Trends in Polymer Science

The Interaction Between Amphiphilic Polymer Materials and Guest Molecules: Selective Adsorption and Its Related Applications

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The interaction between amphiphilic polymer materials and molecules such as drugs, proteins, and DNA plays one of the key roles for the applications in separation, delivery of drugs, biosensors, and tissue engineering. Thus, the fundamental investigation of this interaction is necessary before some polymer materials can be designed for practical applications. Here, various factors are discussed to determine the interactions between amphiphilic polymer materials and guest molecules. Based on this fundamental understanding, a series of amphiphilic polymer materials with selective adsorption to guest molecules has been developed and widely used for applications in smart separation, temporally controlled release, and patterning of guest molecules, such as dyes, drugs, and proteins.

1. Introduction

Amphiphilic polymer materials in various forms, such as micro- and nanogels, hydrogels, membranes, and fibers, have attracted much attention as a result of their wide applications,[1,2] such as water treatment,[3] controlled drug delivery,[4] and smart separation.[5] In these applications, the interaction between these amphiphilic polymer materials and molecules is of great importance. Several main factors were found to determine this interaction, including electrostatic interaction, hydrophobic interaction, π–π stacking, metal-ion complexation, topology structure, and so on. The differences in these interactions suggest the selective adsorption of guest molecules by the polymer materials. These selective adsorption abilities can be potentially used in smart separation, temporally controlled release, and patterning of guest molecules such as dyes,[6] drugs, and proteins.[7]

Different varieties of amphiphilic polymer materials with selective adsorption were required in different fields depending on the interaction between the polymer materials and guest molecules. For example, the lack of clean, fresh water has brought about many problems worldwide as a result of contamination caused by human activities. A great number of strategies are utilized to remove the contaminants in water,[8] such as heavy metal ions, distillates, organic dyes, and micropollutants, of which adsorption with polymer materials is regarded as an effective method for water purification. It is, therefore, significant to investigate the interaction to obtain polymer materials with enhanced adsorption capacities to remove pollutants.

Moreover, amphiphilic polymers are potentially applicable in biomedicine and bioscience based on their ability to selectively adsorb guest molecules.[9] By tuning the interaction between the polymer materials and guest drugs, amphiphilic polymers can be used as the platform to allow for the temporally controlled release of guest drug

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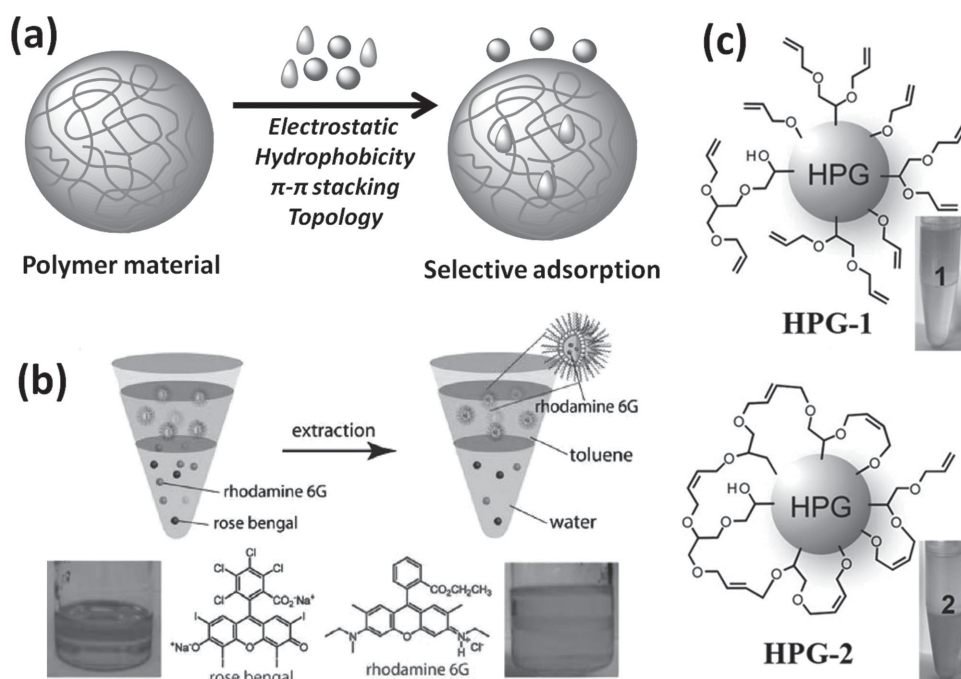
Figure 1. a) Interaction between amphiphilic polymer materials and guest molecules: selective adsorption. b) The separation of hydrophilic dyes based on an electrostatic interaction with reverse micelles of amphiphilic homopolymers.[1] c) Schematic representation of allylated (HPG-1) and ring-closing metathesis crosslinked (HPG-2) hyperbranched polyglycerols (hPG) as well as the corresponding photographs of encapsulated rose Bengal sodium salt in HPG-1 and HPG-2 after a 5 min extraction with water.[21] b) Reproduced with permission.[1] Copyright 2009, American Chemical Society; c) Reproduced with permission.[21] Copyright 2009, American Chemical Society.

molecules, which is a current need for combination therapy in cancer treatment.[10] Meanwhile, some polymer coating materials with selective protein-adsorption abilities are required, which can also be used in the treatment of various types of diseases, for example, cardiovascular disease (CVD). To cure CVD, artificial vascular transplantation was adopted, in which the inhibition of platelet adhesion and formation of a confluent endothelium on the lumen of the scaffold are necessary. It is critical to design bioavailable polymer surfaces with selective adsorption of endothelial progenitor cells (EPCs) and resistance to plasma protein and platelet adhesion.[11] To obtain the proper polymer material for these applications, a fundamental understanding of the interaction between polymer materials and guest molecules is necessary and of great importance.

