

# Block copolymer nanostructures

**One of the most important classes of synthetic systems for creating self-assembled nanostructures is amphiphilic block copolymers. By controlling the architecture of individual molecules, it is possible to generate nanostructures either in an undiluted melt or in solution. These ordered nanostructures are tunable over a broad variety of morphologies, ranging from discrete micelles and vesicles to continuous network structures. Their synthetic nature allows the design of interfaces with different chemical functional groups and geometrical properties. This, in combination with molecular architecture, determines the levels of ordering in self-organizing polymeric materials. For these and other reasons, block copolymer micelles, vesicles, and mesophases are finding applications in several areas, ranging from nanocomposites to biomedical devices.**

Thomas Smart<sup>1</sup>, Hannah Lomas<sup>1</sup>, Marzia Massignani<sup>1</sup>, Miriam V. Flores-Merino<sup>1</sup>, Lorena Ruiz Perez<sup>2</sup>, and Giuseppe Battaglia<sup>1\*</sup>

<sup>1</sup>Department of Engineering Materials, University of Sheffield, Sheffield, UK

<sup>2</sup>Department of Chemistry, University of Sheffield, Sheffield, UK

\* E-mail: [g.battaglia@sheffield.ac.uk](mailto:g.battaglia@sheffield.ac.uk)

Block copolymers occupy a huge area of research because they offer a vast range of possibilities for architecture, size, and chemical composition. Advances in polymer chemistry<sup>1</sup>, such as anionic polymerisation<sup>2</sup> and most recently living radical polymerization<sup>3</sup>, have enabled a vast array of block copolymers to be synthesized with great control over their architecture, molecular weight, chemical composition, and functionality. Their intrinsic multi-properties allow the combination of different polymers and therefore the design of novel materials potentially comprising several different properties (e.g. thermoplastic, rubber, ductile, electrical conductivity, etc.).

In bulk, when the different blocks are chemically immiscible, the balance between the entropically and enthalpically driven phase separation and the chemical bond constraints between the blocks drives the formation of ordered domains<sup>4-10</sup>. In solution, the interactions between the solvent and the different blocks dictate the ability to form well-defined structures. The architecture, molecular weight, volume fractions of blocks, and chemical functionality can all be set in the synthesis, making designer block copolymers a reality. The ability to effectively design nanoparticles and nanostructures to your preference, coupled with the wide range of applications associated with them, have made them an incredibly popular topic of research. Herein,

we explore the latest developments in block copolymer nanoparticles and nanostructures formed in solution. We also look into the applications lined up for them, both immediate and in the near future.

## Dispersed nanoparticles versus ordered nanostructures

Amphiphilic molecules in water are the most studied example of self-assembling molecules in selective solvents. A selective solvent, water in this case, will preferentially dissolve one part of a molecule over another. Molecules such as natural phospholipids, detergents, and soap comprise both hydrophobic (water insoluble) and hydrophilic (water soluble) parts. The hydrophobic segments become packed together in aggregates as it is more entropically favorable for the hydrophobic parts to pack together than for water to order itself around each one separately in solution (this is known as the hydrophobic effect<sup>11–13</sup>). The hydrophilic parts, however, preferentially dissolve in water. There is a bigger enthalpic compensation from forming hydrogen bonds with water molecules than if the hydrophilic parts interacted with each other, leading to short range repulsion between adjacent hydrophilic blocks. The balance between these forces drives the formation of many nanostructures and mesophases<sup>14–16</sup>.

Similarly, block copolymers can be made of hydrophilic and hydrophobic blocks and form similar structures in water<sup>17</sup>. Such an effect can be easily expanded into any selective solvent condition and thus, as long as the block copolymers are made of soluble and insoluble blocks, they can assemble into defined architectures<sup>18</sup>.

