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Tailored Assemblies of Block Copolymers in Solution: It Is All about the Process

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ABSTRACT: Block copolymers have the capacity to self-organize into a myriad of aggregate structures when placed in selective solvents, offering great promise for the construction of delivery vehicles and complex nanoscale assemblies. A key feature of these materials is their propensity to become kinetically trapped in nonequilibrium states, meaning that the structures they adopt depend sensitively on the processing route taken. While this makes it challenging to fully explore the landscape of possible morphologies, it also means that careful attention to the pathway of self-assembly can allow for remarkable control over the resulting nonequilibrium structures. In this Perspective, we highlight several recent advances in processing approaches that provide new levels of tailorability to the structures and encapsulated contents of block copolymer assemblies in solution.

Introduction

Block copolymers dispersed in a selective solvent will self-assemble in much the same fashion as surfactants and lipids. The canonical equilibrium structures for any of these amphiphiles, as dictated by the interfacial balance between solvated and solvophobic components, are spherical micelles, cylindrical or wormlike micelles, and bilayer vesicles.[1] The larger the relative area occupied by the solvophilic material, the greater the curvature of the lowest energy structure.

The central difference between the physical behavior of block copolymers and their low molecular weight amphiphilic cousins can be captured in a word: ergodicity.[2] Common surfactants with 10−16-carbon aliphatic tails have critical aggregation concentrations (CACs) in the micromolar to millimolar range.[3] Only when the concentration exceeds the CAC are aggregates formed, and even then the assemblies are highly dynamic, with rapid exchange of molecules between micelles and the unimer state in solution. The addition of a second hydrocarbon tail, as in phospholipids, yields vanishingly small solubilities and therefore little exchange of amphiphiles between aggregates and solution. Nonetheless, lipid bilayers are usually quite fluid, allowing vesicles to adopt their minimum-energy shape, subject to a fixed area and internal volume.[4]

Amphiphilic block copolymers typically possess tens or hundreds of solvophobic repeat units in each chain, resulting in an energy penalty to transfer a single polymer from an aggregate to solution that is many times larger than thermal energy (a notable exception being the poloxamer triblock copolymers[5]). This was elegantly demonstrated by the experiments of Bates and co-workers that revealed micelles of poly(butadiene-*block*-ethylene oxide) (PB−PEO) copolymers in water do not exchange chains on a time scale of months.[2,6] By studying an all-hydrocarbon system chosen to yield weak solvophobic interactions, Lodge, Bates, and co-workers showed that exchange kinetics decline precipitously with molecular weight due to the exponential dependence of the activation barrier on chain length.[7] In the absence of exchange, local adjustments to the structures of these aggregates may still be possible due to the fluidity of their cores, for example fusion or fission of micelles. However, even these processes are completely prevented when the nonsolvated block is glassy or semicrystalline in nature, leading to truly kinetically trapped structures.

This kinetic stability of block copolymer assemblies, relative to surfactants and lipids, is an oft-cited reason for their appeal in delivery applications[8−10] and is also the key to their utility as building blocks for constructing new and interesting nanostructures. Nonergodicity implies that the same polymer can potentially take on numerous different structures that are kinetically (meta)stable; thus, the morphology it adopts is highly path dependent. In some ways this is a curse, since it means that block copolymer assemblies inhabit a many-dimensional parameter space of processing variables that may be impossible to fully explore. However, systematic approaches to survey this space can transform the curse into a blessing, since the propensity to form kinetically trapped structures provides opportunities for obtaining a wide diversity of structures from only a limited set of building blocks.

Seminal work by Eisenberg's group over the past two decades has established a dominant paradigm for processing block copolymer assemblies in which a common solvent is gradually decreased in quality for one block by addition of a selective solvent, driving the copolymer to aggregate.[11−13] While these assemblies may temporarily be in equilibrium at the onset of aggregation, further addition of nonsolvent pushes the CAC toward zero and even drives the solvophobic block to solidify, locking the copolymer into one of a wide range of possible morphologies. Numerous other groups have built upon this concept in subsequent years, extending to a variety of polymer chemistries and further expanding the diversity of structures accessible, for example the helices prepared by Liu and co-workers[14] or segmented micelles by Jiang's group.[15] We make no attempt to thoroughly cover this literature here but refer the reader to several more comprehensive reviews.[16−20]

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Instead, this Perspective seeks to highlight several advances made in recent years that diverge from this paradigm and establish new approaches to processing of block copolymer assemblies in solution. These methods include systematic ways to subtly tune interactions between the core and corona blocks as well as new physical approaches to form or remodel self-assembled structures. This suite of techniques provides access to different classes of morphologies not previously accessible and new abilities to control encapsulated contents.