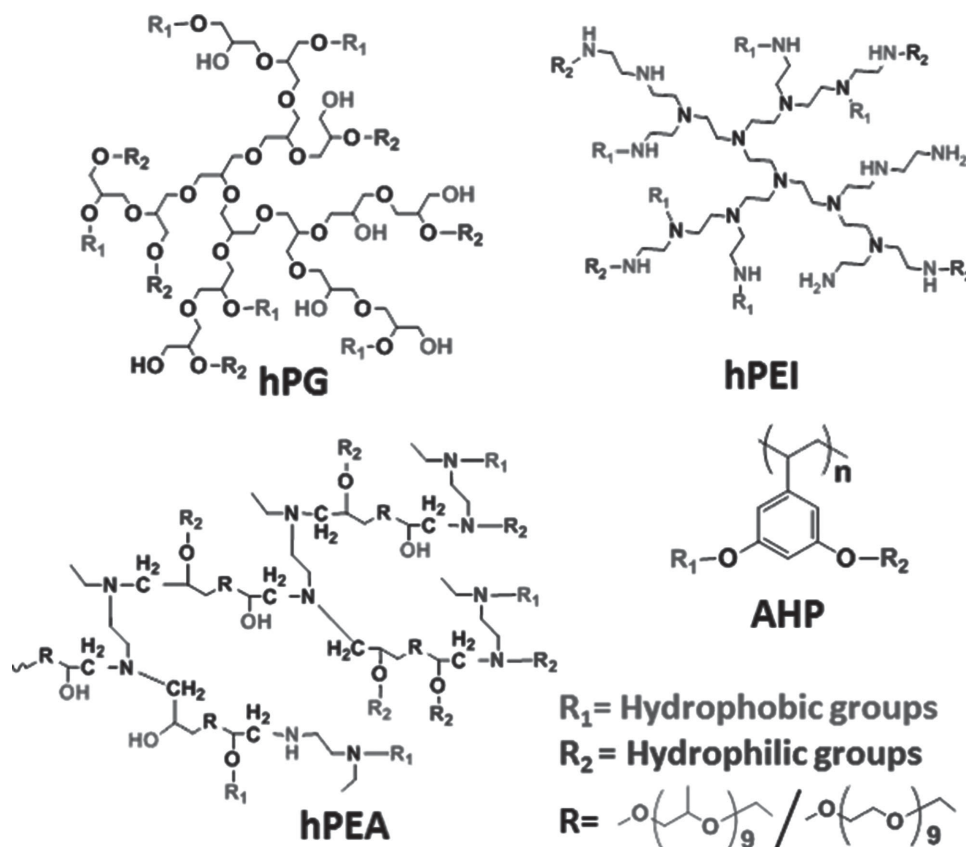Based on the great importance of the interaction between polymers and guest molecules, the intent of this article is to review the recent developments in the investigation of the interaction between amphiphilic polymers and guest molecules as well as the corresponding applications in smart separation of different guest molecules, temporally controlled release of these guest molecules, and the patterned array of the guest molecules. Particular attention is paid to the main progress made in the study of amphiphilic polymer materials for separation and patterns, including our own efforts.

2. Interaction Between Amphiphilic Polymers and Guest Molecules: Selective Adsorption

The amphiphilic polymer can recognize and encapsulate the guest molecule via the formation of complexes through noncovalent interactions, such as electrostatic interactions, hydrophobic interactions, π–π stacking, metal-ion complexation, and hydrogen bonding. The differences in the interactions lead to the selective adsorption of the guest molecules by these amphiphilic polymers, which can be investigated by comparing the guest encapsulation ability of different amphiphilic polymers, as shown in Figure 1a. Guest molecules possessing strong interactions with amphiphilic polymer materials can be encapsulated, while others with weak interactions cannot.

An electrostatic interaction is usually discovered between ionic amphiphilic polymers and guest molecules with charges, and a high encapsulation ability is observed when guest molecules are encapsulated by amphiphilic polymers with opposite charges. Stiriba and co-workers[12] reported that inverse micelles formed by alkyl-ended poly(ethylene imine) (PEI) (Scheme 1) could encapsulate anionic dyes through the existence of cationic cores. Thayumanavan and co-workers[13] reported that inverse

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■ *Scheme 1.* Some typical chemical structures of amphiphilic polymers for encapsulation of guest molecules.

micelles based on a carboxylic-acid-containing amphiphilic homopolymer (AHP) (Scheme 1) could selectively extract cationic dyes into the organic phase, as shown in Figure 1b. A similar phenomenon was also reported by Wan et al.,[14] that is PEI functionalized with alkyl epoxide and methyl iodide showed a larger encapsulation ability for anionic dyes than that without quaternization. These investigations make its potential to distinguish guest molecules with opposite charges with alkyl-ended PEI inverse micelles. As most biomolecules, such as amino acids, peptides, proteins, and DNA, are positively charged or negatively charged under mild physiological conditions, electrostatic interactions are beneficial for the separation and temporally controlled release of various biomolecules.[1]

The interactions between amphiphilic polymers and guest molecules can also be extensively affected by the hydrophobic moieties in the amphiphilic polymers. Haag and co-workers[15] described a class of dendronized polyethylene glycol (PEG) without hydrophobic alkyl graft chains that was unable to encapsulate the hydrophobic guest pyrene. Frey and co-workers[16] reported that the hydrophilic dye encapsulation ability of inverse micelles formed by alkyl-ended polyglycerol (PG) (Scheme 1) increased obviously with increasing alkyl chain length. All of these results indicate that encapsulation abilities for both hydrophobic and hydrophilic guest molecules by amphiphilic polymers are dependent on hydrophobic interactions.[17] Meanwhile, our group synthesized a series of hyperbranched poly(ether amine) (hPEA) (Scheme 1) and investigated the interaction between hybrid hPEA nanogels and 12 different types of typical guest dye molecules. We

proposed the parameter distribution coefficient (K) to quantify this interaction and found that K is dramatically influenced by the hydrophobicity of the hybrid hPEA nanogels.[6] Meanwhile, the parameter K can reflect the strength of the interaction between hPEA and dyes, with a large K value indicating a strong interaction. The large difference in K suggests the selective adsorption of the hybrid hPEA nanogels to guest dye molecules. This conception of K allows for the evaluation of the interaction between hydrophilic guest molecules and amphiphilic polymers, providing a guideline for the design of polymer materials.[6]

Another significant interaction between amphiphilic polymers and guest molecules is π–π stacking, which has been universally discovered between aromatic amphiphilic polymers and guest molecules. Haag and co-workers introduced different

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biphenylmethyl ether groups into hyperbranched polyglycerol (hPG) and then investigated the encapsulation abilities of the obtained polymers for hydrophobic pyrene.[18] A higher encapsulation ability of pyrene was observed for the polymer with the unfunctionalized biphenyl group due to stronger π–π stacking. Meanwhile, the specific π–π interaction between the electron-poor aromatic groups and electron-rich aromatic groups also played a very important role in this process. This phenomenon indicates that the aromatic substitutes of the amphiphilic polymers play a significant role in the encapsulation of aromatic guest molecules, which was also discovered to be important in the transport of Nile red and other aromatic guest molecules.[19]

