA-Ada assembled into noncovalently connected micelles, as termed by the authors. In the micelles, the hydrophobic core consisted of PtBA-Ada and the hydrophilic shell of PGMA-CD. On the surface of the micellar shell a large number of  $\beta$ -CD cavities were present, which could be further applied for the modification of the micellar surface. The noncovalently connected micelles could be transformed to hollow nanoparticles through shell cross-linking and removal of the core.

Taylor and co-workers also developed another kind of cross-linked polymeric supra-amphiphile through solution-phase

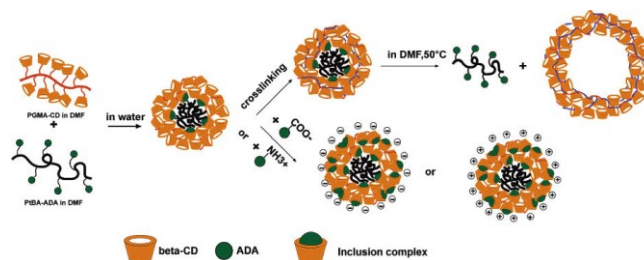


Fig. 14. The fabrication of PGMA-CD/PtBA-Ada micelles and their characters on the modification of micellar surface. Reprinted from ref. 34 with permission from the American Chemical Society.

macromolecular self-assembly induced by halogen bonding (Fig. 15).<sup>35</sup> Here, the RAFT polymerization was used to synthesize iodoperfluoroarene-bearing polymethacrylates as the polymeric halogen-bond donors. A block copolymer with amine groups as the halogen-bond acceptors was then associated with the polymeric donors to form a cross-linked polymeric supra-amphiphile. In water or organic solvent, the supra-amphiphiles would aggregate to stable, higher-order nanoparticles, as confirmed through dynamic light scattering, transmission electron microscopy and nuclear magnetic resonance spectroscopic investigations. The highly stable structures may find application in the fields of pollutant absorbance or detection. Despite such progress, cross-linked polymeric supra-amphiphiles have rarely been constructed to date owing to their complicated and atypical structure. However, it is anticipated that the unique stability and potential biomedical applications of cross-linked polymeric supra-amphiphiles will attract increasing attention in the future.

The diverse intrinsic topological structures of polymeric supra-amphiphiles can lead to tunable and colorful self-assembly behaviors. Based on noncovalent interactions, supramolecular polymers provide a novel strategy and approach for building amphiphilic polymers with novel topological features, which has expanded the scope of the formed self-assembled structures greatly.<sup>36</sup> To demonstrate effective control of the aggregation behavior by the topological structure of amphiphiles, Wu and co-workers developed several groups of polymeric supra-amphiphiles with similar hydrophobic/hydrophilic ratios and compositions, but different topologies: hemitelechelic, quadritelechelic and ditelechelic (Fig. 16).<sup>37</sup> By efficient host-guest complexation between  $\beta$ -cyclodextrin-poly(L-lactide) ( $\beta$ -CD-PLLA) and azobenzene-

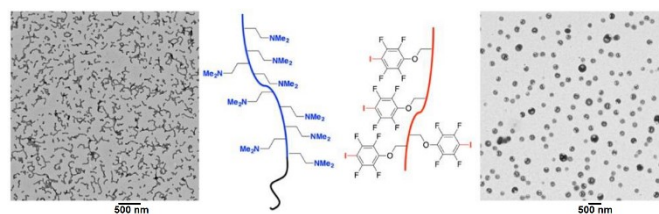


Fig. 15. The cross-linked polymeric supra-amphiphile and its different higher-order structures assembled in water or organic solvent. Reprinted from ref. 35 with permission from the American Chemical Society.