Tuning Coronal Interactions through Polyvalent Organic Acid−Base Complexation

While the manipulation of solvent quality for the core-forming blocks is a well-studied avenue by which to dictate aggregation of block copolymers in solution, a relatively unexplored route is the incorporation of tunable interactions between corona blocks, for example, multivalent complexation of the hydrophilic portions of amphiphilic block copolymers. Wooley, Pochan, and co-workers have recently investigated the use of organic multiamines to tailor assembly of poly(acrylic acid) (PAA)-containing di- and triblock copolymers and have found that these multivalent complexes provide three facets of nanostructural control.[21−28]

First, micelle geometry can be manipulated simply by varying the type and amount of added multiamine. A single species of block copolymer placed in identical solvent mixtures can be coerced to form, e.g., spheres, cylinders, or disk-shaped micelles by using the appropriate multiamine.[22,23] Importantly, this work has also led to the discovery of micelle structures not previously observed or anticipated, including stable toroidal micelles (cylindrical micelles that rid themselves of all end-caps) as shown in Figure 1b,[21,28] disk micelles,[22,25] and helical cylindrical micelles.[27] Remarkably, these helices are many micrometers in length, with each aggregate possessing a single, well-defined pitch and handedness, and under some conditions, double helices are formed as shown in Figure 1c. While nearly any amphiphilic block copolymer can be assembled into the classical morphologies of spheres, cylinders, and vesicles (given an appropriate copolymer composition and solvent mixture), this wide flexibility to produce multiple structures from a single copolymer composition, as well as the ability to construct helical and toroidal micelles, stems from the added organic multiamines. By forming complexes with the corona polyacid chains, the multiamines shift the preferred interfacial curvature between hydrophilic and hydrophobic blocks, thereby redefining micelle geometry and introducing long-range interactions and spontaneous curvature that yield well-defined micelle superstructures such as toroids and helices.

Second, by taking advantage of the nonergodicity of these multiamine/block copolymer mixtures, the Wooley and Pochan groups have used a kinetic solvent titration pathway to assemble incompatible block copolymers into mixed micelles, e.g., cylinders with cores separated into two distinct hydrophobic phases.[24] This process takes place by first complexing together distinct PAA-containing block copolymers containing different hydrophobic blocks in pure THF, forming "inverse" micelles with PAA cores and mixed hydrophobic coronas. Next, by titrating with water, the micelles are forced to invert, driving the incompatible hydrophobic blocks into shared micelle cores that separate into multicompartments.[24] While several other groups have reported multicompartment core micelles formed from a single block copolymer species containing unlike insoluble blocks (see, e.g., refs 29−33), a major advantage of the complexation strategy is the possibility to mix any number of different block copolymers. The Wooley and Pochan groups are actively exploring the possibilities for forming aggregates with mixed, multicompartment cores using this method.

Third, during the titration of THF/block copolymer/multiamine solutions with water, large windows of solvent composition exist in which the block copolymer/multiamine complexes no longer remain stably suspended, but instead precipitate out of solution. In this fashion, Wooley, Pochan, and co-workers have

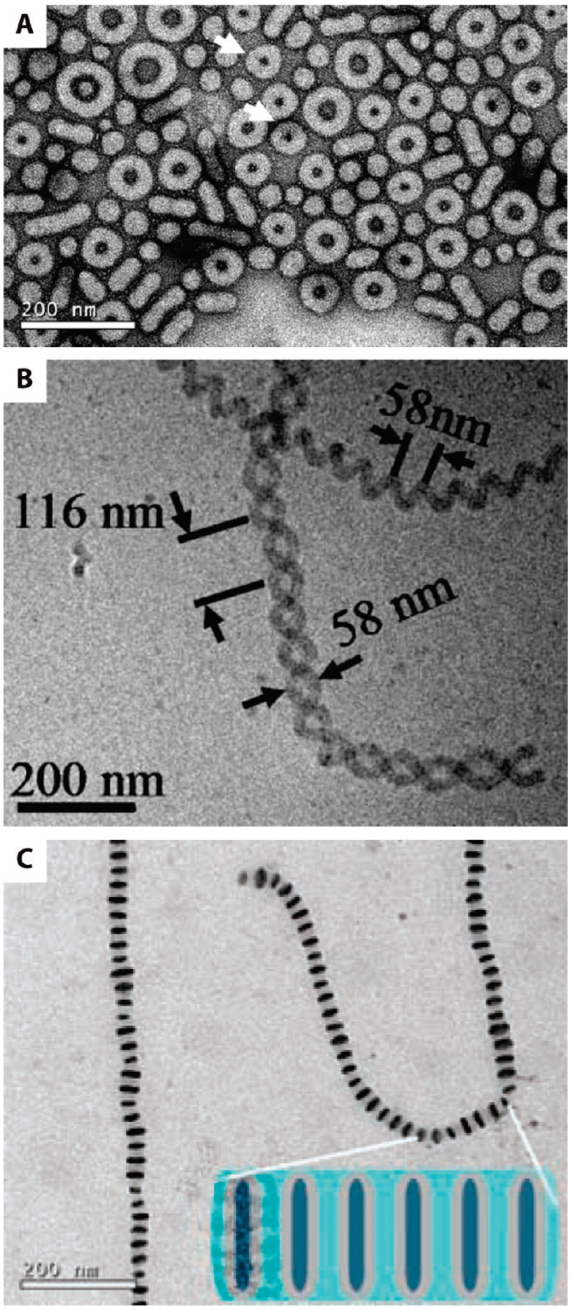

Figure 1. Micelle structures prepared by the Wooley and Pochan groups by complexing poly(acrylic acid)-containing block copolymers with organic multiamines. (A) Toroidal micelles. Reproduced with permission from ref 28. Copyright 2009 The Royal Society of Chemistry. (B) Single- and double-helical cylinder micelles. Reproduced with permission from ref 27. Copyright 2008 The Royal Society of Chemistry. (C) Segmented cylindrical micelles. Reproduced with permission from ref 24. Copyright 2007 AAAS.