The topological structure of amphiphilic polymers can also affect the encapsulation of guest molecules. For example, the encapsulation ability of Congo red (CR) for alkyl-ended hPG increased with molecular weight, a property that was ascribed to the increasing size of the hydrophilic hyperbranched topology.[16] Frey and co-workers[20] compared the encapsulation ability of hPG with linear PG and found that the linear esterified PG showed no phase transfer for several types of water-soluble dyes, which could easily be transported by analogous hPG. Similarly, linear PEI grafted with alkyl groups only transported dyes to an insignificant extent.[12] Haag and co-workers described the closed-shell architecture of the crosslinked allyl-ended hPG via the ring-closing metathesis reaction. As shown in Figure 1c, the encapsulated hydrophilic rose Bengal (RB) and thymol blue (TB) sodium salts could be transferred to the water layer from the organic-soluble complex with HPG-1, while the dye complex with shell-crosslinked HPG-2 was sufficiently stable enough that the dye remained in the chloroform layer.[21] The size of the guest molecules can also affect their encapsulation by amphiphilic polymers. Haag and co-workers investigated the encapsulation ability of a type of functionalized PEI for three anionic dyes and found RB and TB sodium salts were easily encapsulated, while CR was not entrapped very well. Because CR possessed a greatly extended structure compared with the other two dyes, the space for complexing CR might be insufficient for this type of polymers, suggesting the encapsulation ability of some amphiphilic polymers is dependent on the guest molecule size.[22] The difference in topology and size also provides us an efficient way to separate various drugs and biomolecules with the proper polymer materials.[23]

Besides the interaction between amphiphilic polymer and guest molecules discussed above, there is also a type of important host–guest interaction that exists between some types of guest molecules and polymers involving moieties such as cyclodextrins (CDs), crown ethers, calixarenes, cucurbiturils (CBs), and pillararenes, and this host–guest interaction can always be used in molecular recognition and supramolecular nanotechnology.[24] The aforementioned investigations provide the important fundamental understanding of the interaction between amphiphilic polymers and the guest molecules and provide some guidelines regarding what factors can be used to determine the selective adsorption of the polymer materials for guest molecules. This will be very helpful in the design and application of amphiphilic polymers for the separation of dyes and proteins, delivery of drugs, and use in other fields.
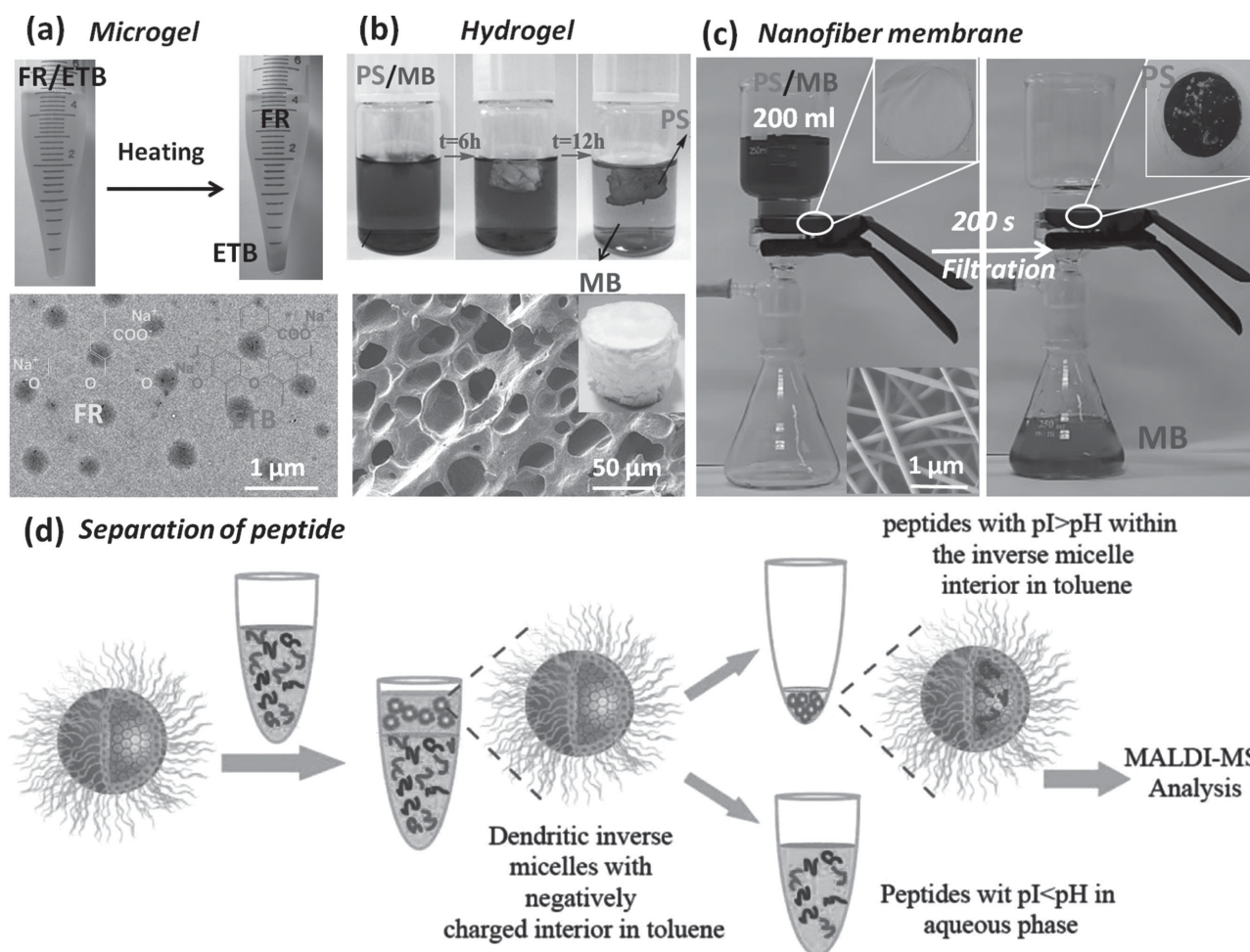
3. Separation of Guest Molecules

The difference in the interaction between the amphiphilic polymers and different guest molecules results in the selective adsorption or encapsulation of guest molecules by the amphiphilic polymers, which provides possibility in the separation of guest molecules. Varieties of materials, such as micro- and macrogels, membranes, tubes, and fibers fabricated by the aforementioned amphiphilic polymers, are used for the separation of guest molecules depending on their difference in charge, hydrophobicity, size, as well as topology. Recently, we fabricated a series of temperature-responsive hybrid nanogels of PEA and investigated the effect of the molecular structure of PEA on the interaction between the responsive PEA and guest hydrophilic dyes. PEA possessed strong interaction with some dyes but very weak interaction with others and can be used in separation of dye mixture.[25] Then, we also fabricated a multi-responsive microgel of hPEA (hPEA-mGel) through the co-assembly of allyl-ended hPEA and pentaerythritol tetra(3-mercaptopropionate) (PTMP) in an aqueous solution, followed by thiol-ene photo-click crosslinking. The obtained hPEA-mGel possessed a uniform size of ≈250 nm in diameter and was responsive to temperature and pH as well as exhibited selective adsorption to fluorescein dyes (Figure 2a). hPEA-mGel was added into the fluorescein/erythrosin B (FR/ETB) mixed aqueous solution. Upon heating, ETB precipitated with hPEA-mGel, while FR stayed in the water phase, suggesting an efficient separation of fluorescein dyes with a similar structure.[26] The homologous compounds always possess similar solubility in a specific solvent and can often be separated by column chromatography. As a result, the selective adsorption ability of hPEA-mGel to guest molecules with a similar structure is very significant, which provides a more efficient and lower cost alternative for the separation of homologous compounds than the traditional chromatography separation.

