# Recent Progress in Stimuli-induced Morphology Transformations of Block Copolymer Assemblies

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## Abstract

Synthetic polymers are well known to self-assemble into a wide range of remarkable architectures with properties directly arising from their nanoscale morphologies. The rapid development of post-polymerisation modification reactions and techniques like polymerisation induced self-assembly (PISA) have fuelled new research into 'smart' polymer assemblies that can undergo well-defined morphological transformations in response to external stimuli. These transformations can be used to modulate the properties of polymer assemblies in a 'switchable' fashion, offering great potential to generate smart materials that can dynamically adapt to changes in complex environments. This review aims to highlight key developments from the past five years in this rapidly evolving field, and we discuss innovations in polymer design, stimuli-responsivity mechanisms, transformation behaviours, and potential applications of shape-transformable polymeric nanostructures.

## Introduction

The ability to undergo controlled structural transformations is an increasingly important feature of discrete polymer self-assemblies for producing a wide range of useful stimuli-responsive behaviours. The ability to respond to external signals by altering nanoscale morphologies (e.g., spherical micelles, cylindrical micelles, vesicles)[1-2] is an exciting design prospect for developing polymeric nanoparticles with various shape-dependent functionalities.[3-5] While there has been substantial progress in synthesising stimuli-responsive polymer self-assemblies, the precise mechanisms of how such assemblies transform between different discrete nanomorphologies is still being elucidated. Developing a deeper understanding of structural transformations offers the possibility of rationally designing novel materials that can respond to their environments in increasingly nuanced ways.

The most widely studied polymer self-assemblies are derived from block copolymer amphiphiles (BCAs),[6] which are polymers composed of two or more repeat unit types grouped into discrete segments that exhibit different solvent affinities. To self-assemble, at least one of the block segments must be poorly soluble when dispersed in a solvent, which drives the system to form nanomorphologies that minimise unfavourable solvent–polymer interactions. By controlling the relative volume fraction of each block, it is possible to rationalise, and even predict in some instances, the self-assembled morphology of a given BCA at equilibrium.[7] For example, the solution conformation of a simple di-block BCA can be approximated as a cylinder or conical wedge that assembles into the morphology that achieves the most efficient packing (Figure 1). From this basic principle, it follows that a sufficient

change in the relative block volume fractions of a BCA can engender a controlled transformation from one self-assembled morphology to another. Discher and co-workers reported a particularly striking early example of this phenomenon in their study of self-assembled poly(ethylene oxide)-poly(lactide) (PEO-PLA) BCAs, which transitioned from vesicles to worms to micelles via a 'jellyfish' intermediate as the core-forming PLA block was slowly hydrolysed over several days (Figure 1c).[8] Importantly, these morphology transitions were used to control the delivery of an encapsulated drug, thereby demonstrating the high potential for using structural transformations to switch between polymer nanomorphologies with different functions. Since this early report, substantial work has focused on developing BCA assemblies that can transform in response to a wide variety of external signals in controllable manners.

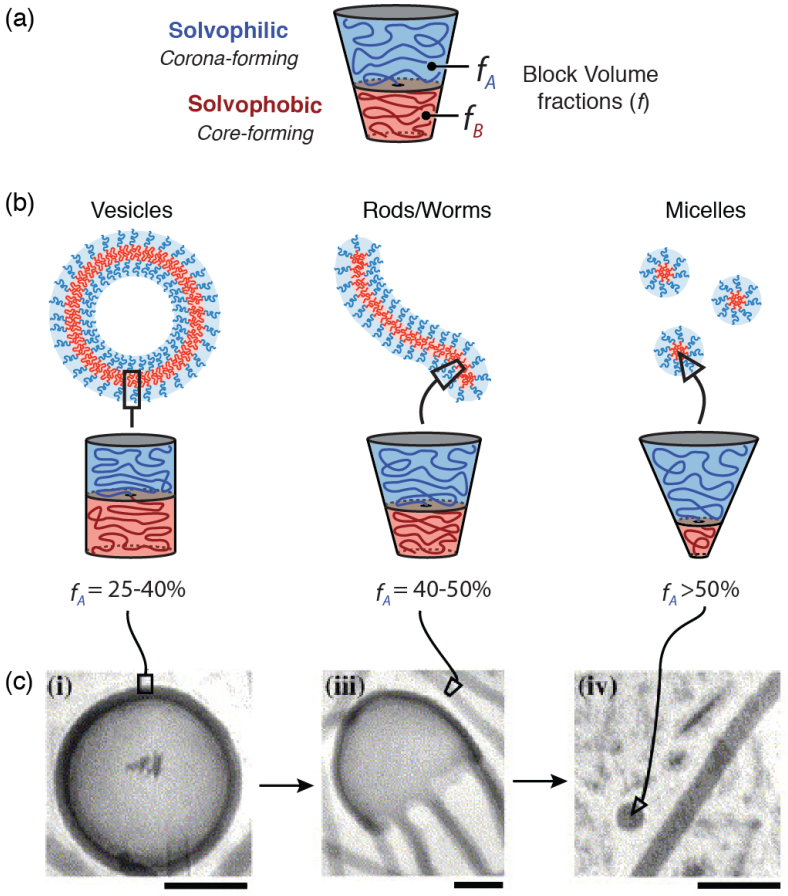


**Figure 1.** (a) General structure of a di-block BCA. (b) Self-assembly of di-block BCAs can be controlled by changing block volume fractions ($f$). (c) Micrographs showing nanostructural morphology transformations between PEO-PLA BCA assemblies, driven by hydrolysis of the core-forming PLA block. Scale bars are 100 nm. Micrographs adapted from Discher and co-workers.[8] Copyright 2006 Elsevier.

Stimuli-responsive BCAs are typically prepared by incorporating functional groups that exhibit property changes (e.g., amphiphilicity, charge, polarity, and sizes) in response to an external cue (e.g., temperature changes, light, pH changes, enzymes, and chemicals) into their building blocks. Temperature responsive systems usually exhibit phase-changing behaviours (i.e., transitioning from a hydrophilic state to a hydrophobic state above a critical

temperature);[9] pH responsive systems can have a significant charge and hydrophilicity difference upon environmental pH changes due to their ionisable functional groups (donating/accepting protons);[10] photo responsive systems show unique responses to light signals (e.g., isomerisation, decomposition);[11] and enzyme responsive systems can respond to specific molecules in biological samples that result in decomposition or crosslinking in the system.[12] Furthermore, groups that can respond to and interact with specific molecules (e.g., $CO_2$,[13] water,[14] and metal ions[15]) have also been reported to cause morphology transformations in BCAs. Therefore, when triggered by specific signals, the physical or chemical property changes of such functional groups are amplified by their connectivity along the polymer backbone, leading to a drastic change in the hydrophile-to-hydrophobe block volume fractions within the BCA, thereby driving an overall morphology transformation in solution.