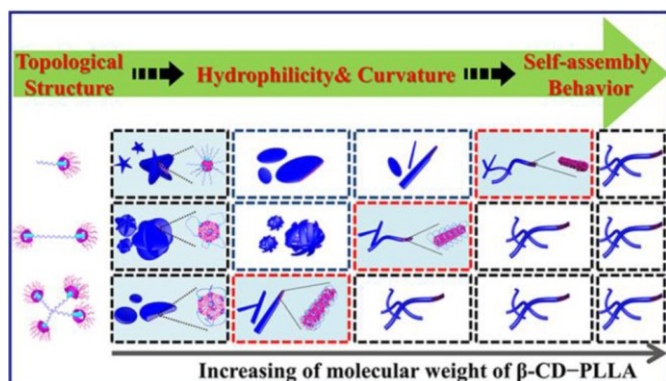


Fig. 16. The self-assembled morphologies effected by topology of the polymeric supra-amphiphiles. Reprinted from ref. 37 with permission from the American Chemical Society.

poly(ethylene glycol) (azo-PEG), polymeric supra-amphiphiles with different topologies were obtained facily. In this investigation, 15 kinds of polymeric supra-amphiphiles were fabricated through mixing three azo-PEGs with various topological building blocks and five  $\beta$ -CD-PLLAs. By utilizing this noncovalent approach to produce these polymeric supra-amphiphiles, the effect of topology on the self-assembled morphologies was well investigated.

In summary, linear, branched and cross-linked topologies have been constructed for polymeric supra-amphiphiles based on binding sites for noncovalent interactions or dynamic covalent bonds. On the basis of the diverse topologies and structures of polymeric supra-amphiphiles, tunable physicochemical properties and desirable emergent functions have been achieved. It is the expectation, in the future, that new and intricate topologies will be designed and developed, which may provide more useful insight into the realization of practical applications of polymeric supra-amphiphiles.

### 3. Applications of Polymeric Supra-amphiphiles

Polymeric supra-amphiphiles serve as a bridge between colloid science, polymer science and supramolecular chemistry. Linked by noncovalent interactions or dynamic covalent bonds, they can be fabricated facily with dynamic properties. Small-molecule supra-amphiphiles often exist in fast equilibrium between assembly and disassembly. In their polymeric counterparts however, the combination of multiple interactions and entanglement of the polymer chains slows molecular exchange, resulting in more stable complexes. Thus, the stability and dynamic properties of these self-assemblies can be balanced conveniently, which is vital for further applications.

In regard to the fabrication of polymeric supra-amphiphiles as materials, ideally, control over the structures, properties, and functions can be achieved through regulating the building blocks/monomers. Polymeric supra-amphiphiles can achieve customized functions through the strategic design, synthesis or choice of building blocks with desirable properties. For linear polymeric supra-amphiphiles, the simple and clear structures

make them ideal models for investigating the assembly behavior. For branched polymeric supra-amphiphiles, the side-chain conformations, extended backbones and noncovalent interactions result in many unique properties. For example, aggregates assembled from branched polymeric supra-amphiphiles exhibit stimuli responsiveness owing to the responsive properties of the side chains. The stability and dynamic properties can be balanced through adjusting multiple noncovalent interactions. Furthermore, branched polymeric supra-amphiphiles constructed by noncovalent interactions are suitable to act as nanocarriers, since the size and morphology of the aggregates can be adjusted easily. These parameters are vital for control over enhanced permeation and retention (EPR) effects (i.e., the tendency of assemblies of particular sizes to preferentially accumulate in tumor tissues). For cross-linked polymeric supra-amphiphiles, in addition to the stable self-assembled structures, the abundant cross-linking sites make them ideal candidates for constructing functional hydrogels.

#### 3.1 Polymeric supra-amphiphiles as a new kind of surfactant

Surfactants refer to organic compounds composed of both a hydrophilic part (their heads) and a hydrophobic part (their tails). On the interfaces between a liquid and a solid or between two liquids, the surfactants can induce a significant decrease of surface tension by adsorption. Owing to this property, surfactants find widespread applications in industry, colloidal research, and our daily life in personal care products. As the structures of polymeric supra-amphiphiles mimic those of traditional surfactants, they can also be utilized as surfactants to act as emulsifiers, foaming agents, and dispersants.<sup>1</sup> Compared with conventional surfactants, polymeric supra-amphiphiles allow for more convenient and flexible design of structures. Physicochemical properties at the interfaces, such as interfacial tension, can be adjusted conveniently. Moreover, properties such as the adaptiveness, reversibility, and stimuli-responsiveness of noncovalent interactions may endow the polymeric supra-amphiphiles with additional advantages in practical applications.

Emulsions are termed as dispersions of two immiscible fluids such as oil and water, which include direct emulsions (oil in water), inverse emulsions (water in oil) and double emulsions. A double emulsion is a multiphase system that integrates direct emulsions and inverse emulsions to form a water/oil/water structure. In the presence of surfactants, emulsions are obtained through shearing one phase into the other phase.