The geometry and degree of order of these architectures depends on the concentration and the volume ratio between insoluble and

soluble blocks – the insoluble soluble ratio (ISR). At very dilute concentrations, the soluble block compatibility with the host solvent is sufficient to maintain the copolymer as dissolved molecules (unimers). At a certain concentration called the critical aggregation concentration (CAC), block copolymers start to self-assemble so as to separate the insoluble blocks from the solvent. As the molecular mass and the ISR increase, the CAC decreases<sup>19</sup>. At concentrations higher than CAC, block copolymers self-assemble into dispersed isotropic phases.

The structures are determined by the enforced curvature in the assembly arising from the relative sizes of soluble and insoluble domains, or from the ISR. The dimensionless packing parameter,  $p$ , originally developed for small amphiphiles in water<sup>14,15</sup>, can be generalized and used to define the relative size of the nonsoluble region of a copolymer<sup>20,21</sup>. The balance between solvent-phobic and solvent-philic interactions gives rise to an optimal surface area of the solvent-phobic block at the interface between the solvent-phobic and solvent-philic blocks ( $a_0$ ). This, together with the length and the volume of the nonsoluble domain, contributes to the packing parameter, defined as<sup>14,15</sup>:

$$p = \frac{v}{a_0 d}$$

Where  $v$  is the volume and  $d$  is the length of the solvent-phobic block. The packing parameter is the ratio between the insoluble chain molecular volume and the volume actually occupied by the copolymer in the assembly. As a general rule, spherical micelles are formed when  $p \leq 1/3$ , cylindrical micelles are formed at  $1/3 < p \leq 1/2$  and membranes arise when  $1/2 < p \leq 1$ . As shown in Fig. 1, both cylindrical and spherical micelles consist of a nonsoluble core surrounded by a soluble corona.

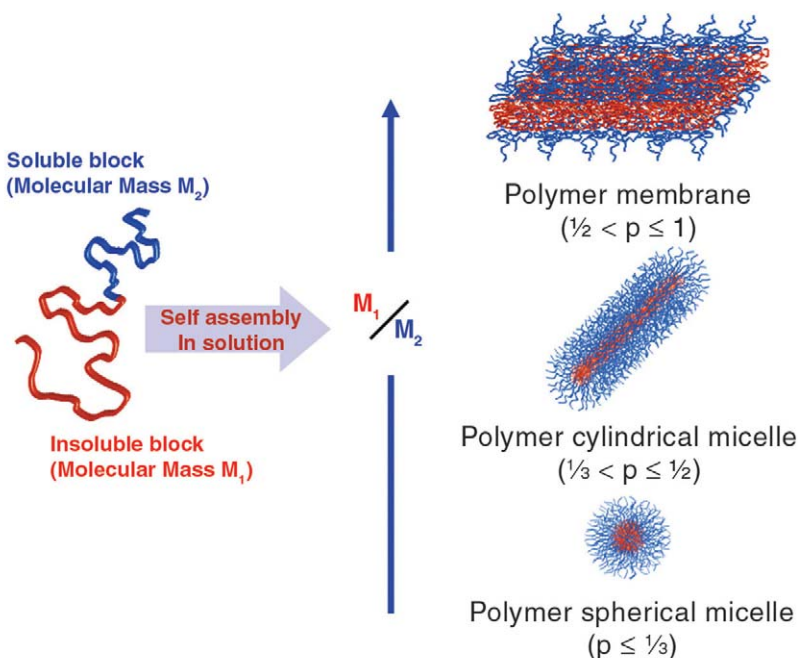


Fig. 1 Different geometries formed by block copolymers in selective solvent conditions.

Membranes consist of two monolayers of block copolymers aligned so as to form a sandwich-like membrane: soluble block–insoluble block–soluble block. It is worth noticing that spherical micelles are self-contained assemblies and their diameter depends uniquely on the molecular characteristics of the block copolymer (i.e. chemistry and molecular mass). Conversely, for both cylindrical micelles and membranes, the molecular characteristics of the block copolymer only control the cylinder diameter and the membrane thickness, respectively.