While there have been several comprehensive reviews discussing stimuli-responsive polymers, including their structural design, mechanisms, and applications, [16-20] there is less work that explores recent developments of stimuli-induced nanomorphological transformations of BCA assemblies. As an exciting and growing research area, Grubbs *et al*.[1] and Zhang *et al.*[21] have published relevant review articles in 2013 and 2017 respectively, summarising the design, kinetics, transformation behaviours, and possible functions of such systems. Since Zhang *et al.* published their review, there has been a surge of interest in preparing BCA assemblies that undergo well-defined morphology transformations upon stimulation, especially with the rapid development of PISA.[22-24]Therefore, novel BCA assemblies that can undergo reversible and irreversible nanomorphology transformations have been prepared to study and disclose the mechanisms underlying such behaviours. Considering the substantial developments in this field over the past five years, this review aims to highlight key examples from the literature that showcase the conceptual progress that has been made in recent years. To narrow the scope of our discussion, we will focus on morphology transformations of BCA-derived assemblies. For transformations involving solvent exchange[25-26], supramolecular polymers,[27-29] and single-chain polymer nanostructures,[30-32] we direct interested readers to excellent reviews and articles on those topics. While many different signals have been reported to induce the nanomorphology transformation of BCAs, we have divided our discussion into two main sections according to the two major categories of physical stimuli (e.g., temperature changes and light) and chemical/biological signals (e.g., pH changes, PISA, and enzymes). We hope this review highlights the new and exciting developments in stimuli-induced morphology transformations of BCA assemblies, and frames perspectives for future research.

## Nanomorphology transformation triggered by physical signals

### Transformations induced by temperature changes

While many stimuli can be applied to polymer assemblies to drive nanomorphology changes, physical signals (e.g., temperature changes, light, sonication) have been among the most extensively studied.[33-34] The ease with which temperature can be controlled makes thermally-induced transformation systems especially attractive. Many polymers show lower critical solution temperature (LCST) properties whereby a coil-to-globule phase transition occurs at a specific temperature.[35-37] A well-known example is poly(*N*-isopropylacrylamide) (PNIPAM), which undergoes an LCST transition at 32 °C and has been widely incorporated as a thermo-responsive segment in

various block copolymer systems to drive morphology transformations.[38] Leveraging the well-established LCST behaviour of PNIPAM, Wang, Hua and co-workers recently developed a system whereby reversible morphology transformations between polymer assemblies was achieved by manipulating hydrogen bonding interactions through heating and cooling cycles.[39] The authors prepared a cellulose-grafted bottlebrush copolymer carrying hydrophobic adenine-derived pendant groups (Cell-*g*-PAAc-*b*-PDMA), which assembled into spherical nanoparticles (MA) upon solvent exchange (Figure 2). Upon addition of a di-block copolymer containing thymine-derived pendants connected to a PNIPAM domain (PNIPAM$_{90}$-*b*-PTAc$_{20}$), these two copolymers co-assembled into worm-like micelles through the formation of complementary hydrogen bonding interactions between the adenine pendants on MA and thymine pendants on PNIPAM$_{90}$-*b*-PTAc$_{20}$. Due to the LCST behaviour of PNIPAM, the worm-like micelles could be reversibly transformed into spherical micelles by raising the temperature from 20 and 60 °C. This transformation is attributed to the hydrophobic collapse of PNIPAM above its LCST, which causes the PNIPAM chains to migrate to the hydrophobic cores of the worm-like micelles and thereby break the hydrogen bonds between nucleobase pendants. The transformation could also be reversed to reform the worm-like micelles by stirring the solution at 20 °C for at least 2 h. This work demonstrates an elegant approach for using LCST transitions to modulate the strength of supramolecular nucleobase interactions independent of their natural melting temperatures and is a promising basis for achieving predictable reversible morphology transformations with tuneable transition temperatures.

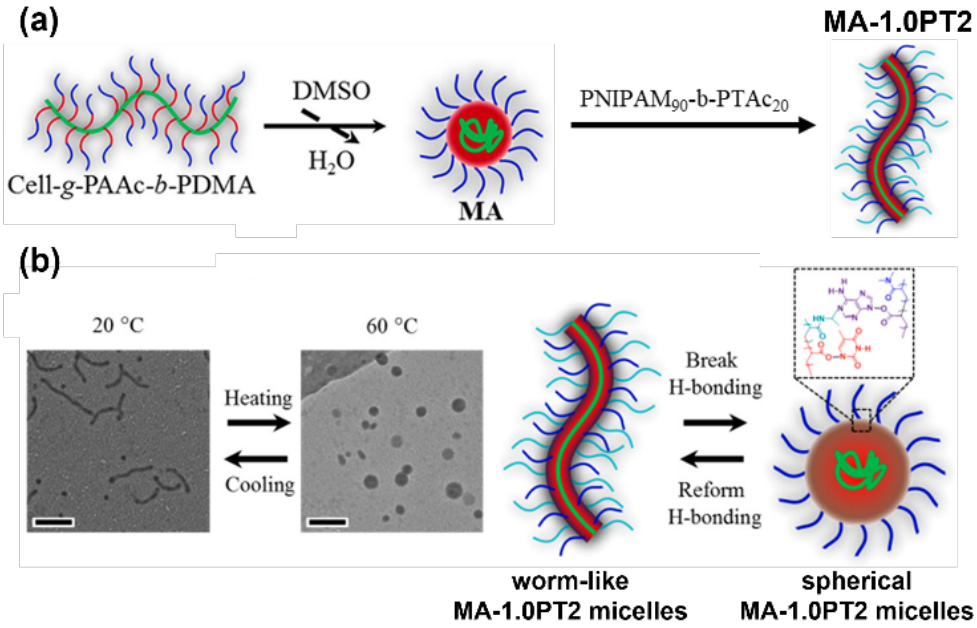


**Figure 2.** (a) Preparation of adenine-containing MA nanoparticles via a solvent exchange method and MA-1.0PT2 worm-like micelles by mixing MA with thymine-containing PNIPAM$_{90}$-*b*-PTAc$_{20}$; (b) The reversible morphological transition between worm-like micelles and spherical micelles (MA-1.0PT2) between 20 °C and 60 °C and the mechanism of the reversible shape change (scale bars = 200 nm). The shape transformation is attributed to loss of hydrogen bonding between the nucleobases following hydrophobic collapse of the PNIPAM chains at high temperature, which could be reversed upon cooling. Reprinted with permission from Yan *et al*.[39] Copyright 2020 American Chemical Society.