To put hPEA materials into further practical application for separation,

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Figure 2. a) Photographs of a FR/ETB separation by hPEA-mGel before (left) and after (right) heating above the cloud point and the representative TEM image of the hPEA-mGel.[26] b) Photographs of Ponceau S/Methylene Blue (PS/MB) separation before and after 12 h by hPEA hydrogels at 25 °C and the representative SEM image of hPEA hydrogels.[27] c) Equipment for molecular filtration and photographs before and after filtration the PS/MB solution. The inset is a photograph of a PEA nanofiber membrane before and after adsorbing PS as well as the representative SEM image of the PEA nanofibers.[29] d) A schematic representation of the amphiphilic dendrons forming inverse micelles that are capable of selectively extracting complementary peptides from aqueous solutions.[7] a) Reproduced with permission.[26] Copyright 2012, Royal Society of Chemistry; b) Reproduced with permission.[27] Copyright 2012, Royal Society of Chemistry; c) Reproduced with permission.[29] Copyright 2014, Royal Society of Chemistry; d) Reproduced with permission.[7] Copyright 2008, American Chemical Society.

we fabricated macroscopic hybrid hydrogels of hPEA by the direct hydrolysis of trimethoxysilane-ended-hPEA in water, which also exhibited selective adsorption ability (Figure 2b). These hybrid hPEA hydrogels were added to a mixed Ponceau S/Methylene Blue (PS/MB) aqueous solution. After 12 h, the whole aqueous solution became blue, the color of MB, whereas the hybrid hydrogel exhibited a red color, which is the color of PS, indicating the selective adsorption of PS from the PS/MB mixture. The whole process for the separation of PS/MB was analyzed by UV–vis spectra, which revealed that the purity of PS in a hybrid hydrogel is ≈100% after separation. Moreover, the PS adsorbed in hPEA hydrogels can be released when dialyzing against a basic aqueous solution, and the hydrogels were recycled and reused for the dye separations.[27] As it is easy to separate the hydrogels from a mixed dye aqueous solution without heating and centrifuging, hPEA hydrogels could potentially be used for the more convenient and energy-saving separation of dyes than hPEA in micelle and microgel form. However, these hPEA hydrogels were fragile, and the repeated use of them in dye separations was limited as a result of their poor mechanical stability. Therefore, poly(vinyl alcohol) (PVA) was introduced into hPEA hydrogels by a hydrolysis reaction between the hydroxyl groups of PVA and the trimethoxysilyl groups of hPEA in the presence of water. The obtained PVA-enhanced hydrogels were tough and flexible with a compress stress that was hundreds of times larger after modification with

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PVA. Meanwhile, the selective adsorption behaviors of the hPEA hydrogels were not obviously affected by the introduction of PVA, resulting in the selective adsorption of PS from a Ponceau S/Bismarck brown Y (PS/BY)-mixed aqueous solution by these PVA-enhanced hPEA hydrogels. These characteristics, such as the good mechanical performance and selective adsorption ability for guest dyes, make PVA-enhanced hPEA hydrogels potentially applicable for practical separation.[28]

The separation of guest molecules by immersing the macro-hydrogel into an aqueous solution is a static process, and a specific amount of time is usually needed for equilibration.[28] This slow separation process may limit the application of the hydrogels in some cases when a rapid separation is required. Then, molecular filtration through a membrane can be used to achieve a dynamic and rapid separation of guest molecules, which is very promising but challenging. Recently, we fabricated PEA nanofiber membranes through electrospinning and photo-crosslinking linear PEA that contained coumarin in the backbone, and the obtained membranes still possessed similar selective adsorption abilities as PEA hydrogels. A mixture solution of PS/MB passed through a PEA nanofiber membrane at a high flow rate of 60 mL min^{-1}, and almost all of the PS was captured by the PEA nanofiber membrane, whereas most of the MB passed through and remained in filtrate solution, suggesting the efficient separation of PS and MB (Figure 2c). Meanwhile, these PEA nanofiber membranes could be regenerated by a wash with a NaOH aqueous solution, and they still separated the mixture of PS/MB with high efficiency even after 10 filtration-regeneration cycles. Therefore, this filter is believed to possess potential applications in guest molecule separation and water purification.[29]

Amphiphilic polymers with selective adsorption for biomolecules can also be used for the separation of proteins and peptides.[30] The purification of native or recombinant proteins is important for research in the biosciences, particularly proteomics. Meanwhile, the selective separation of peptides from peptide mixtures is especially valuable in protein detection and possesses a potential application in proteomics and pathogen detection. As a result of the different electrostatic interaction between charged peptides and ionic amphiphilic polymers, the inverse micelles of amphiphilic dendrimers developed by Thayumanavan and co-workers can selectively extract peptides from their aqueous solutions based on their isoelectric points (pI) as a result of the charged interiors in the inverse micelles (Figure 2d). After the liquid/liquid extraction, peptides with pI > pH were within the inverse micelle interior in the toluene phase, while peptides with pI < pH were in the aqueous phase.[7] Moreover, Wang and co-workers described the functionalization of multiwalled carbon nanotubes (MWCNTs) with cationic poly(diallyl-dimethyl-ammonium chloride) (PDDA) and used the obtained materials to extract the acidic protein in human blood. As bovine serum albumin (BSA) possessed a negative charge, whereas hemoglobin (Hb) possessed a positive charge using ultrapure water as a medium, BSA was efficiently adsorbed by PDDA and separated from the mixture.[31] Similar results were obtained when PDDA was replaced by another cationic amphiphilic polymer, hyperbranched PEI.[32] The electrostatic interaction between proteins and amphiphilic polymers plays a key role in the separation of proteins by these ionic amphiphilic polymers.