From a theoretical point of view, the most stable condition will be an infinitely long cylinder and infinitely large membranes. However, thermal fluctuations and the intrinsic fluid nature of these aggregates force finite dimensions. This means that in order to avoid contact between the solvent and the insoluble domains, a certain level of molecular frustration and consequently, curvature, is necessary<sup>22</sup>. When molecular frustration is confined to a specific part of the assembly, cylindrical micelles are stabilized by end-caps into wormlike structures<sup>23</sup> and membranes are stabilized by curved edges into disk-like micelles (sometimes known as bicelles<sup>14</sup>). When the molecular frustration is shared among all the molecules, the cylinders bend, forming toroidal micelles, while membranes close up, forming core-shell spherical structures known as vesicles. The two scenarios are

energetically very different. Indeed, to form end-caps or curved edges, molecules assemble into structures with more interfacial curvature. Experimentally, it is most common to observe the formation of wormlike micelles and vesicles, respectively. It can be argued that in order to form end-caps on the cylinders only a smaller fraction of molecules are required compared with the formation of curved edges on membranes. Hence, energetically wormlike micelles and vesicles are more favorable than toroids and disk-like micelles. However, as the molecular mass of the copolymer increases, the energies change and local frustration becomes more unfavorable, as demonstrated by Bates and colleagues<sup>24–26</sup>. In this way cylindrical micelles made of large molecular mass copolymers either grow very long<sup>24</sup> or prefer to form more curved toroid-like structures<sup>25,26</sup>. Similar structures have been observed by Förster *et al.*<sup>27</sup> studying the salt-controlled transition from spherical to cylindrical micelles in ionic block copolymers. Experiments conducted within Pochan's and Wooley's laboratories have also demonstrated that by introducing an extra interaction between block copolymers, both toroidal micelles<sup>28</sup>, disk-like micelles<sup>29,30</sup>, and even long helical cylindrical micelles<sup>31</sup> can be stabilized.

Spheres, cylinders, vesicles, and occasionally toroidal and disk-like micelles are the result of equilibrating the different interactions between the two blocks and the solvent. This rule is independent of