**Transformations induced by light**

A wide range of photo-responsive functional groups have been successfully used to prepare photo-responsive polymer assemblies.[40-43] Compared with other stimuli-responsive systems (e.g., temperature changes, pH, and chemical/bio-molecular action), light irradiation has several adjustable parameters, including wavelength, intensity, and irradiation time. Consequently, systems based on photo-responsive groups that undergo reversible dimerisation (e.g., anthracene and coumarin), photochromic units that undergo reversible isomerisation (e.g., azobenzene and stilbene groups), and photo-induced cleavages (e.g., o-nitrobenzyl esters and ethers) upon light irradiation have been extensively studied and developed for various applications.[11, 44-46] In 2019, Chen *et al*. developed a photo-responsive system based on azobenzene *cis-trans* isomerisation, with self-assembled states that could be reversibly switched between expanded and slim forms by applying alternating UV/visible light signals.[47] The authors prepared self-assembled worm-like fibres through PISA of poly(methylacrylic acid)-*b*-poly(4-((4-butylphenyl)diazenyl)-phenyl methacrylate) (PMAA-*b*-PMA(0C)Az) by reversible addition−fragmentation chain-transfer (RAFT) polymerisation in ethanol. The PMA(0C)Az segments were localised within fibre cores due to the hydrophobicity and π-π stacking interactions of the azobenzene units. Upon exposure to UV and visible light signals, the core-forming segments underwent *cis-trans* isomerisation, resulting in changes to the dimensions of the PMA(0C)Az blocks that manifested in controllable expansion and slimming of the worm-like fibres (Figure 3).

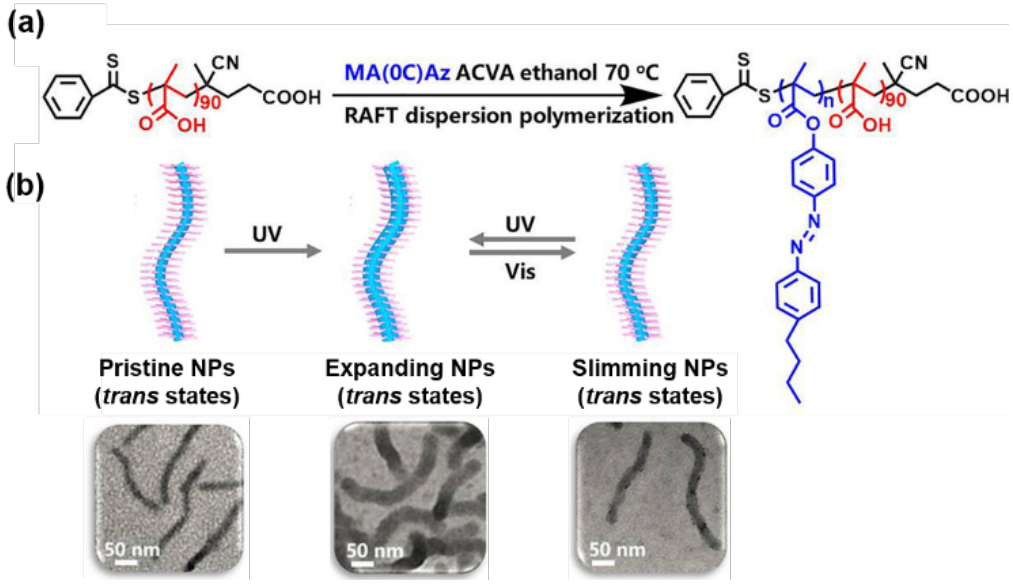


**Figure 3.** (a) Synthesis of azobenzene-containing wormlike NPs was achieved via RAFT PISA in ethanol at 70 °C; (b) Light-triggered reversible slimming of a wormlike NP. Reprinted with permission from Chen *et al*.[47] Copyright 2019 American Chemical Society.

While BCA assemblies have been studied as promising candidates for drug delivery, biosensing, and catalysis applications, an increasingly important challenge for their practical application is precisely controlling their dimensions to obtain uniform sizes. By adding surfactants with nitrobenzyl esters and coumarin esters to polystyrene-*b*-poly(2-vinylpyridine) (PS-*b*-P2VP), Lee *et al*. successfully prepared BCA particles that could undergo controllable shape and colour transformations upon photoirradiation.[48] When such surfactants are irradiated by the

light of specific wavelengths, the originally hydrophobic 5-hexyloxy-2-nitrobenzyl-16-*N,N,N*-trimethylhexadecan-1-ammonium bromide (*N*-CTAB) photo-responsive groups are cleaved off, leaving carboxylate groups on the surfactants. As the surfactant molecules interact closely with the BCA particles, the light-cleavage process not only adjust the amphiphilicity of the surfactant itself but also the interfacial activity with the PS-*b*-P2VP particles (i.e., *N*-CTAB surfactants favour PS while COOH surfactants favour P2VP segments). Therefore, these light-induced changes in surfactant structure led to distinct morphological transitions of the particles from spheres with a concentric onion-like inner structure to ellipsoids with axially stacked disc-like layers (Figure 4). The authors further mixed the BCA particles with two light-responsive surfactants with different activation wavelengths (254 and 420 nm). The results showed that continuous wavelength-dependent shape-switching could be achieved in this system, which demonstrated the method to be a robust strategy for preparing BCA nanoparticles with shape-transformable properties.

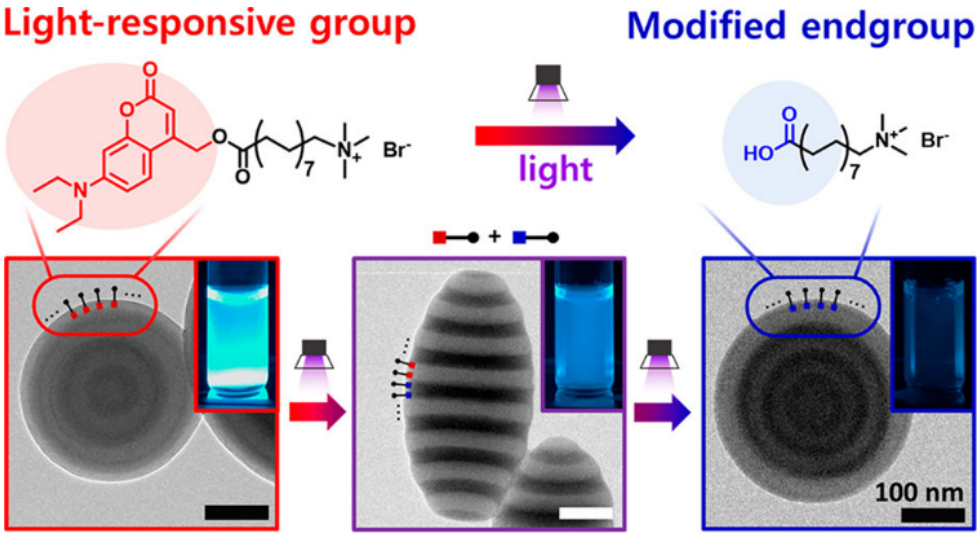


**Figure 4.** Illustration of the photo-induced shape transformation of PS-*b*-P2VP particles enabled by photoactive *N*-CTAB Surfactants. Reprinted with permission from Lee *et al*.[48] Copyright 2019 American Chemical Society.