In addition to electrostatic interactions, other interactions are also used in the protein separations. Ulbricht and co-workers introduced bisphosphonato-*m*-xylylene methacrylamide segments into the polymer chains. The existence of specific π-cation interactions between arginines and the binding sites in these segments allowed for the selective adsorption of the arginine-rich lysozyme instead of the lysine-rich cytochrome C in the obtained polymer materials, although these two proteins possessed similar sizes and pI values.[33] The traditional methods for the separation and purification of proteins, such as electrophoresis, are always dependent on the different sizes and pI values of proteins; however, this type of "antibody-like" polymer material that possesses the special bonding site exhibits a unique selective adsorption ability for the corresponding proteins and can clearly distinguish and separate proteins with similar pI values and sizes.[33] Therefore, these types of polymer materials provide an efficient alternative for the separation and purification of proteins that are difficult to separate by electrophoresis. However, the universality of this method is still limited as it can only separate specific types of proteins.

4. Temporally Controlled Release of Guest Molecules

Amphiphilic polymers and their assemblies have been widely investigated as polymer carriers for the delivery of therapeutic drugs, genes, and bioactive molecules due to improved water solubility, bioavailability, and extended duration of circulation in the blood.[34] Due to the existence of the combination effect of guest drug molecules, temporally controlled release of these molecules is often required in combination therapy used in cancer treatment. Synergistic, potentiative, and antagonistic effects of drug combinations have already been discovered between different types of therapeutic drugs.[35] Drug combination is

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regarded as one of the most efficient strategies to cure different types of diseases in the clinic. Compared with monotherapy, combination therapy is able to have an effect on a variety of disease targets simultaneously, making the therapy more active and less toxic through avoiding non-specific accumulation of drugs in healthy tissues and hitting different disease targets simultaneously.[36] Because the delivery behavior of guest drugs is determined by their interactions with polymer carrier materials, a temporally controlled release of two drugs was achieved through tuning of the interaction between different drugs and polymer materials, which is beneficial for combination therapy.

Haag and co-workers demonstrated an interesting bifunctional nanocarrier system based on the structure of dendritic PG, in which two types of hydrophobic guest molecules, pyrene and Nile red, were encapsulated as two different model drugs.[10] Pyrene was encapsulated into the hydrophobic core of modified hPG via hydrophobic interactions as well as π–π stacking to form a unimolecular micelle system, while Nile red was solubilized in the outer shell as a result of the relatively weaker hydrophobic interaction and π–π stacking. The temporally controlled release of Nile red and pyrene could then be achieved, triggered by pH values and enzymes, respectively. Nile red was released under acidic conditions, where the aggregated polymer structures collapsed into unimolecular micelles. Furthermore, after addition of the enzyme, the ester bonds in the hPG were broken, removing the hydrophobic aromatic moieties from the core of the micelles and causing the release of pyrene. This bifunctional nanocarrier system is a promising candidate for simultaneous delivery of different hydrophobic drugs for combination therapy. Similarly, Thayumanavan and co-workers described a type of composite nanostructure that was composed of a pH-responsive block copolymer micelle based on poly(2-(diisopropylamino)ethylmethacrylate-*block*-2-aminoethylmethacrylate hydrochloride) (PDPA-*b*-PAMA) as the core and a redox-responsive nanogel based on poly(oligoethyleneglycol monomethylether methacrylate-*co*-glycidyl methacrylate-*co*-pyridyl disulfide ethyl methacrylate) (P(EGMA-GMA-PDSEMA)) as the shell. Two types of guest molecules, 1,1′-dioctadecyl-3,3,3′,3′-tetramethyl-indocarbocyanine perchlorate (DiI) and pyrene, were then incorporated in the nanogels and micelles, respectively, via different interactions. The pH-triggered release of pyrene and glutathione-triggered release of DiI were then achieved, suggesting that the composite nanostructures can independently release the incorporated hydrophobic guest molecules in response to redox or pH changes. Meanwhile, compared with the PDPA-*b*-PAMA block copolymer micelles, the composite nanoassemblies were significantly less toxic and could be potentially used as drug nanocarriers for combination therapy.[37] The temporally controlled release of the model molecules from these nanocarriers is based on the selective adsorption of the polymer nanocarriers to guest model molecules, which provides some guidelines for the design of the polymer materials with ability to release guest molecules temporal distinctly.

In addition to the temporally controlled release of model drugs mentioned above, the co-delivery of two therapeutic drugs was also carried out in cells and shown to be dependent on the different interactions between amphiphilic polymer nanocarriers and guest drug molecules. Farokhzad and co-workers described the co-delivery behavior and synergistic cytotoxicity of cisplatin and docetaxel (Dtxl) in prostate cancer cells[38] (Figure 3a). The cisplatin pro-drug was conjugated in functionalized poly(lactic acid) complexed with platinum(IV) (PLA-Pt(IV)). The obtained polymer was then co-assembled with a carboxyl-ended poly(lactic acid-*co*-glycolic acid)-*block*-poly(ethylene glycol) copolymer (PLGA-PEG-COOH) through a nanoprecipitation step to encapsulate Dtxl. At pH 7.4 and 37 °C, Dtxl was released from the obtained nanoassemblies faster than cisplatin, a property that can be ascribed to the different interaction between the polymer nanoassemblies and guest drugs. Dtxl was encapsulated in the nanoassemblies via hydrophobic interactions, which were much weaker than the complexation interactions between the nanoassemblies and cisplatin. Similarly, Ge and co-workers developed a redox-responsive core crosslinked micelle conjugated by cypate and cisplatin pro-drugs.[39] As the complexation interaction between the polymer micelles and cisplatin was weaker than the conjugation interaction between the polymer micelles and cypate, cisplatin was released in the presence of reductants while the conjugated cypate remained in the core. As a result, the photothermal temperature increased and reactive oxygen species (ROS) were generated under 805 nm near-infrared (NIR) laser irradiation. The significant synergistic effect of photothermal therapy and chemotherapy was then demonstrated against cisplatin-resistant human lung cancer A549R cells under NIR irradiation via the enhancement of endo/lysosomal disruption and drug diffusion. Use of these polymer-drug conjugates provides a convenient method to distinctively and temporally release therapeutic drugs, which is beneficial for increasing the activity of the therapy. Therefore, these multi-drug carriers based on different interactions between polymers and drugs are also potentially useful for efficiently curing other types of human diseases, such as diabetes, rheumatoid arthritis, and malignant tumors, with minimum