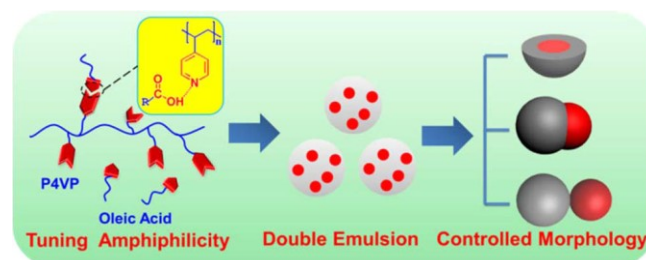


Fig. 17. Tuning the amphiphilicity of the side-chain polymeric supra-amphiphiles for controlling the phase separation in a double emulsion. Reprinted from ref. 38 with permission from the American Chemical Society.

They have been widely utilized in industry for applications such as surface coating, pesticides, cosmetics and in food products owing to their good metastability. In micro/nanotechnology, particles with different morphologies could be fabricated by the use of emulsions as versatile templates. However, uncontrollable phase separation hinders the process of solidification. To address this issue, Wang and co-workers used a supramolecular strategy for controlling the phase separation through the preparation of double emulsions (Fig. 17).<sup>38</sup> Hydrogen bonding between the carboxyl group of oleic acid and pyridine moiety of poly(4-vinyl pyridine) resulted in the formation of side-chain polymeric supra-amphiphiles. Simply through controlling the chain length of the aliphatic acid or the polymer/acid ratio, phase separations could be achieved in different degrees. Polymer particles could be generated with controllable anisotropic structures through partial wetting. In addition, the authors established a theory of spreading and wetting to explain and predict the observed phenomenon of partial wetting.

Polymeric supra-amphiphiles have also been used as versatile and powerful tools for the fabrication of novel kinds of vesicles. Reverse vesicles, referring to the aggregates composed by a hydrophobic core surrounded with a reverse bilayer. Compared with normal vesicles formed in water, the hydrophobic parts of reverse vesicles are exposed to nonpolar solvents (in the core and exterior of the constructs). Gao and co-workers constructed a novel kind of reverse vesicle by using a side-chain polymeric supra-amphiphile in dichloromethane (Fig. 18).<sup>39</sup> In the polymeric supra-amphiphile, the  $\beta$ -CD-modified linear or star-like poly(glycerol methacrylate)s constituted the backbone and cholesterol-terminated linear polylactides served as the side chains. The side chains were linked to the backbone by the host-guest interaction of cholesterol and  $\beta$ -CD groups. Through regulating the branching degree or molecular weight of the backbone, the diameter and polydispersity of the assembled reverse vesicles could be well adjusted.

### 3.2 Polymeric supra-amphiphiles as smart nanocarriers

In recent years, smart stimuli-responsive nanocarriers for cancer therapy have gained considerable attention.<sup>40</sup> Smart carriers refer to drug delivery systems that sense and respond to changes in their environment, leading to responsive and controlled drug release. Dispersed aggregates, for example, micelles and vesicles have been proposed as potential candidates to construct these smart nanocarriers. Compared with the assemblies fabricated by covalent amphiphiles, supra-

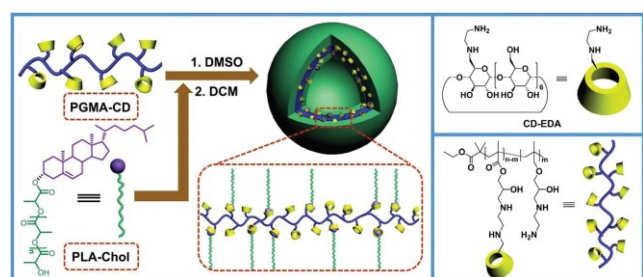


Fig. 18. The preparation of reverse vesicles based on side-chain polymeric supra-amphiphile. Reprinted from ref. 39 with permission from the Royal Society of Chemistry.

amphiphiles provide a more convenient route for the fabrication of responsive assemblies as nanocarriers, owing to their dynamic nature.<sup>41</sup> In addition, the stability can be enhanced using polymeric components; the stability of aggregates against dilution, which ensures the drug/gene circulates to specific pathological sites and be released into target cells, is also necessary for a drug/gene carrier. As a result, polymeric supra-amphiphiles are ideal candidates for the fabrication of such smart nanocarriers.