### Nanomorphology transformation triggered by chemical and biological signals

#### Transformations induced by pH changes

In general, polymers with pH-responsive functional groups mainly include systems that can go through reversible ionisation at different pH environments (e.g., amines, carboxylates) and systems with acid/base labile linkages that undergo pH-dependent cleavage (e.g., hydrazones, imines, acetals).[49] Such systems are mainly based on manipulating the swelling/deswelling behaviours of polymers or the overall amphiphilic properties at different pH values. For example, Kim and co-workers successfully prepared a shape-switchable polymer nanoparticle system that could transform between lens and football morphologies with subtle temperature and pH changes near physiological conditions.[50] The nanoparticles were produced from solvent-evaporative emulsion droplets containing a mixture of polystyrene-*b*-poly(4-vinylpyridine) ($PS_{27k}$-*b*-$P4VP_{7k}$) and a random copolymer of N-(2-(diethylamino)ethyl)acrylamide (DEAEAM) and NIPAM. To investigate the shape transformation behaviours, the

authors characterised the nanoparticles at temperatures of 20, 35, and 50 °C and pH values of 6.0, 6.5, and 7.0 (Figure 5). By increasing the solution pH values and increasing the system temperature, the solubility of poly(DEAEAM-*r*-NIPAM) component is decreased, leading to a morphology transformation from lens-shaped to football-shaped nanoparticles. The system was labelled with fluorescent dyes rhodamine B and coumarin at the PS and P4VP blocks, respectively, which showed colourimetric response from purple to blue during the lens-to-football transformation, highlighting the potential use of this system as an optical sensor for detecting the local temperature and pH changes.

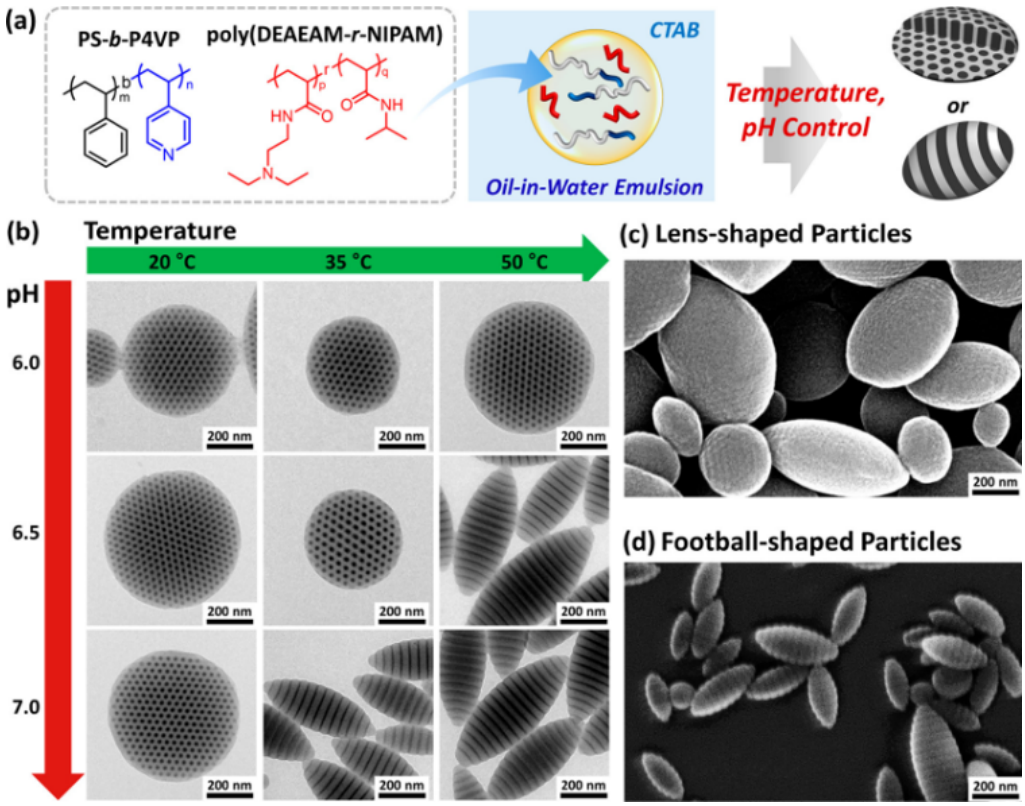


**Figure 5.** (a) Chemical structure of polymers used in experiments and schematic illustration showing the method to produce shape-transforming $PS_{27k}$-*b*-$P4VP_{7k}$ particles using temperature and pH dual-responsive poly(DEAEAM-*r*-NIPAM) surfactants; (b) TEM images of PS-*b*-P4VP particles formed in different buffer solutions (pH 6.0, 6.5, and 7.0) under different temperature conditions (20, 35, and 50 °C). The P4VP domains are stained with iodine vapour; SEM images of representatives of (c) lens-shaped particles and (d) football-shaped particles. Reprinted with permission from Lee *et al*.[50] Copyright 2019 American Chemical Society.

While many studies have focused on observing the self-assembly behaviours of BCAs, it remains unclear whether the distribution of hydrophilic and hydrophobic groups within block copolymer chains would affect the size and morphology of their self-assemblies as well as their dynamic responses to changes in their environment. To answer this question, Zhang and co-workers developed a series of pH responsive copolymers to study the importance of controlling the distribution of functional groups within a polymer chain.[51] Specifically, the authors synthesised a series of linear copolymers containing 50 mol% acrylic acid (AA) and 50 mol% butyl acrylate (BA) but with different composition profiles, including symmetric di-block copolymers (B), linear gradient copolymers (G), asymmetric di-block copolymers (D), and asymmetric tri-block copolymers (T) (Figure 6). Their experiments showed that

copolymers with different spatial distribution profiles, despite identical compositions, assembled into diverse nanomorphologies and exhibited very different self-assembly behaviours in response to pH changes. Compared with the di-block copolymer poly(AA-*b*-BA) which formed kinetically-trapped assemblies, asymmetric and gradient-like AA-BA copolymers showed dynamic nanomorphological responses to pH changes, forming spherical micelles, worm-like micelles, vesicles, and also reversible changes in size. By further controlling the block length of AA-BA asymmetric di-block copolymers, D10 were prepared and observed to self-assemble into spherical, worm-like, and vesicular morphologies under different pH conditions. Therefore, the authors demonstrated that not only the individual properties of respective monomers but also their spatial distributions determined the final properties of polymer assemblies. These systematic results provide more comprehensive insights into the compositional factors that govern nanomorphological transformation behaviours of BCA assemblies.