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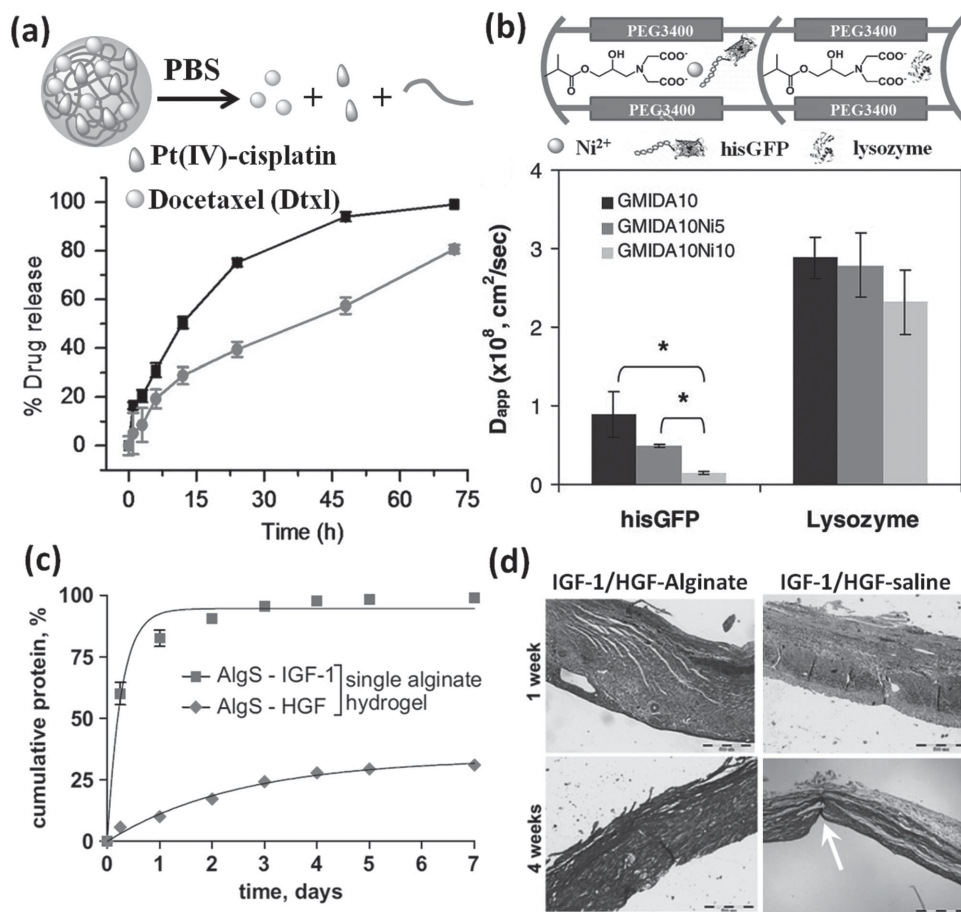
Figure 3. a) In vitro temporally controlled release of Pt(IV)-cisplatin (red circle) and docetaxel (black square) in PBS at 37 °C from the nanoassemblies.[38] b) Apparent protein diffusivity of dual-protein release from monolithic PEG-*co*-GMIDA hydrogels containing 10×10^{-3} M GMIDA only (GMIDA10), 10×10^{-3} M GMIDA, and 5×10^{-3} M Ni^{2+} (GMIDA10Ni5), or 10×10^{-3} M GMIDA(Ni^{2+}) (GMIDA10Ni10) ligands. Average $\pm$ standard deviation, $n = 3$, *$p < 0.02$, 10 wt% PEGDA for all formulations. GMIDA(Ni^{2+}) and GMIDA reversibly complex with hisGFP and lysozyme, respectively.[42] c) Temporally controlled release pattern of IGF-I/HGF from affinity-binding alginate biomaterial. IGF-I and HGF release from affinity-binding alginate microspheres were analyzed by ELISA using antibodies specific to human IGF-I and HGF.[43] d) Representative images of Masson's trichrome staining (collagen-rich areas in blue and healthy myocardium in red) scar area; the scale bar is 500 μm. The temporally controlled IGF-I/HGF delivery maintains scar thickness, attenuates infarct expansion, and reduces fibrosis.[43] a) Reproduced with permission.[38] Copyright 2010, National Academy of Sciences; b) Reproduced with permission.[42] Copyright 2008, American Chemical Society; c,d) Reproduced with permission.[43] Copyright 2011, Elsevier.

drug resistance and adverse patient side effects.[40]

The temporally controlled release of different proteins can also be achieved by controlling the interactions between polymer carriers and guest protein molecules. Protein delivery has also attracted much attention due to its potential application in the field of diagnostics and treatment of various diseases such as cancer and inflammatory diseases.[41] Lin and Metters described a type of affinity hydrogel that could deliver two proteins independently.

They incorporated methacrylated iminodiacetic acid (GMIDA) ligands and Ni^{2+} into poly(ethylene glycol) hydrogels (PEG-*co*-GMIDA), then encapsulated two types of model proteins, hexahistidine-tagged green fluorescent protein (hisGFP) and lysozyme, in the obtained affinity hydrogel via two different interactions: metal-ion chelation and electrostatic interaction, respectively (Figure 3b). The metal-ion chelation interaction was very strong between Ni^{2+} in the hydrogels and hexahistidine in the hisGFP, while lysozyme

was encapsulated in the hydrogel only through an electrostatic interaction. Therefore, the apparent protein diffusivity (D_{app}) of hisGFP in the PEG-*co*-GMIDA hydrogel was low and decreased very obviously with increasing Ni^{2+} concentrations, while the D_{app} of lysozyme was much higher and almost independent of the Ni^{2+} concentration, suggesting that independently localized delivery control of hisGFP and lysozyme could be achieved under mild physiological conditions.[42] Because some types of native protein growth factors can be

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functionalized with hexahistidine tags allowing for a metal-ion chelation interaction with PEG-*co*-GMIDA hydrogels, these versatile and biocompatible affinity hydrogels can encapsulate hexahistidine-tagged and non-hexahistidine-tagged growth factors simultaneously and temporally release them in a distinctive manner. This characteristic is potentially useful in tissue engineering, where temporally controlled delivery of multiple growth factors is required.

Similarly, Cohen and co-workers demonstrated that myocardial repair could be promoted by the temporally controlled delivery of insulin-like growth factor-I (IGF-I) and hepatocyte growth factor (HGF) from a type of alginate hydrogel for the treatment of acute myocardial infarction (MI). Two growth factors were loaded in the alginate hydrogel microspheres, in which the affinity-binding of proteins were tunable through reversible interactions between the proteins and alginate-sulfates. As IGF-I is a basic protein with a pI value of ≈8.2, while HGF is an acidic protein with a pI value of ≈5.5, the electrostatic interactions between the alginate-sulfate hydrogels and these two growth factors were different. Therefore, the cumulative release behaviors of IGF-I and HGF from the microspheres were significantly different from each other, and the release rates of HGF and IGF-I were variable at different time intervals (Figure 3c). IGF-I was released rapidly at the beginning and then much more slowly after 6 h, while HGF was released continuously over time, properties that were ascribed to differences in the reversible interactions between the proteins and alginate-sulfates. The effect of temporally controlled delivery of IGF-I and HGF on the thickness and morphology of the scar was further investigated in a rat model of acute myocardial infarction (Figure 3d). Four weeks after intramyocardial injection