produced particles of block copolymers with internal nanophase separation.[26] The overall size of particles is controlled by the solvent mixing process, while the size and symmetry of the nanoscale organization within are determined by the composition and molecular weight of the block copolymer.[26] In a similar vein, micelles formed at high water content can be "shocked" by rapidly adjusting the solvent composition to a point where micelles are no longer stably suspended but instead begin to aggregate. This defined assembly pathway has been used to generate the cylindrical nanostructures shown in Figure 1c, which consist of one-dimensional stacks of micelles, yielding alternating layers of hydrophobic and hydrophilic blocks perpendicular to the cylinder backbone (in contrast to the normal geometry of a cylindrical micelle with a hydrophobic core and hydrophilic corona).[24]

There are numerous subtleties to the multiamine/polyacid complexation process that are important in dictating the observed behavior and only partially understood at present. For example, helical cylinder micelles are formed only using tri- or tetraamines and not diamines and are only observed at large molar excesses of amines relative to the acid groups within the PAA blocks.[27] Further, the aggregates formed through a specific pathway are in large part kinetically trapped but may continue to transform over time; thus, their long-term stabilities will be important to assess and understand. Another key area for investigation is the extension of these concepts to other types of polyvalent interactions. For example, Discher and co-workers have recently applied a strategy that relies on mediating the ionic interactions between PAA blocks by binding of divalent calcium ions to prepare polymer vesicles and wormlike micelles with phase-separated domains of PAA and PEO corona chains,[34] while Liu and co-workers have prepared "bumpy" spherical microparticles in a similar fashion.[35] Possibilities for further extension to truly specific multivalent interactions would seem to be a fertile area for investigation. While the work summarized here has demonstrated the promise of this approach, the full range of opportunities provided by harnessing multivalent interactions to construct complex nano- and microstructures of block copolymers clearly demands more effort.

Epitaxial Growth of Assemblies with Crystalline Core Blocks

Instead of focusing on interactions between the coronal chains, alternative routes to controlling micelle structures can be achieved by tuning the interactions between chains in the micelle core. An excellent example is the work by Winnik, Manners, and co-workers on block copolymers with polyferrocenylsilane (PFS) core blocks. When held below the melting temperature of the PFS block, these polymers tend to form cylindrical micelles[36,37] or elongated tapelike nanostructures.[38] The widths of these structures are governed by a competition between crystallization of the PFS core, which favors extended platelike crystalline lamellae, and the stretching of the corona block, which limits the lateral extent of the plates.[38] Remarkably if precrystallized "seed" micelles are exposed to further amounts of dissolved PFS-containing block copolymer—introduced by injecting a small amount of copolymer dissolved in a good solvent—addition of the new chains to the ends of the existing micelles occurs through epitaxial growth of PFS crystals in the micelle cores.

The "living" nature of these polymer aggregates provides access to a number of unique and interesting nanostructures. As illustrated in Figure 2a, starting with PFS-*block*-polyisoprene cylindrical micelles as seeds, then extending these micelles on each end with PFS-*block*-polydimethylsiloxane yields "triblock-*co*-micelles", as shown in Figure 2b.[39] This approach can be extended to polar corona blocks as well, for example poly(2-vinylpyridine), allowing the block comicelles to be used as templates for deposition of inorganic materials such as gold nanoparticles and lead sulfide quantum dots (Figure 2c)[40] or oxide coatings including titania (Figure 2d), zirconia, alumina, and magnetite.[41] By starting with a tapelike seed formed from a polymer with a relatively short corona block, then epitaxially growing cylindrical micelles of a block copolymer with a longer corona block, "scarflike" structures, as shown in Figure 2e,f, can also be generated.[42] Further diversity in the chemical composition of these composite micelles is possible by introducing a polyferrocenylgermanium (PFG) block, which can undergo heteroepitaxial growth from the PFS seeds due to the similar crystal structures of PFS and PFG.[42]