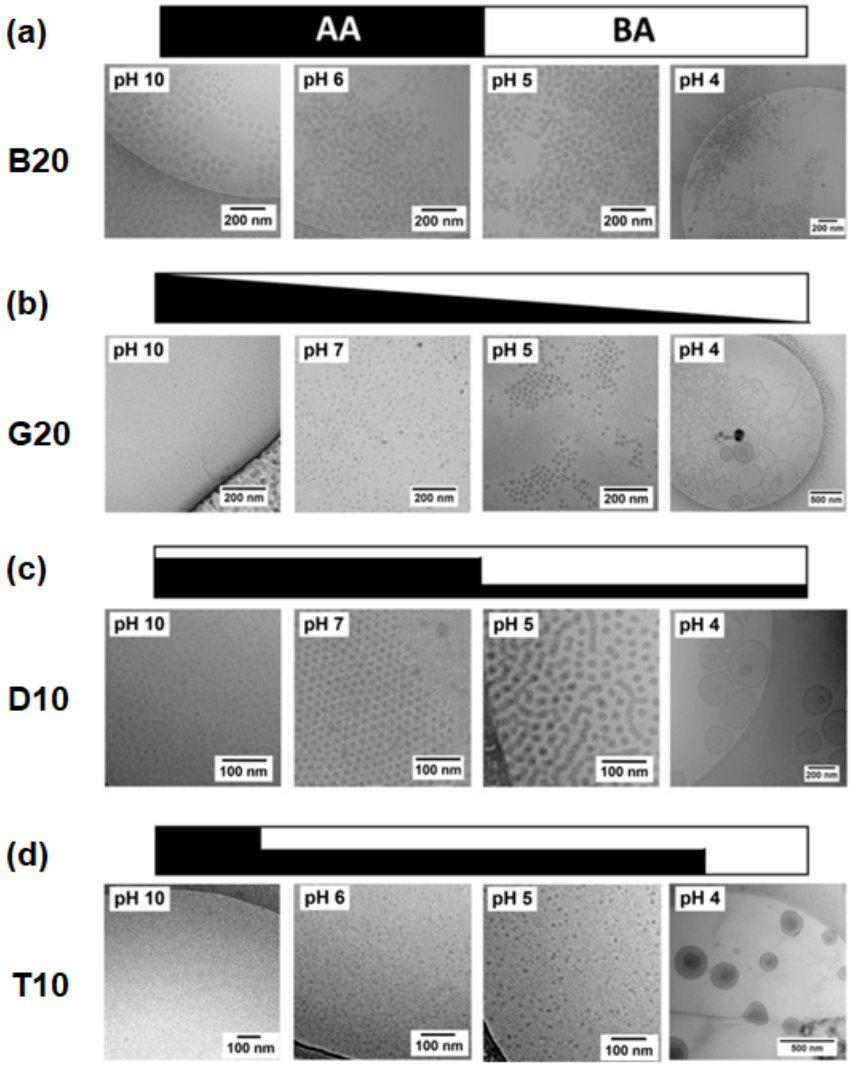


**Figure 6.** Targeted composition profiles and their representative cryogenic transmission electron microscopy (Cryo-TEM) images of (a) di-block copolymers B20; (b) linear gradient copolymers G20; (c) asymmetric di-block copolymer D10; (d) tri-block copolymer T10 self-assemblies directly dispersed in different pH buffers. Reprinted with permission from Schubert *et al.*[51] Copyright 2020 John Wiley and Sons.

**Transformations induced by PISA**

PISA is an emerging area that enables the direct preparation of self-assembled polymer nanostructures during polymerisation and provides insights into the morphology evolution of polymer assemblies.[52-58] In a typical PISA experiment, a soluble 'living' polymer precursor undergoes chain-extension using a monomer that will polymerise into a second block that is insoluble in the chosen solvent. Therefore, due to the progressive increase in the block volume fractions of solvophobic segments, the growing polymer self-assembles into a diverse range of nanostructured morphologies, including spheres, cylinders, vesicles, and bilayers depending on the length of the second insoluble block. For example, Yuan and co-workers described the use of PISA to achieve post-assembly structural transformations between a range of different polymer nanomorphologies (Figure 7).[59] The authors used RAFT polymerisation to prepare di-block copolymers of 2-dimethylaminoethyl methacrylate (DMAEMA) and benzyl methacrylate (BzMA), which formed vesicles or micelles depending on the degree of polymerisation (DP) of each block. Subsequent chain extension using 2-perfluoroctylethyl methacrylate (FMA) resulted in transformations of the 'seed' into a range of complex and unprecedented 'daughter' assemblies as the DP of the FMA block increased. The formation of such diverse polymer nanomorphologies through seeded post-assembly polymerisation highlights the state of play in recent research on PISA that will inform future development in polymerisation-induced structural transformations of polymer self-assemblies.

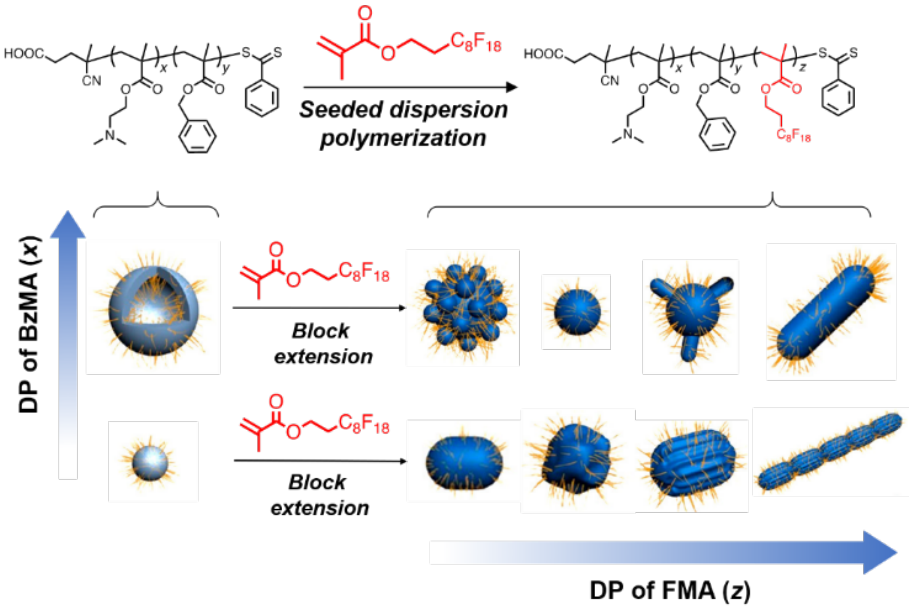


**Figure 7.** Chain extension of di-block copolymer of 2-dimethylaminoethyl methacrylate and BzMA using FMA produced tri-block copolymer. When performed as post-assembly chain extension reactions, PISA could be used to achieve morphology evolution.[59] Figure reproduced from Zeng *et al.*,[60] with permission from John Wiley and Sons.