with a temporally controlled delivery of IGF-I and HGF, the curing effect was much better than in the control where IGF-I and HGF were delivered separately, which was indicated by a larger value of scar thickness and smaller infarct expansion (marked with white arrow in the figure). These results show that therapeutic effects can be enhanced through the temporally controlled delivery of growth factors, resulting in a much more rapid process of tissue repairing after diseases such as acute myocardial infarction.[43] Similarly, sequential delivery of two types of growth factors, basic fibroblast growth factor (bFGF) and bone morphogenetic protein-2 (BMP-2) for osteogenesis of human mesenchymal stem cells (hMSCs), can also be achieved by polycaprolactone (PCL)/gelatin fibers and PEG hydrogels through different electrostatic interactions, and this sequential delivery of bFGF and BMP-2 exhibited stronger osteogenic commitment.[44] In summary, the temporally controlled release of drugs and proteins possesses a better therapeutic effect in some types of diseases with minimum drug resistance and adverse patient side effects. However, it remains challenging to design polymer materials that can encapsulate multiple types of drugs with precise control of drug release order. Meanwhile, it is still very difficult to release a specific type of drugs exactly as required while not affecting the other drugs co-encapsulated.

5. Patterning of Guest Molecules

The patterned arrays of guest molecules, which are arrays of guest molecules that are spatially distributed in a certain small space, can be realized based on the selective adsorption of guest molecules onto the patterned polymer surface. As one of the most popular guest molecule patterns, the

micropattern of proteins is convenient and beneficial for investigating the interaction between various types of proteins and other biomolecules, which is useful in many fields, including biomedical devices, biosensor technology, and tissue engineering.[45] The protein microarray can be obtained by adsorbing proteins selectively onto specific regions of a pre-patterned surface. Generally, the pre-patterned surface is covered by amphiphilic polymers or two types of polymers, one of which possesses a strong adsorption ability for protein, while the other is resistant to protein.

Hydrophobic interaction is a critical factor in the adsorption of protein to the polymer surface. As a result, the binding properties of proteins increase with increasing hydrophobicity of the polymer surface. For example, protein binding to the hydrophobic polystyrene (PS) phase region of the polymer blend was highly selective. Knoll and co-workers described the protein nanoarrays formed on a polystyrene-polymethylmethacrylate block copolymer (PS-*b*-PMMA) surface by the non-specific adsorption of proteins. Through phase separation of the PS-*b*-PMMA block copolymer films, nanopatterns with hexagonally arranged PS phase regions were generated. Due to the stronger adhesion of immunoglobulin-G (IgG) on the PS surface than that on the PMMA surface, IgG could be only be selectively adsorbed on the PS phase region, resulting in the formation of protein nanoarrays.[46] Budkowski and co-workers[47] demonstrated patterned protein adsorption using concanavalin A (ConA) and lentil lectin (LcH) adsorbed on the patterns fabricated by self-organizations of blend polystyrene (PS)/poly(ethylene oxide) (PEO) films. Fluorescence images of ConA adsorbed onto the self-organized PS/PEO polymer pattern are shown in Figure 4a. As the PEO chain is hydrophilic and widely used for the resistance of non-specific adsorption of

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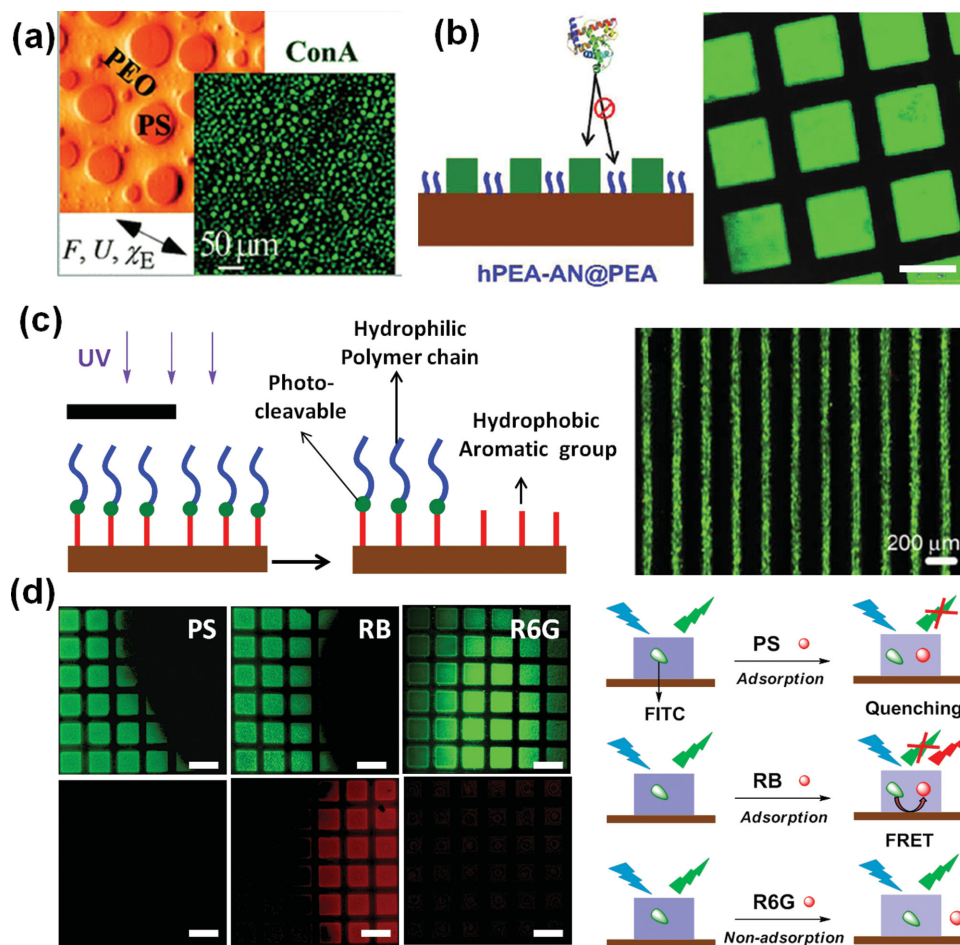
Figure 4. a) Fluorescence images of ConA adsorbed onto a self-organized PS/PEO polymer pattern.[47] b) The mechanism and the fluorescence image for BSA-FITC adsorbed onto micropattern formed by both hPEA-AN layer and thiol-containing graft PEA brushes. The scale bar is 75 μm.[49] c) Mechanism for the formation of micropatterns by UV light irradiation and fluorescence image of the micropatterned MC-3T3 E1 cells on the polymer-modified glass surface after treatment with the LIVE/DEAD viability/cytotoxicity Kit.[50] d) Left: The fluorescence images of hPEA-patterned hydrogels functionalized with FITC through a green channel (top) and red channel (bottom) after being partially immersed in PS, RB, and R6G aqueous solutions (the right half). The excitation wavelength is 488 nm, and the scale bars are all 100 μm. Right: The proposed mechanism of hPEA hydrogels functionalized with FITC for the recognition of these three red dyes through the fluorescence response.[52] a) Reproduced with permission.[47] Copyright 2009, American Chemical Society; b) Reproduced with permission.[49] Copyright 2011, American Chemical Society; c) Reproduced with permission.[50] Copyright 2009, Elsevier; d) Reproduced with permission.[52] Copyright 2013, Wiley.