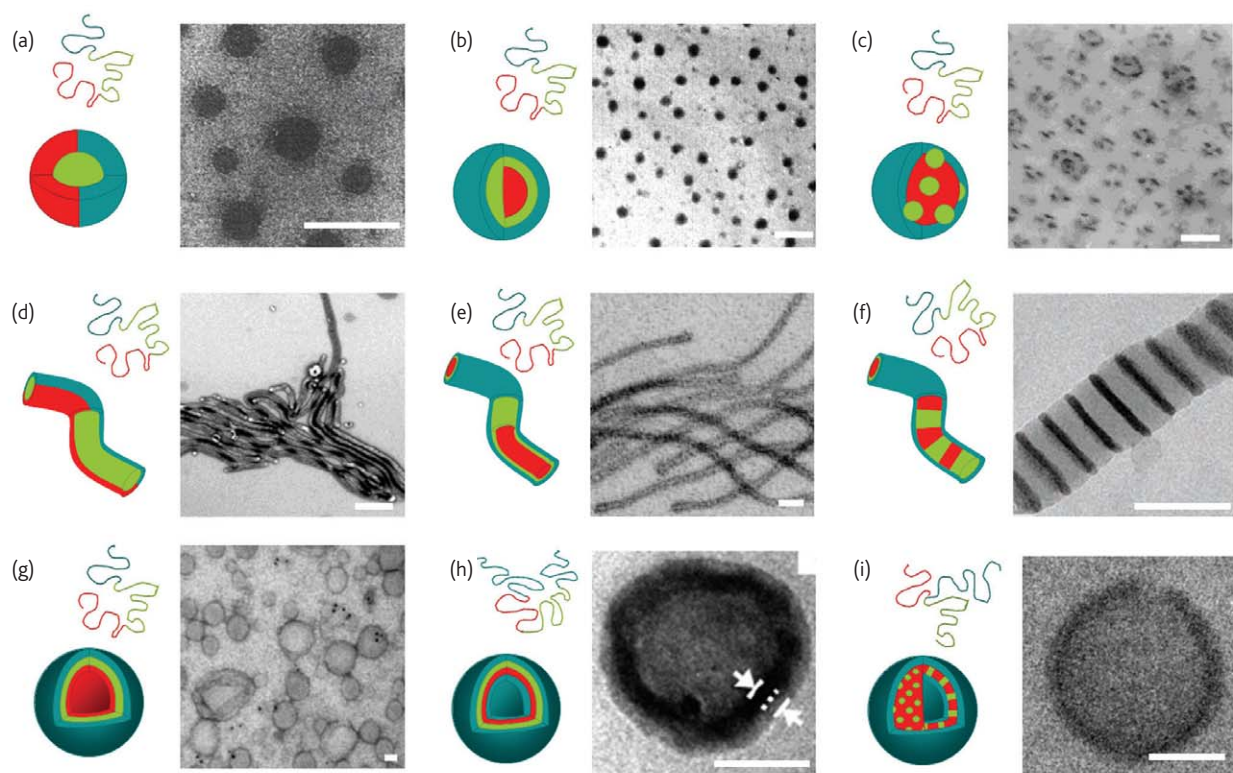


Fig. 2 Assemblies formed in selective solvent conditions by multiblock copolymers: (a) Janus spheres<sup>32</sup>, (b) core-shell spheres<sup>33</sup>, (c) raspberry-like spheres<sup>34</sup>, (d) Janus cylinders<sup>35</sup>, (e) core-shell cylinders<sup>36</sup>, (f) segmented cylinders<sup>29</sup>, (g) asymmetric (Janus) membrane vesicles<sup>37</sup>, (h) double-layer membrane vesicles, and (i) vesicles with hexagonally packed cylinders<sup>38</sup>. Scale bar 50nm. (Reproduced with permission from<sup>29,32–38</sup>. © 2007 American Association for the Advancement of Science; 2003, 2000, 2003, and 2003 American Chemical Society; 2000, 2004 Wiley-VCH; and 2006 American Chemical Society, respectively.)

whether the different soluble and insoluble parts are arranged as a diblock (AB), triblock<sup>23,39,40</sup> (ABA or BAB), or even multi-block<sup>41</sup>. This also applies when a third (or even a fourth) chemically different block is added. The overall ISR will dictate whether the copolymers assemble into spheres, cylinders, or membranes.

Although, the overall geometry is the same, multi-block copolymers have an extra level of control within the nanoparticles, introduced by the extra interaction between the blocks. ABC copolymers, where A and B are soluble, and C is insoluble, have been studied and developed for the formation of core-shell spherical micelles<sup>33,42</sup> (Fig. 2b). Depending on the A/B ratio and the solvent condition (i.e. selective solvent plus good solvent), the two soluble blocks have been observed to form cylindrical and spherical domains on the corona of cylindrical micelles<sup>43</sup>. ABC copolymers, where A and C are soluble, and B is insoluble, assemble into asymmetric 'Janus' (as in double-faced Roman god) particles<sup>44</sup>. As shown in figures 2a, 2d, and 2g, depending on the ISR, Janus particles can be spherical<sup>32,45</sup>, cylindrical<sup>35</sup>, or vesicular<sup>37</sup>. When A is soluble and B and C are both insoluble, the internal structure of the aggregate depends on the B/C ratio. Symmetrical copolymers (i.e. B and C with the same volume fraction) form insoluble core-shell spheres<sup>29,46</sup>, cylinders<sup>36,46</sup> (Fig. 2e), and disk-like micelles<sup>29,30</sup>. When B and C have a different volume fraction, the insoluble domains will