Although PISA is a powerful technique to prepare polymer assemblies with diverse morphologies, chemists have noticed that the process of PISA is mediated by long, stabilising chains, which often leads to kinetically trapped spheres that cannot undergo morphology transformations.[61] To overcome this issue, Yuan and co-workers reported a convenient and general strategy that facilitates morphological transformations by incorporating

solvophilic monomers into the copolymers.[62] The authors first synthesised a di-block copolymer poly(*N,N*-dimethylaminoethyl methacrylate)-*b*-poly(benzyl methacrylate) (PDMA-*b*-PBzMA), which remained in kinetically trapped spheres during polymerisation. With the introduction of only 7 mol% solvophilic 3-(triethoxysilyl)propyl methacrylate (TESPMA) as the comonomer, they prepared PDMA-*b*-P(BzMA-co-TESPMA) copolymers through RAFT dispersion polymerisation, which showed striking morphology transformations. Worms, "octopi", "jellyfish", vesicles, and large compound vesicles (LCV) were obtained as the DP of the core-forming block was increased (Figure 8). Moreover, this non-specific effect is further confirmed by the copolymerisation of BzMA with other solvophilic monomers, including *N,N*-dimethylaminoethyl methacrylate (DMA), *N,N*-diethylaminoethyl methacrylate (DEA), and 2-hydroxypropyl methacrylate (HPMA), which were also shown to overcome kinetic trapping. The reported methodology highlights a promising approach for the ongoing development of PISA and the ability to precisely control the morphologies of polymer assemblies via this method for practical applications.

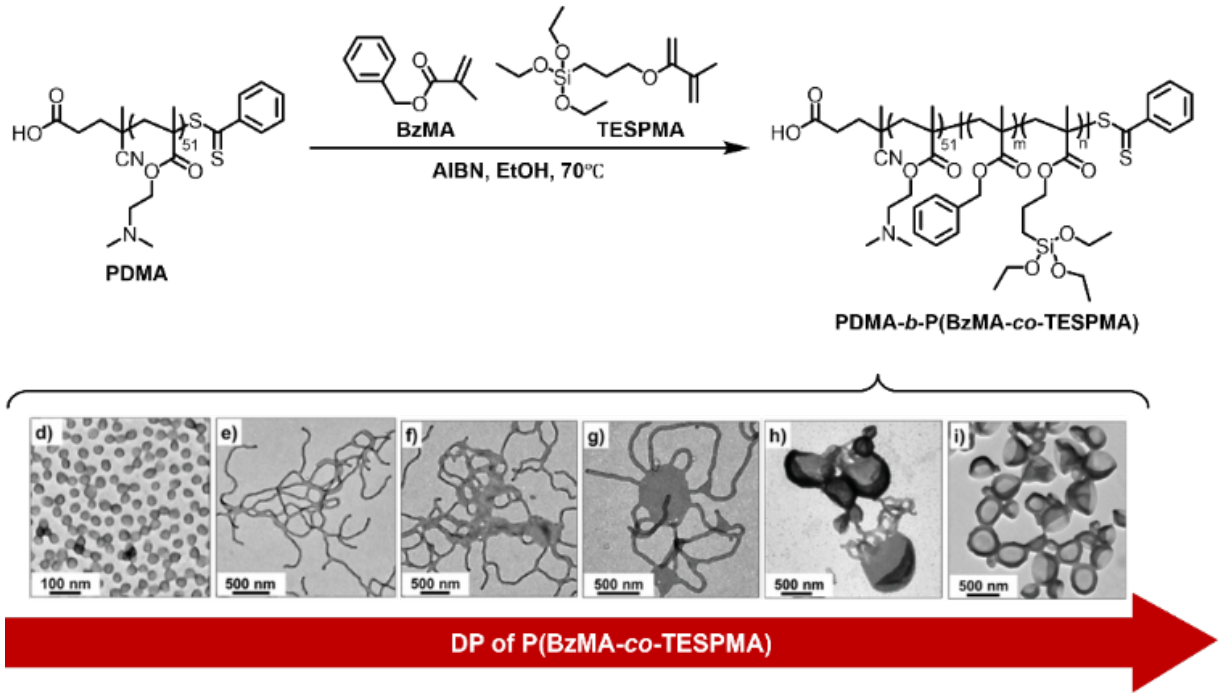


**Figure 8.** Reaction scheme for the RAFT dispersion copolymerisation of BzMA and TESPMA in ethanol at 70 °C and representative TEM images for the dispersions of assemblies extracted after d–i) 3, 5, 6, 7, 8, and 15 h of polymerisation. Reprinted with permission from Li *et al*. [62] Copyright 2019 John Wiley and Sons.

### Transformations induced by enzymes

Amongst the various examples of stimuli-responsive polymers, systems that respond to enzymes are particularly attractive for biomedical applications due to their high turnover numbers, excellent substrate specificity, and biocompatibility. Consequently, the past several years have seen tremendous progress in designing enzyme-responsive polymer assemblies.[63-64] When triggered with specific enzymes, such materials can undergo self-assembly, disassembly or morphological transformations, thereby changing the overall properties of the self-assembly polymer ensemble. For instance, Qiao, Wang, and co-workers reported the development of transformable

polymer-peptide biomaterials composed of a chitosan backbone, antimicrobial peptides, and poly(ethylene glycol)-tethered enzyme-cleavable peptides.[65] At first, the polymer-peptide conjugates self-assembled into nanoparticles with pegylated coronas. Cleavage of the peptide by gelatinase secreted from bacteria engendered a transformation of the assembled nanoparticles into fibrous structures (Figure 9). As a result, the previously hidden antimicrobial peptide presented itself on the surface of nanofibres leading to bacterial cell death. Such transformable polymer-peptide conjugates offer a novel strategy for developing long-term and high-performance antimicrobial agents.