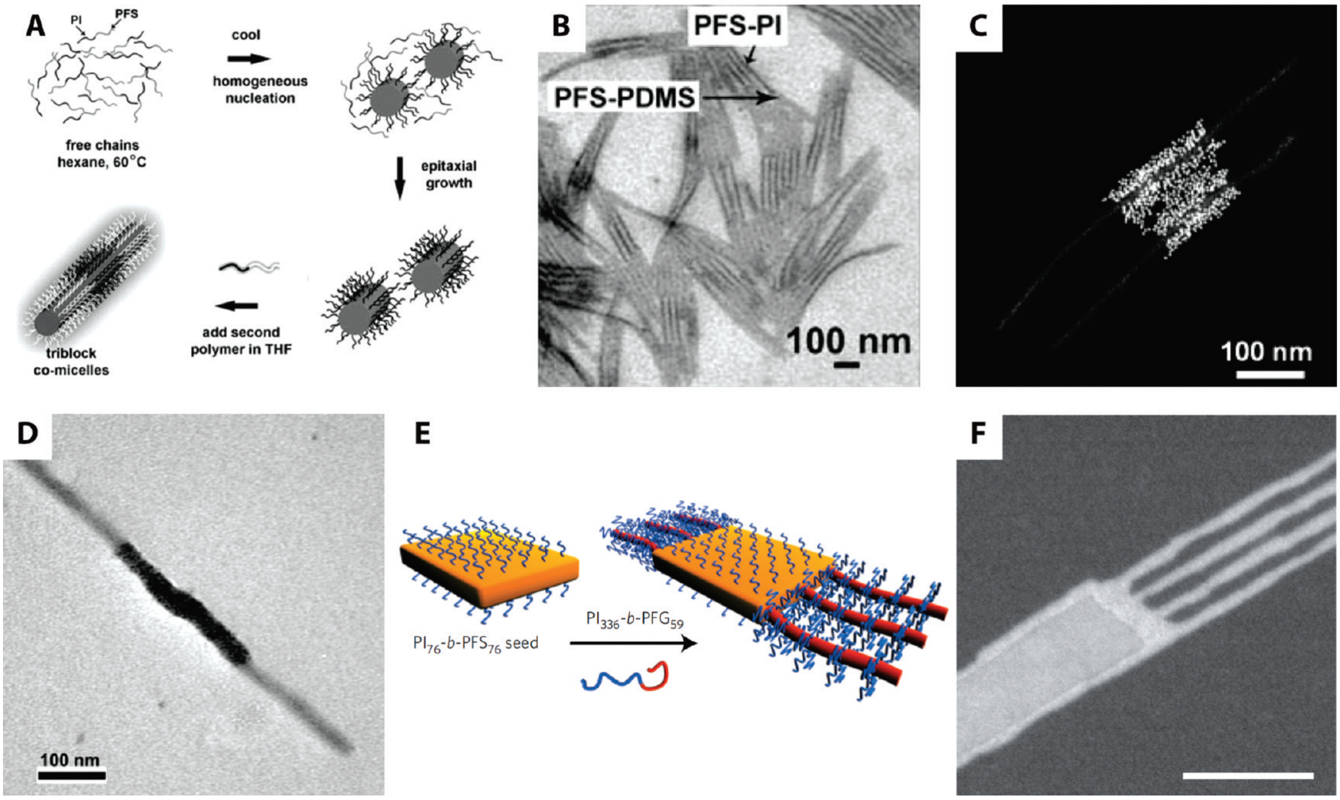

Figure 2. "Living" micelle structures prepared by Winnik, Manners, and co-workers through epitaxial crystallization of the core blocks. (A) Illustration of the process by which seed micelles containing polyferrocenylsilane (PFS) cores can be extended to yield triblock comicelles and (B) TEM micrographs of the resulting structures. (A, B) Reproduced with permission from ref 39. Copyright 2007 AAAS. (C) Triblock comicelles decorated with PbS quantum dots. Reproduced with permission from ref 40. (D) Triblock comicelles decorated with TiO_2. Reproduced with permission from ref 41. Copyright 2009 Wiley-VCH Verlag GmbH & Co. KGaA. (E) Schematic and (F) scanning force micrographs of heteroepitaxially grown scarflike micelles. Reproduced with permission from ref 42. Copyright 2009 Macmillan Publishers Ltd.

While this work presents many opportunities for preparing micelles with controlled structures, it also raises many fascinating questions. What is required for the ends of micelles to remain "alive" for the epitaxial addition of polymer chains? Can this method be generalized to other semicrystalline polymers, particularly those with attractive electronic and/or optical properties? While reasonably narrow distributions of micelle length have been obtained,[39] is it possible to further control the "reactivity" of the chain ends to obtain polydispersity indices approaching unity, in analogy to living anionic or controlled radical polymerizations? Can well-defined branching points be introduced to organize components in two or even three dimensions?

Self-Assembly through Instabilities of Immiscible Liquid Interfaces

The approaches described above—whether the emphasis is on the core or corona blocks—all rely on carefully tuned interactions between block copolymer chains dispersed in a homogeneous liquid phase. In practice, fine adjustments to solvent quality are commonly achieved by combining two different, but miscible, solvents: a good solvent for all components of the polymer and a selective solvent whose presence drives aggregation.