Considering the acidic tumor microenvironment, pH-responsive nanocarriers have been most commonly used for drug delivery.<sup>42</sup> This pH-responsive approach may be of more general application than conventional surface targeting of cancer cells. pH-responsive nanocarriers have been constructed from polymeric supra-amphiphiles through convenient synthetic procedures. For example, as shown in Fig. 19, Chen and colleagues fabricated a pH-responsive linear polymeric supra-amphiphile from benzimidazole (BM) modified poly(3-caprolactone) (BM-PCL) and  $\beta$ -CD terminated dextran (Dex- $\beta$ -CD).<sup>43</sup> Through host-guest interactions, the BM block was able to bind to  $\beta$ -CD when it exhibited hydrophobic properties at normal physiological pH. Once the conditions were changed to be acidic (pH < 6), a dramatic decrease of the binding constant was induced, resulting in the dissociation of the  $\beta$ -CD and BM stalk. Consequently, the polymeric supra-amphiphiles aggregated into micelles at normal physiological conditions, while the micelles were destroyed in acidic conditions. On the basis of this pH-responsive nature, the supramolecular micelles have great potential as anti-cancer drug carrier.

In biological systems, biochemical reactions are catalyzed efficiently and selectively by enzymes. Moreover, the activity and concentration of enzymes reflect the condition of cells' health closely. In inflamed or tumor tissues, certain enzymes are often overexpressed.<sup>44</sup> Thus, controllable gene/drug release can be achieved in the diseased areas based on enzyme-responsive polymers. Compared with complicated covalent synthesis, supramolecular methods to fabricate enzyme-responsive aggregates can integrate enzymatic substrates into the assemblies conveniently. Based on electrostatic

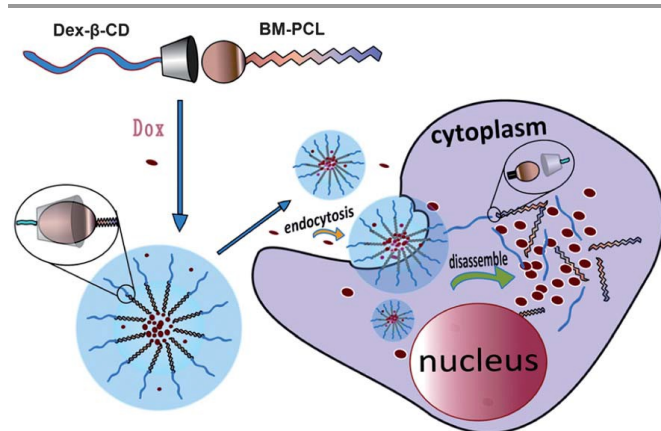


Fig. 19. The fabrication of a polymeric supra-amphiphile Dex-b-CD/BM-PCL for drug release induced by the intracellular microenvironment. Reprinted from ref. 43 with permission from the Royal Society of Chemistry.

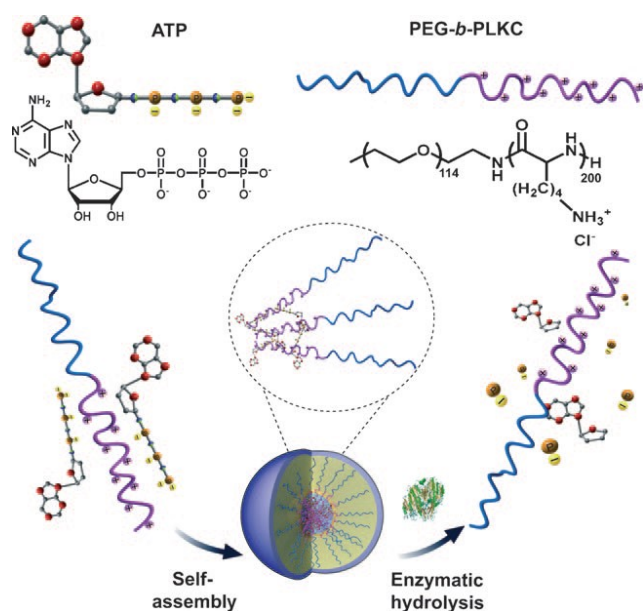


Fig. 20. The enzyme-responsive side-chain polymeric supra-amphiphile. Reprinted from ref. 3 with permission from John Wiley & Sons, Inc..