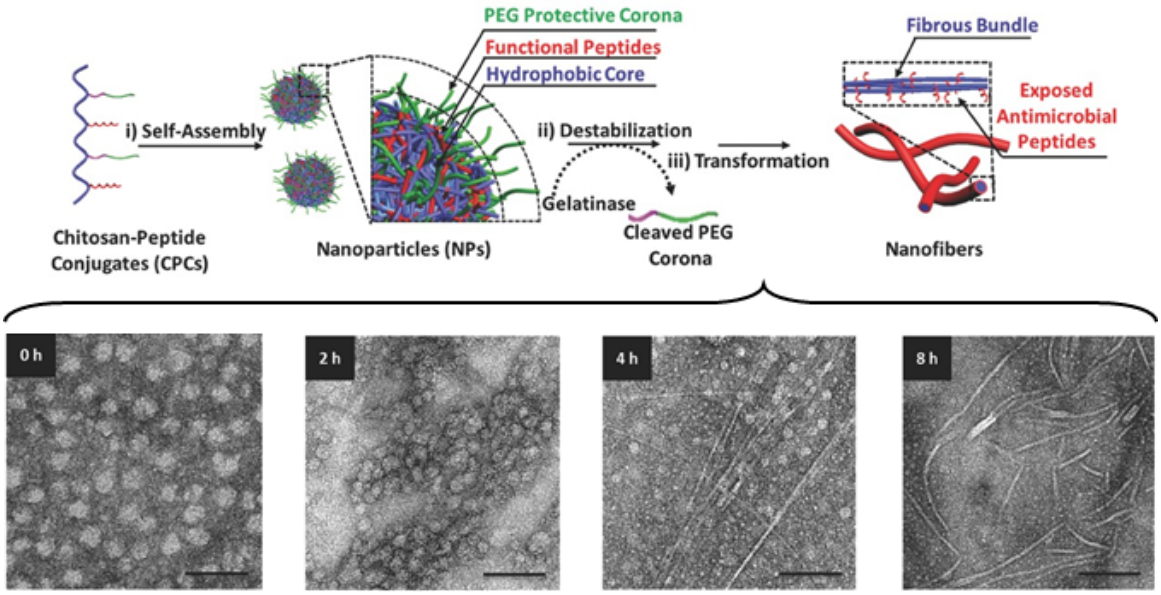


**Figure 9.** Illustration of the self-assembly of CPCs and the principle of enzyme-induced morphology transformation. i) The CPCs self-assembled into nanoparticles with PEGylated corona; ii) the protecting corona was peeled off through cutting off the cleavable peptide in the presence of gelatinase; iii) Destabilisation of the hydrophobic/hydrophilic balance spontaneously promoted the reorganisation of the self-assemblies into fibrous nanostructures via chain–chain hydrogen bonding interactions of chitosan. And representative TEM images of CPC-1 nanoparticles after immersed in gelatinase (10 μg $mL^{-1}$) tris buffer solution (pH 7.4) with various times (Scale bars = 100 nm). Reprinted with permission from Qi *et al*.[65] Copyright 2017 John Wiley and Sons.

While many stimuli-responsive polymer self-assemblies are designed and rationalised by thermodynamic considerations such as the surfactant packing model described above, polymer-derived nanomorphologies are often trapped in nonequilibrium states and may not reach equilibrium within experimentally convenient timescales. To study the molecular rearrangement of stimuli-responsive block copolymer self-assemblies underlying equilibrium and nonequilibrium states, Gianneschi and co-workers designed three enzyme-responsive peptide−polymer amphiphile (PPA) block copolymers, each comprised of a hydrophilic thermolysin-cleavable peptide brush connected to different hydrophobic core-forming blocks comprised of poly(ethyl acrylate), polystyrene, or poly(lauryl acrylate).[66] The authors hypothesised that the use of different core-forming blocks would result in different phase transitions following cleavage of the peptide 'bristles' from the hydrophilic brush domain. All three PPA types were initially assembled into uniform spherical micelles (20-30 nm hydrodynamic radius, $D_h$) via a solvent switch dialysis protocol using DMF and water. The micelles were then incubated with thermolysin at 37 °C to remove the peptide segments, and subsequent nanomorphological transformations were studied using dynamic light scattering (DLS) and cryo-TEM. The authors found that the behaviour of the assemblies depended strongly on the nature of the

core-forming blocks. Assemblies containing poly(ethyl acrylate) remained as dynamic spherical micelles; assemblies containing polystyrene formed aggregates that precipitated from solution; and assemblies containing poly(lauryl acrylate) transformed into kinetically frozen vesicular structures ($D_h$ = 200-300 nm).

The authors also performed their solvent switch assembly protocol directly on the enzyme-treated PPAs to show that the 'ideal' equilibrium nanomorphology was spherical micelles in all three cases. These results were rationalised in terms of the glass transition temperatures (*T*g), which relates to chain mobility, and hydrophobicity of the core-forming blocks. The PPAs in the poly(ethyl acrylate)-containing assemblies have low *T*g and relatively low hydrophobicity, which allows them to rearrange following peptide cleavage to preserve the thermodynamically-preferred spherical micelle nanomorphology. By contrast, the PPAs in the polystyrene-containing assemblies have high *T*g and high hydrophobicity, which inhibits their ability to rearrange following peptide cleavage. Consequently, the PPAs rapidly aggregate and precipitate from solution, presumably during incipient rearrangement. The poly(lauryl acrylate)-containing assemblies (low *T*g and high hydrophobicity) represent an interesting borderline case whereby the PPAs are dynamic enough to locally rearrange upon peptide cleavage, but too hydrophobic to exchange between nanostructures. Therefore, the assemblies locally reorganise to form kinetically trapped vesicles that cannot transform into their preferred equilibrium geometry. Remarkably, the authors showed they could construct molecular simulation models that accurately predicted the rearrangement behaviours of the different PPAs (Figure 10). This theoretical capability has especially important implications for the rational design of shape-transformable polymer assemblies that exploit nonequilibrium structural motifs to target specific nanomorphological outcomes.

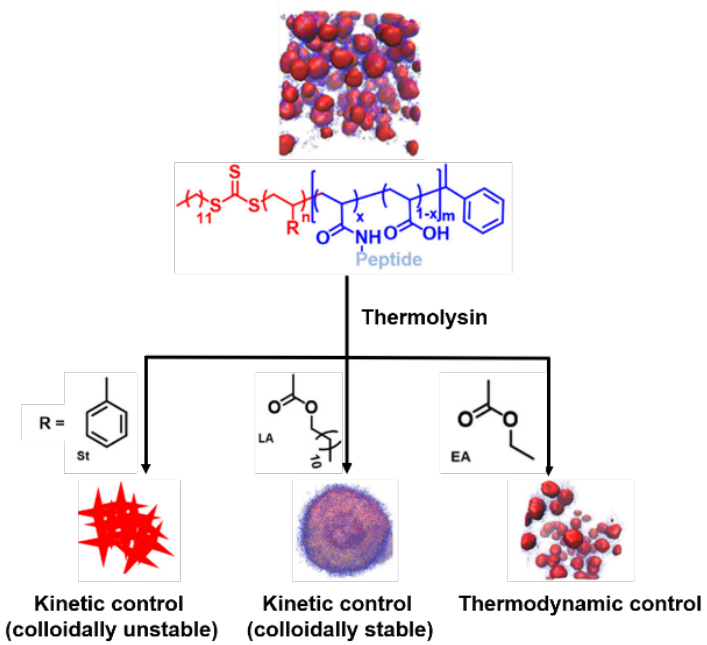


**Figure 20.** Chemical structures of PPAs and their morphological transitions induced by thermolysin-mediated peptide cleavage. Images depict *in silico* simulated nanostructures (except for the styrene-containing system, which is an illustration), with blue and red domains representing hydrophilic and hydrophobic domains, respectively. Reprinted with permission from Wright *et al.* [66] Copyright 2019 American Chemical Society.