An alternative route by which binary solvent mixtures can be used to process amphiphilic block copolymer involves a good solvent that is *immiscible* with the selective solvent. Typically, the block copolymer is dissolved within a volatile organic solvent that is dispersed as micrometer-sized droplets in an aqueous phase to form an emulsion. The volatile solvent is next gradually removed by evaporation, ultimately yielding a dispersion of block copolymer aggregates in water. This processing approach, often called the "emulsion and solvent evaporation" method, has found widespread use in the preparation of hydrophobic polymer micro- and nanoparticles[43,44] and has been exploited by several groups to prepare block copolymer particles with internally microphase-separated structures.[45−50]

Similar approaches have also been applied previously in a few instances to generate amphiphilic polymers micelles[51] or vesicles,[52] though the mechanism of self-assembly was not closely investigated until the recent work of Zhu and Hayward on assembly of polystyrene-*block*-PEO during solvent (chloroform) removal from emulsion droplets.[53−55] As the droplets decrease in size, the amphiphilic polymer concentration within rises, driving increasing adsorption at the solvent/water interface and lowering the interfacial energy between the immiscible liquid phases. As pictured in Figure 3a,b, at sufficiently high polymer concentrations the droplets lose their spherical shapes, undergoing an instability in which new solvent/water interface is spontaneously created, thereby allowing the block copolymer to be dispersed into the aqueous phase. Micropipet tensiometry measurements of the solvent/water interfacial tension during this process have revealed that the onset of instability coincides with an approach of the interfacial tension nearly to zero.[55] This is consistent with the mechanism proposed for "spontaneous emulsification"[56] of small molecule surfactant systems and reactive blending of polymers,[57,58] wherein the surface pressure of adsorbed amphiphiles becomes equal to (or greater than) the bare interfacial tension, leading to a transiently vanishing (or even negative) surface energy and therefore spontaneous creation of new interfacial area.[59,60] Whether these systems ever truly reach zero interfacial tension remains an unresolved question; Granek and co-workers have suggested that the interface will become

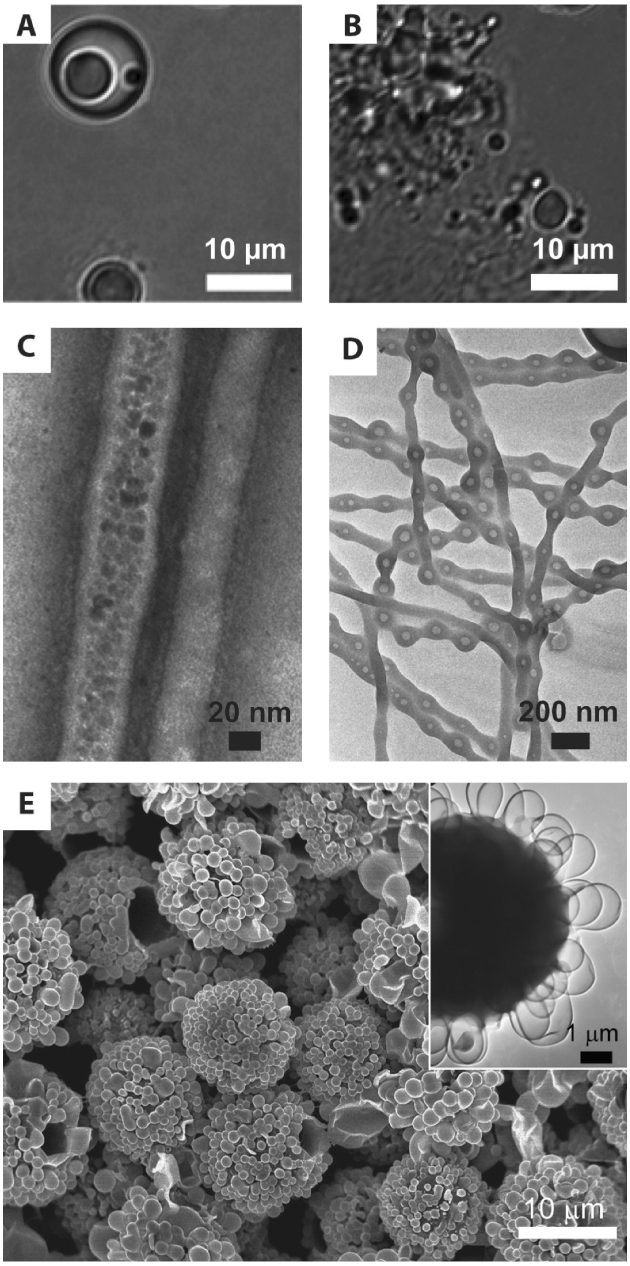

Figure 3. Assemblies of amphiphilic block copolymers generated by the Hayward group via instabilities of liquid interfaces. (A) An optical micrograph of an emulsion drop prior to and (B) during the process of block copolymer dispersal driven by evaporation of organic solvent. (C) Wormlike micelle structures containing encapsulated iron oxide nanoparticles and (D) internal aqueous compartments. (A−D) Reprinted with permission from ref 53. (E) "Budding vesicle" microparticles. Reprinted with permission from ref 54. Copyright 2008 Wiley-VCH Verlag GmbH & Co. KGaA.

unstable even at slightly positive values of the interfacial energy due to the preferred curvature of the adsorbed layer of amphiphiles.[61]