interactions, Zhang and co-workers have fabricated several side-chain polymeric supra-amphiphiles with enzyme-responsive properties. A typical example is the phosphatase-responsive spherical nanoparticles prepared with methoxy-poly(ethylene glycol)<sub>114</sub>-*block*-poly(L-lysine hydrochloride)<sub>200</sub> (PEG-b-PLKC) and adenosine-triphosphate (ATP) (Fig. 20).<sup>3</sup> ATP is the “energy currency” in living bodies and contains four negative charges with enzyme responsiveness. Through electrostatic complexation, ATP could bind to the positively charged PLKC segment of PEG-b-PLKC, forming a side-chain polymeric supra-amphiphile. In aqueous solution, the supra-amphiphile assembled into spherical nanoparticles with average diameters of 70 to 80 nm. When these assembled nanoparticles were exposed to alkaline phosphatase, ATP was decomposed to adenine and phosphoric acid. This decomposition resulted in dissociation of the supra-amphiphile, disassembly of the spherical aggregates and consequent release of the loaded molecules.

Through the mixing of myristoylcholine chloride and the block copolymer poly(ethylene glycol)-*block*-poly(acrylic acid), Zhang and co-workers fabricated an enzyme-responsive side-chain polymeric supra-amphiphile, which could further assemble into spherical aggregates (Fig. 21).<sup>26</sup> The spherical nanoparticles could encapsulate the dye Nile Red. In addition, the spherical nanoparticles, with a diameter from 40 to 150 nm, could be fragmented by treatment with acetylcholinesterase (AChE), due to the hydrolysis of the ester linkage by the enzyme. Under acetylcholinesterase treatment, the Nile Red could be released over several hours. As a control, more than 150 hours was needed for the spherical aggregates to release Nile Red by diffusion alone. It is therefore expected that the spherical aggregates assembled from such enzyme-responsive polymeric supra-amphiphiles could find further application as nanocarriers for drug delivery.

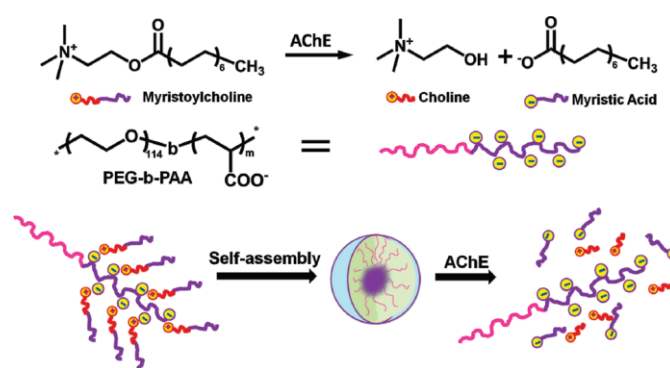


Fig. 21. The aggregation of polymeric supra-amphiphile and its AChE-triggered disassembly. Reprinted from ref. 26 with permission from the Royal Society of Chemistry.

In addition to synthetic polymers, natural macromolecules have also been used for fabricating side-chain polymeric supra-amphiphiles by Zhang and co-workers (Fig. 22).<sup>4</sup> The abundant natural polysaccharide chitosan is produced in biological systems. Chitosan exhibits cationic regions owing to the protonation of the amine groups. When mixed with ATP (containing four negative charges), a side-chain polymeric supra-amphiphile was constructed by electrostatic interactions. In aqueous solution, the polymeric supra-amphiphile assembled into spherical assemblies, which also displayed the enzyme responsiveness (phosphatase responsiveness, in this case) of ATP. These assemblies have better biocompatibility and can be prepared more easily when compared with other enzyme-responsive assemblies. It would therefore be possible to construct enzyme-responsive chitosan-based aggregates on a large-scale and at low cost, exhibiting promise for application as drug carriers.