## Conclusion and future perspectives

There is growing interest in the development and study of self-assembled polymer nanostructures that can undergo controlled morphological transformations, and thereby modulate their physicochemical properties, in response to changes in their surroundings. Such systems have allowed scientists to explore new materials whose shape transformations can be mapped onto useful functions for various applications.[67-69] The examples highlighted in this review demonstrate the remarkable recent progress that has been made in controlling the morphologies of BCAs, as well as understanding how such assemblies transform between different nanomorphologies upon external stimulation. By designing stimuli-responsive polymer assemblies with controlled morphology transformation behaviours, researchers in the field are developing increasingly deeper understandings of how self-assembled BCA nanostructures can transform between different states, and how this can be controlled through specific stimuli relevant for increasingly sophisticated applications in materials science.

Stimuli-triggered morphology transformations have high potential as the basis of new 'smart' macromolecular materials, and there is wide scope for future work in this area. Although many stimuli-responsive BCA systems have shown great potential to achieve specific nanomorphologies in controllable manners, most reported studies are generally responsive to only a single stimulus type, which lacks versatility and significantly limits their applications, as highlighted by Zhang *et al*.[21] With the ever-growing demands of 'smart' materials that can adapt to complex environments, especially for *in vivo* biomedical applications, it is essential to develop multi-stimuli multi-responsive (MSMR) materials that can adapt to dynamic environments through multiple shape-shifting transitions.[70-73] Achieving useful MSMR transformations under physiological conditions requires the construction of BCAs bearing multiple stimuli-responsive elements that can be addressed orthogonally to engender rapid and drastic changes to the properties of BCA assemblies. However, achieving multi-stage morphology transitions under physiological conditions has so far proved highly challenging due to issues of poor stimuli-specificity, limited access to diverse morphologies and slow transformation kinetics.[74] Researchers in pursuit of new MSMR-capable BCA assemblies may draw upon new stimuli-responsive materials that can drive changes in the block volume fractions of BCA building blocks. For example, stimuli-responsive motifs such as self-immolative linkers[60, 75-78] and polymers[79-83] have not yet been used to drive nanomorphological transformations of BCA assemblies, but could provide exciting new approaches for constructing MSMR assemblies. We look forward to seeing the advances that establish new techniques and theoretical models that deepen our understanding of how nanomorphological transformations occur at a molecular level. Moreover, we hope to see the maturation of BCA assemblies that can go through MSMR nanomorphological transformations when exposed to different stimuli. The development of such technologies will advance our understanding of fundamental polymer nanoscience and provide a powerful platform for engineering new solutions to challenges in the development of 'smart' nanotechnologies and nanomedicines.

## Conflicts of interest

There are no conflicts to declare.

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**Data availability statement**

Data sharing is not applicable as no new data were generated or analysed during this study.

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## Figure captions

**Figure 3.** (a) General structure of a di-block BCA. (b) Self-assembly of di-block BCAs can be controlled by changing block volume fractions (*f*). (c) Micrographs showing nanostructural morphology transformations between PEO-PLA BCA assemblies, driven by hydrolysis of the core-forming PLA block. Scale bars are 100 nm. Micrographs adapted from Discher and co-workers.[8] Copyright 2006 Elsevier.

**Figure 2.** (a) Preparation of adenine-containing MA nanoparticles via a solvent exchange method and MA-1.0PT2 worm-like micelles by mixing MA with thymine-containing $PNIPAM_{90}$-*b*-$PTAc_{20}$; (b) The reversible morphological transition between worm-like micelles and spherical micelles (MA-1.0PT2) between 20 °C and 60 °C and the mechanism of the reversible shape change (scale bars = 200 nm). The shape transformation is attributed to loss of hydrogen bonding between the nucleobases following hydrophobic collapse of the PNIPAM chains at high temperature, which could be reversed upon cooling. Reprinted with permission from Yan *et al*.[39] Copyright 2020 American Chemical Society.

**Figure 3.** (a) Synthesis of azobenzene-containing wormlike NPs was achieved via RAFT PISA in ethanol at 70 °C; (b) Light-triggered reversible slimming of a wormlike NP. Reprinted with permission from Chen *et al*.[47] Copyright 2019 American Chemical Society.

**Figure 4.** Illustration of the photo-induced shape transformation of PS-*b*-P2VP particles enabled by photoactive *N*-CTAB Surfactants. Reprinted with permission from Lee *et al*.[48] Copyright 2019 American Chemical Society.

**Figure 5.** (a) Chemical structure of polymers used in experiments and schematic illustration to produce shape-transforming $PS_{27k}$-*b*-$P4VP_{7k}$ particles using temperature and pH dual-responsive poly(DEAEAM-*r*-NIPAM) surfactants; (b) TEM images of PS-*b*-P4VP particles formed in different buffer solutions (pH 6.0, 6.5, and 7.0) under different temperature conditions (20, 35, and 50 °C). The P4VP domains are stained with iodine vapour; SEM images of representatives of (c) lens-shaped particles and (d) football-shaped particles. Reprinted with permission from Lee *et al*.[50] Copyright 2019 American Chemical Society.

**Figure 6.** Targeted composition profiles and their representative cryogenic transmission electron microscopy (Cryo-TEM) images of (a) di-block copolymers B20; (b) linear gradient copolymers G20; (c) asymmetric di-block copolymer D10; (d) tri-block copolymer T10 self-assemblies directly dispersed in different pH buffers. Reprinted with permission from Schubert *et al*.[51] Copyright 2020 John Wiley and Sons.

**Figure 7.** Chain extension of di-block copolymer of 2-dimethylaminoethyl methacrylate and benzylmethacrylate using FMA produced tri-block copolymer. When performed as post-assembly chain extension reactions, PISA could be used to achieve morphology evolution.[59] Figure reproduced from Zeng *et al*.,[60] with permission from John Wiley and Sons.

**Figure 8.** Reaction scheme for the RAFT dispersion copolymerisation of BzMA and TESPMA in ethanol at 70 °C and representative TEM images for the dispersions of assemblies extracted after d–i) 3, 5, 6, 7, 8, and 15 h of polymerisation. Reprinted with permission from Li *et al*. [62] Copyright 2019 John Wiley and Sons.

**Figure 9.** Illustration of the self-assembly of CPCs and the principle of enzyme-induced morphology transformation. i) The CPCs self-assembled into nanoparticles with PEGylated corona; ii) the protecting corona was peeled off through cutting off the cleavable peptide in the presence of gelatinase; iii) Destabilisation of the hydrophobic/hydrophilic balance spontaneously promoted the reorganisation of the self-assemblies into fibrous nanostructures via chain–chain hydrogen bonding interactions of chitosan. And representative TEM images of CPC-1 nanoparticles after immersed in gelatinase (10 μg $mL^{-1}$) tris buffer solution (pH 7.4) with various times (Scale bars = 100 nm). Reprinted with permission from Qi *et al*.[65] Copyright 2017 John Wiley and Sons.