The manner in which the instability leads to deformation of droplets depends primarily on the preferred curvature, and therefore the composition, of the amphiphilic block copolymer but can also be fine-tuned through the composition of water-soluble surfactant used to disperse the organic solvent as an emulsion.[55] Polymers containing larger hydrophilic blocks yield repeated fragmentation into increasingly smaller droplets, ultimately generating spherical or short wormlike micelles.[53] An intermediate hydrophilic content gives rise to a "spinning" process in which thin fluid threads are ejected from the droplet, yielding wormlike micelles with lengths up to tens of micrometers.[53] Finally, at relatively low hydrophilic content, micrometer-scale particles are formed,[54] through poorly understood mechanisms thought to be analogous to "budding" of vesicles from concentrated films of lipid[62−64] or block copolymer[65] or through growth of (sub)micrometer-sized fluid threads that ultimately fold back into bilayer structures. These particles are similar to block copolymer lamellarsomes,[66] in that they display internal microphase separation into bilayer structures but are distinguished by the complex texturing of their surfaces arising from the interfacial instability.[54] Related phenomena were likely responsible for the surface structuring of poly(lactic acid)-*block*-PEO particles described a number of years earlier by Gref et al.[67] We note that Battaglia and Ryan have also reported the occurrence of instabilities at the interface of water and immiscible organic solvent droplets containing bilayer-forming amphiphilic block copolymers.[68] In that case, the observed instabilities reflected a slightly different mechanism, namely the growth of myelin figures (multilamellar tubules), but led to very similar micrometer-scale aggregates with complex surface textures dubbed "myelinsomes".[68]

While the control of aggregate morphology obtained by emulsion processing has not reached the level of sophistication of other processes described above, it does offer unique advantages. For one, it provides a simple way to obtain high-efficiency encapsulation of hydrophobic materials, including other polymers and nanoparticles, within the cores of wormlike micelles,[53] which is difficult to achieve using other methods. Blending of another amphiphilic or hydrophobic block copolymer is also straightforward, providing access to composite micelle structures with multicompartment hydrophobic cores[69] or containing nanoscopic internal aqueous domains,[53] as shown in Figure 3d. In addition, the tendency of bilayer-forming polymers to yield hierarchically structured particles with nano- to microscale surface texturing[54] could yield interesting encapsulation/delivery devices for biomedical applications. For example, Tsapis and co-workers have recently demonstrated how this approach can be extended to form biodegradable capsules with controlled surface texturing that contain perfluorooctyl bromide, a compound of interest for its ability to both generate imaging contrast and carry oxygen.[70]

Many open questions and challenges remain to understand the full potential of this method. An improved fundamental understanding of the instability of the solvent/water interface, especially the interplay between solvent removal rate and the kinetics of mass transport and interfacial reorganization of block copolymer, would help guide future developments. The factors governing the uniformity and efficiency of dispersion of nanoparticles within micelles remain an active area of exploration. In addition to amorphous diblock copolymers, one can also envision the extension of this approach to more complex molecular architectures or crystalline polymers.

Flash Nanoprecipitation

For most biomedical applications of block copolymer assemblies, the ability to encapsulate functional small molecules, polymers, or nanoparticles is critical to providing therapeutic and/or diagnostic properties. Unfortunately, the active components and encapsulating polymers often vary widely in their solubility properties. Thus, finding appropriate solvent conditions under which to process carrier and payload into composite assemblies is typically challenging.

Prud'homme and co-workers have tackled this problem through a processing approach called "flash nanoprecipitation".[71−73] In short, the block copolymer and active ingredients are dissolved

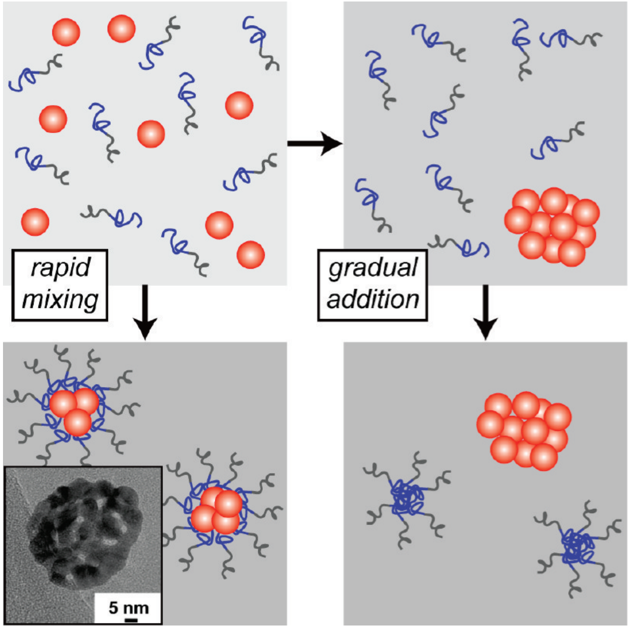

Figure 4. In the flash nanoprecipitation process developed by Prud'homme and co-workers, rapid mixing of solvent with nonsolvent leads to highly efficient encapsulation of hydrophobic molecules and nanoparticles within micelles. Gradual addition of nonsolvent, by contrast, usually leads to macroscopic precipitation of hydrophobic ingredients and therefore inefficient loading of micelles. Inset at lower left: transmission electron micrograph of gold nanoparticles loaded within a micelle of poly(ε-caprolactone)-*block*-poly(ethylene oxide). Reprinted with permission from ref 73.