Aside from the pH and enzyme stimuli that are internal in nature, temperature is a unique stimulus: it can be considered to be either external (heat is applied from outside the body) or internal (e.g., some tumors and infected tissues are naturally at elevated temperatures). Therefore, temperature-responsive materials are widely applied for the construction of nanocarriers.<sup>45</sup> Owing to its sharp and reversible phase transitions with changes in temperature, PNIPAM has been widely used as a thermo-responsive polymer. Hydrogen bonds between PNIPAM and water occur and PNIPAM appears hydrophilic below the lower critical solution temperature (LCST). When the temperature exceeds the LCST, PNIPAM transforms to a hydrophobic polymer owing to the loss of the hydrogen

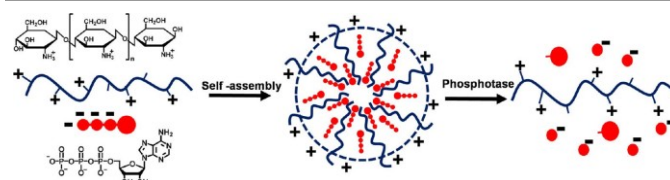


Fig. 22. The construction and assembly of phosphatase-responsive side-chain polymeric supra-amphiphile. Reprinted from ref. 4 with permission from the American Chemical Society.

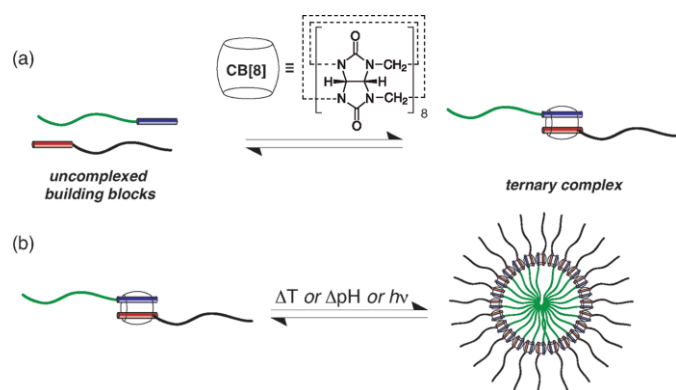


Fig. 23. (a) The fabrication of the polymeric supra-amphiphile driven by CB[8]-based ternary complexation; (b) The multi stimuli-responsive assembly of the polymeric supra-amphiphiles. Reprinted from ref. 46 with permission from the American Chemical Society.

bonds. Moreover, PNIPAM's LCST is close to the physiological temperature, ranging from 30 to 35°C, showing great potential for application as smart responsive materials and drug delivery systems. Through CB[8]-based ternary complexation, Scherman and co-workers fabricated a polymeric supra-amphiphile (Fig. 23).<sup>46</sup> The linear polymeric supra-amphiphile consists of PNIPAM and PDMAEMA, which act as thermo-responsive and pH-responsive blocks, respectively. In aqueous solution, the polymeric supra-amphiphiles aggregated into micelles that exhibited orthogonal responses to temperature, competitive guest binding and pH. The hydrophobic PNIPAM core could be solubilized if the temperature changed from 37 to 15°C, resulting in drug release from the core. When the chemotherapeutic drug doxorubicin (DOX) was utilized as a model, the micelles showed effective encapsulation and controllable drug release. Compared to the conventional multi stimuli-responsive covalent copolymer systems, the triple stimuli-responsive micelles based on this polymeric supra-amphiphile represent a great advantage in their facile fabrication. In viability tests on HeLa cells, the micelles displayed enhanced therapeutic effects upon controlled release of DOX from the nanocarriers. Based on a similar strategy, vesicles assembled from polymeric peptide supra-amphiphiles were also obtained and employed to encapsulate basic fibroblast growth factor.

### 3.3 Polymeric supra-amphiphiles for therapies

In clinical anticancer treatments, chemotherapy is one of the most important therapeutic methods. However, it is still limited by some obstacles, such as severe side effects to cancer patients, drug resistance and low therapeutic efficiency. To address these issues, supramolecular chemotherapy strategies, smart nanocarriers and targeted drug delivery systems have been developed. In addition, based on the polymeric supra-amphiphiles, photodynamic therapy (PDT) and  $\gamma$ -irradiation-responsive hydrogels were developed to enhance the therapeutic efficiency.