present an internal structure the geometry of which depends on the ratio between B and C. Spherical micelles with segregated cores that form spheres<sup>34,47</sup> (raspberry-like micelles) and cylinders<sup>34,47</sup>, segmented cylindrical micelles<sup>29,38,48</sup> (Fig. 2f), and vesicles with hexagonally packed cylinders<sup>38</sup> (Fig. 2i) have all been reported. In addition, Brannan *et al.*<sup>49</sup> have shown that ABCA tetrablock copolymers, where A is soluble, and B and C are both insoluble, assemble into vesicles whose membrane has an internal morphology that changes from lamellar (Fig. 2h) to cylindrical on changing the volume fraction between B and C. All these morphologies seem to suggest that by modulating the different interactions between copolymer and solvent, we can engineer spherical, cylindrical, and membrane-enclosed nanoparticles. In addition, by adding a third chemical component, we can even engineer the same hierarchy of structures confined within the nanoscopic particles.

As the concentration increases, the block copolymer-solvent interaction becomes more intense, leading to an extra interaction between the isotropic phases. In order to minimize the free energy, long range order mesophases are formed. As the concentration increases, the local packing also changes, leading to a decrease of the local curvature. In other words, molecules that at low concentration form spherical aggregates will assemble into cylindrical and eventually

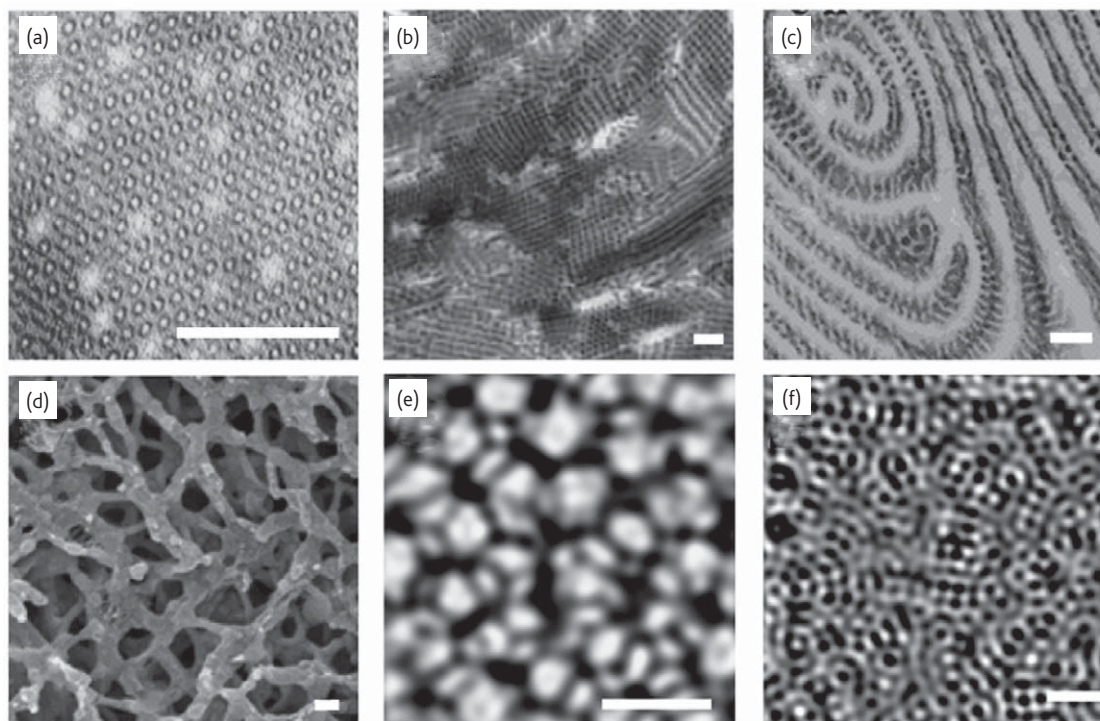


Fig. 3 (a) Cubic micellar phase formed by poly(ethylene oxide)-poly(ethyl ethylene) in an epoxy network<sup>54</sup>. (b) Hexagonally packed cylinders formed by poly(ethylene oxide)-poly(butadiene) in water<sup>53</sup>. (c) Disordered lamellar phase formed by poly(styrene)-block-poly(butadiene)-block-poly-(methyl methacrylate) in an epoxy network<sup>34</sup>. (d) Disordered network formed by poly(ethylene oxide)-poly(butadiene) in water<sup>51</sup>. (e) Hexagonally packed vesicles formed by poly(ethylene oxide)-poly(butylene oxide) in water<sup>55</sup>. (f) *Im3m* bicontinuous phase formed by poly(ethylene oxide)-poly(butylene oxide) in water<sup>56</sup>. (Reproduced with permission from<sup>34,51,53-56</sup>. © 2003 American Chemical Society; 2006 American Physical Society; 2001, 1997 American Chemical Society; 2005 Nature Publishing Group; 2006 American Chemical Society.)

membrane-like aggregates as the concentration increases. Hence as a general rule, going from low to high concentration, spherical micelles pack into cubic phases<sup>50–54</sup> (Fig. 3a) followed by hexagonally packed cylinders<sup>51–53</sup> (Fig. 3b), and eventually, at high concentrations, into lamellae<sup>51–53</sup>. Cylindrical micelles pack directly into hexagonal phases<sup>51–53</sup> while vesicles initially pack into hexagonally packed vesicles<sup>40,55,56</sup> (Fig. 3e), then bicontinuous phases<sup>55,56</sup> (Fig. 3f), and eventually lamellae<sup>40,52,53,55,56</sup>. At high concentrations, membrane forming copolymers have also been observed to form either cubic<sup>51</sup> or hexagonal<sup>56</sup> inverse structures. Such a sequence of phases is strongly affected by the copolymer molecular weight. The size of the copolymer affects how the copolymers pack locally. Jain *et al.