in a water-miscible organic solvent that is rapidly combined with water using a multi-inlet vortex[73] or confined impinging jets[71,72] mixer; Farokzhad and co-workers have developed a microfluidic platform to achieve a similar rapid mixing effect.[74] The final solvent composition is chosen so that all of the hydrophobic components are highly insoluble, i.e., so that the active ingredients precipitate and the block copolymer self-assembles into micelles. However, the time scale of mixing is only a few milliseconds, while the diffusion-limited formation of micelles and precipitates typically occurs at least an order of magnitude more slowly.[72] Thus, the polymer and active ingredients find themselves in a highly nonequilibrium situation immediately after mixing and begin to assemble into composite micelle structures in which small aggregates of the active ingredients become coated with an amphiphilic polymer shell. While a globally demixed state, i.e., macroscopic precipitates of the active ingredient and empty block copolymer micelles, may be lower in overall energy, the formation of composite nanostructures is kinetically preferred. As illustrated in Figure 4, conducting the same mixing process by gradual addition of water to the organic solvent generally leads to precipitation of active ingredients before micellization (or vice versa) and thus very low encapsulation efficiency. Using flash nanoprecipitation, Prud'homme and co-workers have demonstrated essentially quantitative incorporation of hydrophobic gold nanoparticles within poly(ε-caprolactone)-*block*-poly(ethylene oxide) micelles.[73]

This approach holds great potential as a simple and highly efficient way to prepare spherical micelles loaded with any number of different hydrophobic materials. Several interesting avenues for future fundamental investigations remain open, including the applicability of the technique for preparing nonspherical micelle shapes and the potential to assemble multiple amphiphilic polymers with different chemical or physical properties into hybrid micelle structures.

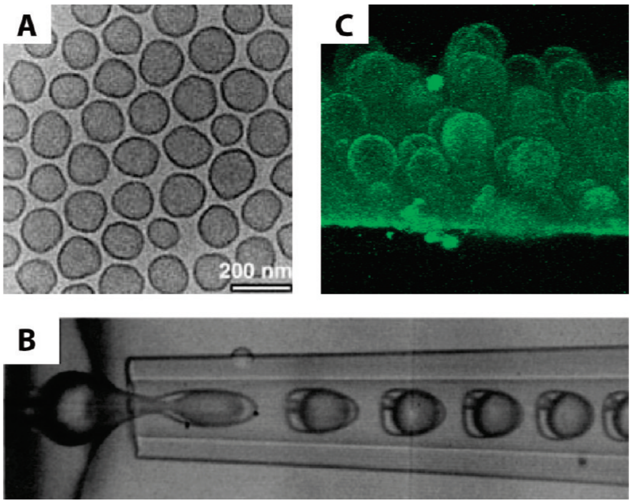

Figure 5. Processes for preparing amphiphilic block copolymer vesicles with well-controlled sizes. (A) In the approach of Förster and co-workers, inkjet printing of an ethanolic polymer solution into water yields vesicles with diameters of order 100 nm and low polydispersities, as shown in this transmission electron micrograph. Reproduced with permission from ref 77. Copyright 2005 Wiley-VCH Verlag GmbH & Co. KGaA. (B) Weitz's group uses concentric multiphase flows in microfluidic flow-focusing devices to prepare double emulsion droplets, as shown in this optical micrograph. Reprinted with permission from ref 78. The droplets are then converted to polymer vesicles with narrow size distributions in the ~10−100 μm range upon evaporation of organic solvent from the middle phase. (C) Rehydration of amphiphilic block copolymer films patterned into islands yields micrometer-scale vesicles with well-controlled sizes, in a method developed by Howse and co-workers. This confocal fluorescence micrograph shows the process of vesicles budding from a patterned copolymer film. Reprinted with permission from ref 80. Copyright 2009 Macmillan Publishers Ltd.

Vesicles of Well-Controlled Size

Block copolymer vesicles, or polymersomes, are of continued interest for their ability to encapsulate aqueous compartments within relatively robust polymer bilayer shells.[75,76] Traditionally, suspensions of polymer vesicles have been prepared by rehydrating a film of amphiphilic block copolymer or through the method pioneered by Eisenberg's group of gradually adjusting solvent quality.[12] A major limitation of these approaches is their inability to control the size of vesicles formed, typically leading to a broad distribution of sizes over the range of ~100 nm to 10 μm. For cases where the hydrophobic component of the polymer remains fluid, the size distributions can be narrowed dramatically for vesicles in the ~100 nm range by either sonication or extrusion of vesicles through porous membranes, while selective generation of larger ("giant") vesicles of ~10 μm size can sometimes be prepared by electroformation, i.e., the use of an electrical potential to drive rehydration of a polymer film coated on an electrode (see, e.g., ref 76 for a review of vesicle size considerations).

Recently, several new processes have been developed with considerable potential for controlling the size distributions of polymer vesicles. Förster and co-workers have used an inkjet printer to generate picoliter-scale droplets of ethanol containing dilute concentrations of poly(2-vinylpyridine)-*block*-PEO copolymers.[77] Upon contact of these droplets with a stirred aqueous bath, the copolymers self-assemble into ~100 nm diameter vesicles with quite narrow size distributions, as shown in Figure 5a (standard deviations < 10% of the mean size). While many vesicles are generated from each droplet, the rapid mixing apparently leads to quite uniform conditions of supersaturation, in similar fashion to the flash nanoprecipitation route described above, thus generating uniform vesicles with sizes determined by the rates of copolymer diffusion and aggregation.