Upon light irradiation, PDT utilizes photosensitizers that produce reactive oxygen species (ROS) to destroy organic assemblies in malignant cancer cells.<sup>47</sup> PDT is less invasive, can

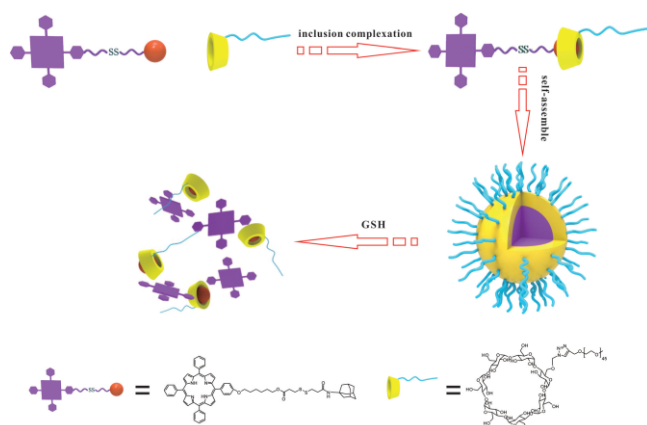


Fig. 24. The construction of polymeric supra-amphiphile for enhanced photodynamic therapeutic efficiency. Reprinted from ref. 48 with permission from the Royal Society of Chemistry.

be repeated and allows precise targeting of an illuminated area compared with other therapies. Porphyrins and their derivatives, which have become some of the most widely applied photosensitizers, are able to produce cytotoxic  $^1O_2$  to treat diseased tissue under appropriate light irradiation. However, the strong tendency of porphyrins to aggregate in aqueous solution is problematic, which could lead to a significant reduction of  $^1O_2$  production. It has been shown that the introduction of hydrophilic blocks is an effective way to hinder the aggregation of porphyrins and therefore improve their therapeutic efficiency.

Through the host-guest interaction of Ada-terminated porphyrin derivatives (TPPC6-SS-Ada) and poly(ethylene glycol)- $\beta$ -cyclodextrin (PEG- $\beta$ -CD), Zhang and co-workers prepared a linear polymeric supra-amphiphile that aggregated into micelles with an average diameter of 85 nm in water (Fig. 24).<sup>48</sup> The hydrophilic blocks of micelles improved the stability of assemblies and more importantly, suppressed the aggregation of hydrophobic porphyrin molecules. Moreover, the micelles possessed glutathione (GSH) responsiveness owing to the disulfide bond present in the TPPC6-SS-Ada block, which could induce a fast release of porphyrin in cancer cells with a higher GSH concentration. As a result, the micelles showed lower dark toxicity but higher photo-toxicity than free porphyrin, i.e., the porphyrin groups could be delivered into cells and achieve better therapeutic efficiency through the design of polymeric supra-amphiphiles with GSH responsiveness.

Hydrogels with stimuli-responsive properties have been developed extensively owing to the demand from biomedical applications. The release rates of drugs can be adjusted by controlling the gel-sol transition. Supramolecular hydrogels constructed from polymeric supra-amphiphiles possess excellent biodegradability and biocompatibility. By utilizing a peptide amphiphile and a diselenide-containing polymer, Xu, Yang and co-workers constructed a crosslinked polymeric supra-amphiphile with  $\gamma$  irradiation responsiveness (Fig. 25).<sup>49</sup> The formation of the supra-amphiphile and its gelation were induced by the combination of hydrogen bonds and electrostatic interactions. Upon  $\gamma$  irradiation, the

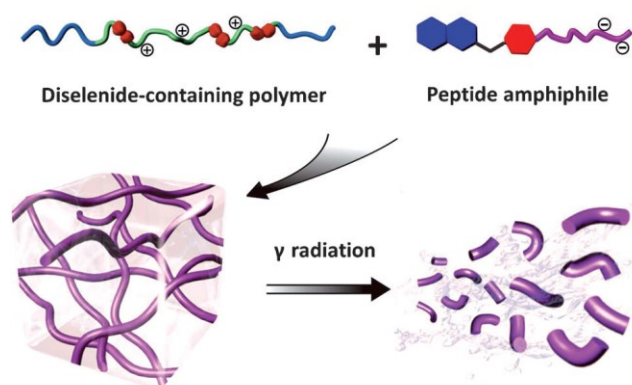


Fig. 25. Hydrogel constructed by a crosslinked polymeric supra-amphiphile and its  $\gamma$ -ray-responsiveness. Reprinted from ref. 49 with permission from John Wiley & Sons, Inc..