*<sup>25, 26</sup> have observed that the boundaries between spheres, cylinders and membranes shift to a smaller ISR as the copolymer molecular mass increases. At high concentrations this resolves into novel phases such as the disordered network<sup>51</sup> seen in Fig. 3d.

The copolymer molecular mass also strongly affects the rigidity of the assembly<sup>57</sup>. This is particularly important for membrane-enclosed structures as the membrane elasticity dictates the level of order at high concentrations. This affects both the boundaries of the phases and the final morphology of vesicular gels and bicontinuous phases<sup>56</sup>. As for isotropic phases, the level of complexity can be increased by adding a third component to the block copolymer and therefore introducing a second level of hierarchy controlled by block-block interactions<sup>34,44,47</sup>. A representative example is the structure in Fig. 3c where one level of hierarchy is dictated by the solvent-copolymer interaction (the lamellae) and a second level of hierarchy is dictated by interactions between the blocks (the cylinders)<sup>34</sup>.

The intrinsic 'soft' nature of copolymers makes them assemble into structures that can tolerate a high level of imperfections. Therefore, block copolymer mesophases exhibit Bragg peaks that cannot be indexed assuming homogeneous crystal structures<sup>58</sup>. While this may limit the application of block copolymers for materials where a homogeneous crystal structure is a key requirement, the intrinsic soft nature makes block copolymers mesophases very sensitive to external fields<sup>9,58</sup>. Modest external fields, such as electrical or shear stimulation, are sufficient to trigger macroscopic arrangements in specific directions.<sup>51</sup> These properties are highly welcomed in modern material science as they allow the generation of highly ordered nano- and microstructured materials on demand<sup>59</sup>. In addition to this, the intrinsic macromolecular nature of the copolymers leads to very slow and kinetically controlled phase transitions<sup>60</sup>. The formation of a specific phase, whether dispersed or over a long-range, occurs at specific solvent-copolymer ratios and the transition from one to another is controlled both by the diffusion of the solvent and by the single chain within the copolymer. We have demonstrated that the diffusion coefficient of water within a membrane-forming copolymer drops by three orders of magnitude when the molecular mass of the copolymer is increased by just one order of magnitude<sup>60</sup>.