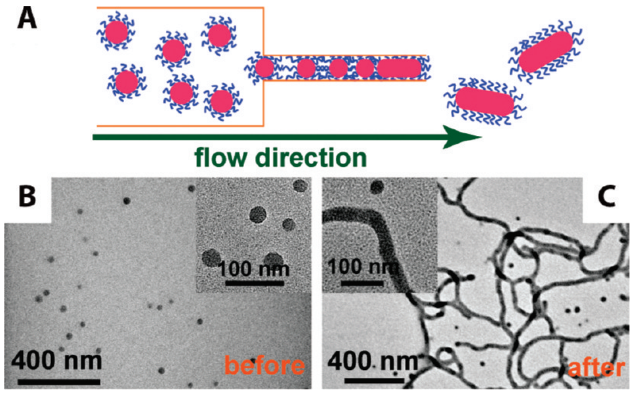

Figure 6. (A) An illustration of the method of Wang, Wu, and co-workers wherein spherical micelles are "extruded" through a nanoporous filter to yield cylindrical micelles. (B) Transmission electron micrographs of spherical micelles prior to extrusion and (C) predominantly cylindrical micelles following extrusion. (A−C) Reprinted with permission from ref 83.

An alternative means of using picoliter-scale droplets to generate uniform vesicles has been developed by Weitz and co-workers.[78] In this case, microfluidic flow-focusing devices as shown in Figure 5b are used to generate three-phase coaxial flows with aqueous phases in the center and at the periphery and a layer of water-immiscible organic solvent in between. Under appropriate flow conditions, the interfacial-tension-induced breakup into droplets leads to double emulsions with only a single water droplet within each solvent droplet and narrow size dispersities for both. Inclusion of an amphiphilic block copolymer in the solvent phase allows these double emulsion droplets to be converted into polymer vesicles with well-controlled sizes of ~10−100 μm through evaporation of the solvent. While this method requires careful attention to both emulsion stability and wetting[79] considerations during solvent evaporation, it offers highly efficient encapsulation of the inner aqueous phase (nearly 100%) and potential for further tailoring of vesicle structure by including additional fluid streams in the microfluidic device, e.g., leading to asymmetry between the compositions of inner and outer leaflets or the encapsulation of multiple aqueous compartments with distinct contents.

In a third approach, Howse and co-workers have taken advantage of dewetting of polymer solutions coated on lithographically patterned substrates to generate micrometer-scale "islands" of the amphiphilic polymer poly(butylene oxide)-*block*-PEO.[80] Upon hydrating these patterned films of diblock copolymer, vesicles are spontaneously generated with a narrow size distribution (Figure 5c) and an average size that nearly matches that predicted based on the area of the patterned islands. While the method has so far only been demonstrated for vesicles with diameters of 1−10 μm, the potential for extension to nanopatterned surfaces offers the possibility that this single processing method could provide excellent control of size over a wide range of vesicle dimensions.

Squeezing Micelles through Nanopores

Cylindrical micelles are particularly attractive structures for *in vivo* drug delivery applications due to the potentially large payload per micelle and the ability to circulate through the bloodstream for longer periods than chemically similar spherical micelles.[81] Unfortunately, the range of conditions over which cylindrical micelles are formed is often quite narrow,[82] in contrast to spherical micelles that are typically found over wide ranges of composition space. Very recently, Wang, Wu, and co-workers have demonstrated an intriguingly simple approach to convert spherical into cylindrical micelles by squeezing them through a membrane containing nanopores with diameters slightly smaller than the size of the micelles,[83] in some ways reminiscent of the vesicle-sizing method described above. This process is performed under solvent conditions where the core block is only moderately insoluble and thus able to deform and reorganize relatively easily. As shown in Figure 6, the spherical micelles presumably become "jammed" within a pore, causing them to fuse and eventually to be ejected as a cylindrical micelle. At present, these micelles are only metastable, reverting to their spherical form over a period of days, but postprocessing steps to lock in the cylindrical morphology can easily be envisioned. If this method can be generalized to other polymer chemistries and shown to preserve the presence of encapsulated species, it could prove to be a very powerful route to cylindrical micellar structures.

Conclusions

The processing of block copolymer solution assemblies has undergone rapid development over the past several years. In addition to basic considerations of how solvent quality affects the solubility of the core-forming block that are always present, approaches to subtly tune coronal interactions through polyvalent complexation and to harness epitaxial crystallization of micelle cores provide new levels of morphological control. Modifications to the physical processes of self-assembly, whether through rapid mixing of miscible solvents, emulsion processing of immiscible solvents, patterned dewetting of copolymer films, or membrane "extrusion" to mold micelle shapes, have also greatly expanded the types of block copolymer-based assemblies that can be achieved. As we have sought to highlight here, this suite of recently developed processing tools makes researchers in the field better equipped than ever to craft truly tailored assemblies of block copolymers in solution.

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