supramolecular hydrogel showed a gel–sol transition with structural disruption, which could thus be used as a smart hydrogel. The hydrogel constructed by the diselenide-containing polymeric supra-amphiphile has great potential for application in combined chemo- and radio-therapy with programmable responsiveness, if the  $\gamma$  irradiation can be decreased to a clinical dosage (8 Gy).<sup>50</sup>

Polymeric supra-amphiphiles exhibit the advantages of facile preparation, dynamic properties and relatively high stability, which is vital for further applications as surfactants, and in drug delivery and therapies. However, some problems still remain to be addressed before realization of their potential practical applications. Some readily available building blocks with stable properties should be considered to construct polymeric supra-amphiphiles for commercialization, rather than the current expensive motifs (albeit with attractive properties).

#### 4. Summary and Outlook

Although the use of polymeric amphiphiles is wide-spread in a range of applications, a number of key challenges still exist, mainly focused on the slow dynamics and low adaptivity originating from their covalent nature. The advent and phenomenal development of the field of supramolecular chemistry has provided some clues to how these issues might be addressed through the use of dynamic and noncovalent interactions. Specifically, the use of supra-amphiphiles, and, the topic of this review, polymeric supra-amphiphiles, has developed to show that such noncovalent constructs might well possess the solutions to the mentioned challenges.

Supra-amphiphiles, with their facile fabrication, diverse and tunable functions, and dynamic and adaptive properties, seem to provide a perfect replacement or complement for traditional amphiphiles in many fields. However, the relative low stability of supra-amphiphiles (originating from the use of soft noncovalent interactions) has been their Achilles' heel, thus hindering their real practical applications. Polymeric supra-amphiphiles are amphiphiles containing polymers or small molecules and polymers linked by noncovalent interactions or dynamic covalent bonds. They are a promising route to achieve

a balance between dynamic features, functionality and good stability. The concepts, fabrication, properties, and applications of a range of polymeric supra-amphiphiles were introduced here. Fabrication through noncovalent interactions has yielded polymeric supra-amphiphiles with simple preparation and dynamic features. Furthermore, molecular exchange is slowed down by the multiple interactions and entanglement of polymer chains, endowing polymeric supra-amphiphiles with higher stability compared with small-molecule analogues. In addition, the facile combination of polymeric components and a range of biomaterials (including enzymes) that possess orthogonal addressability shows great promise for the preparation of tailored drug carriers, which would be very difficult to achieve through the traditional approaches of covalent chemistry. These exciting developments clearly indicate the long-term potential and promise for the continued development of polymeric supra-amphiphiles.

Nevertheless, many problems still face researchers active in this and related areas of application, and need to be addressed utilizing the full gamut of chemistries, techniques and materials available. In addition to the search for new motifs with intriguing properties, readily available and inexpensive building blocks could also be considered to potentially replace polymeric amphiphiles. Specifically, for the further advancement of the field, detailed experimental and computational studies for guiding and predicting the construction of functional and addressable polymeric supra-amphiphiles and their assemblies should be conducted. Detailed physicochemical investigations into the properties of polymeric supra-amphiphiles including viscosity, surface tension and aggregation number are rarely reported, although these parameters are crucial to design polymeric supra-amphiphiles for expected applications. Furthermore, in light of potential bio-medical applications, it is very important to ascertain the final fate of the hydrophobic polymeric segments when the polymeric supra-amphiphiles disassemble into separate parts.

Finally, despite extensive studies on polymeric supra-amphiphiles, realization of their potential practical applications remains an obstacle. Such obstacles will only be successfully addressed through the combination of careful materials design and development with cross-disciplinary collaboration with relevant colleagues active in clinical and other environments. Such approaches are sure to lead to successful application of this exiting class of materials, helping to address grand challenges faced by our global community.

#### Conflicts of interest

There are no conflicts to declare.

#### Acknowledgements

This work was financially supported by the Ministry of Science and Technology of China (2018YFA0208900) and National Postdoctoral Program for Innovative Talents (BX201600082). H.

E. S. acknowledges the EPSRC (EP/N509619/1). C. F. J. F. acknowledges the Tsinghua Xuetang programme for support.

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