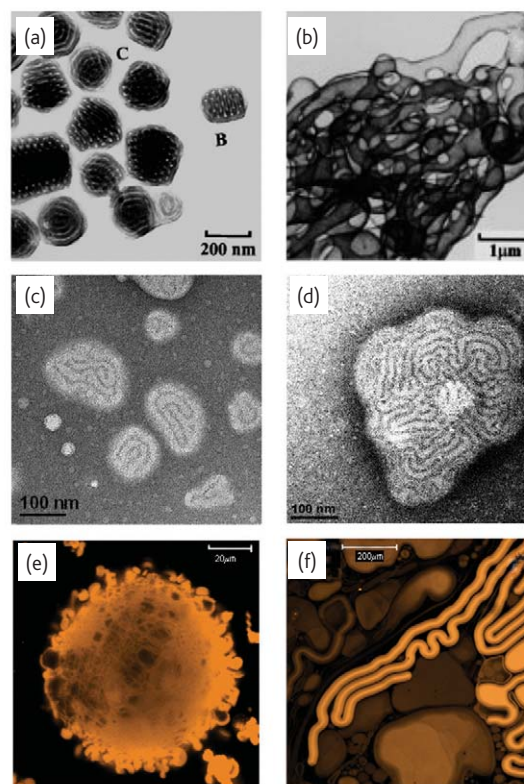


Fig. 4 (a) and (b) Transmission electron micrographs (TEM) of mesosize aggregates with regular hollow internal structures made from a 2 wt% solution of PS(410)-*b*-PAA(13) in DMF/H<sub>2</sub>O mixture<sup>63</sup>. (c) and (d) TEM of lamellarsomes produced by membrane-forming copolymers in water<sup>64</sup>. (e) and (f) Confocal laser scanning micrographs of a myelin-like structures produced by a membrane-forming copolymer in water and stabilized by chloroform<sup>65</sup>. (Reproduced with permission from<sup>63–65</sup>. © 1997 American Physical Society; 2007 Royal Society of Chemistry; and 2006 Wiley-VCH.)

Because of these slow kinetics, metastable or intermediate phases have longer lifetimes. Eisenberg and colleagues<sup>61,62</sup> reported a zoo of morphologies in their original work on block copolymer assembly in water. In a later work they also reported the formation of mesosize aggregates with regular hollow internal structures made from a 2 wt% solution of poly(styrene)<sub>410</sub>-*b*-poly(acrylic acid)<sub>13</sub>, commonly known as PS(410)-*b*-PAA(13), where 410 and 13 denote the number of monomers in the polymer chain, in DMF/H<sub>2</sub>O mixture<sup>63</sup> (Fig. 4a and 4b). We have recently demonstrated that long-range ordered mesophases can be dispersed into nanometer-sized particles by fast dissolution of membrane-forming copolymers in water<sup>64</sup> (Fig. 4c and 4d). Similarly, we have demonstrated that by playing with the copolymer-solvent interface, membrane-forming copolymers can self-assemble into long tubular structures with ordered internal structures<sup>65</sup> (Fig. 4e and 4f).

## Biomedical applications

Undoubtedly, the ability to generate nanoparticles and nanostructures in solution and particularly in aqueous solution can be of tremendous

benefit for biomedical applications such as therapeutics delivery, tissue engineering, and medical imaging.

In the late 1980s, hydrogels formed by the assembly of block copolymers in water were intensively studied for controlled release applications<sup>66</sup>. The complex mesophase structures formed by the copolymers are ideal for encapsulating and releasing several therapeutic agents in a controlled fashion. In addition, the temperature sensitivity of poly(ethylene oxide) (PEO)-based systems makes these materials very appealing for injectable controlled release systems<sup>67–69</sup>. This has now expanded into a series of block copolymer-based hydrogels that are rapidly finding applications as functional scaffolds for tissue engineering<sup>70–72</sup>. Recently, the self-assembling motif has been exploited for the design of peptide copolymers which form very long cylindrical micelles that mimic the extracellular matrix<sup>73–76</sup>.