protein, proteins could only adhere to the PS domains of the PS/PEO blend, while the adhesion of proteins to the PEO domains was negligible. Therefore, only the PS domains exhibited the green fluorescence of ConA. The fabrication of these protein micropatterns can be potentially used as a platform in homogeneous cell culture experiments, which might be used for the investigation of cell adhesion, growth, and differentiation.[47]

Synergistic interactions of protein adsorption and protein resistance are often used in the fabrication of protein micropatterns. Our group developed an ultrafast and universal approach to fabricate a thiol-containing graft PEA brush on the gold surface, which exhibited excellent protein-resistance. This type of PEA consisted of thiol groups in the backbone as anchors on the gold surface and hydrophilic PEG in the graft chains to reduce protein adsorption.[48] As shown in Figure 4b, a binary micropattern of anthracene-ended hPEA (hPEA-AN) gel array

was fabricated on the surface of gold by photolithography, and then, the domains without hPEA-AN gel were covered with thiol-containing graft PEA brushes via the complexing interactions between thiol groups and the gold surface. As the PEA brush was especially resistant to non-specific protein adsorption, while the proteins could be adsorbed by hPEA-AN gels, a protein array with clear boundaries could be fabricated through this method based on synergistic interactions for

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the potential use in bioassays and microsensors.[49]

The micropattern of protein based on selective adsorption can be extended into cell micropatterning. Generally, cell attachment to a substrate is dependent on the interaction between the surface of the substrate and a series of proteins, such as collagen, fibronectin, matrigel, laminin, and cell-interactive peptides, collectively referred to as extracellular matrix (ECM).[50] Ishihara and co-workers described a type of micropatterned polymer surface formed by the phase-separation of block copolymer composed of hydrophilic poly(2-methacryloxyethyl phosphorylcholine (MPC)) and hydrophobic poly(dimethylsiloxane) (PDMS) and then fabricated micropatterned cells through the selective adhesion of cells to the polymer surface. Due to the presence of the large amount of phospholipid groups, the MPC polymer exhibited a higher level of hydrophilicity and a strong resistance to the adsorption of both fibronectin and cells. On the contrary, fibronectin was selectively adhered to the hydrophobic PDMS phase regions. With the increasing size of the hydrophobic PDMS phase region of the polymer surface, adhesion of the cells was enhanced when media with serum was used.[51] These hydrophobic–hydrophilic interactions between polymer materials and proteins are beneficial for the fabrication of cell micropatterns. Kitamori and co-workers also described a novel strategy to fabricate cell micropatterns through photolithography, which was based on combining hydrophilic MPC polymers and a photo-cleavable linker in the patterns (Figure 4c). After photo-cleavage of the linkers between the hydrophilic MPC polymer and the substrates by UV irradiation through a mask, the relative hydrophilic MPC polymer surface of the UV-irradiated region turned into a moderately hydrophobic aromatic compound surface

as a result of removing the MPC polymer. This was helpful for the adhesion of the cells. The obtained cell micropatterns were stable and the viability of the adhered cells was maintained for a long time. After 5 weeks of culturing, micropatterned live MC-3T3 E1 cells were still observed under a fluorescence microscope (Figure 4c). This is an ideal example showing that the selective adsorption of protein by the polymer surface can be used to control the spatial growth of cells, providing some fundamental understanding into the interaction between cells and material surfaces.[50]

In addition to the protein micropatterns mentioned above, polymer patterns with selective adsorption abilities can also be used in molecular recognition. By combining the selective adsorption for guest dyes and the fluorescence response, we recently demonstrated that patterned hPEA hydrogels functionalized with fluorescein isothiocyanate (FITC) could be used for the recognition of three red dyes. Half of the patterned hPEA hydrogels functionalized with FITC were immersed into RB, PS, and Rhodamine 6G (R6G) solutions, respectively, and fluorescence images were then observed through two channels, under an excitation of 488 nm (Figure 4d). The part of the pattern immersed in RB or PS solution was nearly dark, while the remaining part of the pattern exhibited green fluorescence emission. However, the fluorescence emission of the patterns did not change after immersing into the R6G solution. These phenomena were ascribed to the efficient adsorption of PS (or RB) molecules rather than of R6G molecules by the hPEA hydrogels, resulting in the quenching of the green fluorescence emission from the patterned FITC-labeled hPEA hydrogels by the PS (or RB) molecules. Meanwhile, the part of the patterns immersed in RB solution exhibited red fluorescence emission, which may have been caused

by fluorescence resonance energy transfer (FRET) between the excited FITC and fluorescent RB. Due to these characteristics, hPEA hydrogel patterns can potentially be used as sensors for the molecular recognition of different red dyes.[52]

6. Conclusion and Outlook

Depending on the interaction between the amphiphilic polymer and guest molecules, such as a hydrophobic interaction, electrostatic interaction, π–π stacking interaction, metal-ion complexation interaction, or topology matches, a variety of amphiphilic polymer materials with selective adsorption to guest molecules have been developed and fabricated in different forms, such as micelles, micro-/macrogels, membranes, fibers, and coatings. These polymer materials possess selective adsorption abilities for different types of guest molecules, such as dyes, drugs, peptides, proteins, DNA, and other biomolecules, which are beneficial for their applications in the separation of different guest molecules, temporally controlled release of guest molecules, and patterning of guest molecules. Although significant progress in the materials for separation, drug delivery, and patterns has been made in recent years, many challenges still remain that require in-depth investigations. For example, a great amount of effort should be placed in molecular design to increase the efficiency and rate of guest molecule separation. Meanwhile, more polymer materials need to be designed to meet the increasing requirement for molecule separations, such as the separation of biomolecules and chiral molecules. Investigations into the interactions between polymers and guest molecules can provide some guidelines for the design of polymer materials with selective adsorption for the special guest molecules. We believe that amphiphilic polymer materials will lead to

benefits in various fields, including the separation of analogues, temporally controlled delivery of multiple drugs, and smart coatings of biosensors and biological mediums.

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