Similarly, the size of block copolymer micelles and vesicles makes them ideal for therapeutics delivery. Nanoparticles greater than 200 nm in diameter are highly susceptible to opsonization and subsequent phagocytosis by the cells of the immune system<sup>77</sup>. However, particles should also be large enough to avoid excretion via the kidneys. The nanosized dimensions of block copolymer vesicles and micelles provide the advantage of allowing application to the body via direct injection into the blood circulation. Furthermore, the size of micelles and vesicles<sup>78</sup> allows their efficient accumulation in solid tumors via the enhanced permeability and retention (EPR) effect<sup>79–81</sup>. In addition, there are numerous examples in the literature of the application of amphiphiles to increase the solubility of hydrophobic therapeutic agents, and their subsequent use in drug delivery studies<sup>82</sup>. This can be expanded to hydrophilic therapeutic agents by using vesicles as they are able to enclose aqueous volumes within their structure, allowing encapsulation of both hydrophilic molecules within their aqueous core and hydrophobic molecules within the membrane<sup>83,84</sup>.

Compared with small amphiphiles, block copolymers offer the advantages of targeting a wider range of compositions and especially molecular weights. Indeed, by varying the copolymer size, we can adjust the size, mechanical properties, and release ability<sup>85,86</sup>. It is also important to mention that the CACs of amphiphilic copolymers are very low and, in some cases, essentially zero. Thus copolymers have very slow chain exchange dynamics and assemble into locally isolated, non-ergodic structures<sup>26,87</sup>. In an ergodic system there is an equilibrium between molecules in the assembled structure and molecules in solution, but with block copolymers the molecules are essentially locked in the structure, making them non-ergodic. Such slow dissociation rates enable vesicles and micelles to retain their payloads for very long time periods<sup>85</sup>. Furthermore, the absence of molecularly dissolved amphiphilic copolymers in solution prevents cytotoxic interactions with biological phospholipid membranes. These can range from complete cellular membrane dissolution (and hence cell death) in the case of small-molecule surfactants<sup>88</sup>

to up-regulation of gene expression and altered cell genetic responses<sup>89</sup>.

The synthetic nature of copolymers also allows the design of interfaces containing various biochemically active functional groups. Several examples of ligand-decorated micelles<sup>90–92</sup> and vesicles<sup>93,94</sup> have been reported for targeted delivery applications. In particular, the nonfouling and nonantigenic properties<sup>95,96</sup> of PEO, and more recently<sup>97,98</sup>, of poly(2-(methacryloyloxy)ethyl phosphorylcholine) (PMPC) have been combined with hydrophobic polymers in the design of biocompatible nanocarriers. The neutral, and yet very hydrophilic nature of these polymers, permits the design of dense corona with the ability to stabilize either micelles or vesicles that have very limited interactions with proteins and particularly, plasma proteins<sup>96</sup>. Consequently, micelles and vesicles will exhibit very long circulation times *in vivo*<sup>99–101</sup>. Particularly remarkable are the data recently reported by Geng *et al.*<sup>99</sup> showing that PEO-based wormlike copolymer micelles can have circulation times as long as several weeks<sup>102</sup>. As well as the soluble corona, the insoluble domains can also be engineered so as to exploit the sensitivity of specific hydrophobic polymers to external stimuli such as pH<sup>91,103–105</sup>, oxidative species<sup>106</sup>, temperature<sup>107,108</sup>, and hydrolytic degradation<sup>102,109–111</sup>. Block copolymer micelles and vesicles are therefore finding applications for the delivery of anticancer drugs<sup>90,91,102,109,110,112</sup> and as contrast agents for medical imaging<sup>99,113</sup>.

Recently, we also reported the use of pH-sensitive block copolymer vesicles that achieve high transfection efficiency, exploiting the pH driven transition from vesicles to DNA-complexes<sup>114,115</sup>. It is not only amphiphilic polymers that can assemble into micelles but, in an aqueous environment, *cis*-platin and poly(ethylene oxide)-*b*-poly( $R,\alpha$ -aspartic acid) (PEO-PAA) block copolymers self-assemble into polymer-metal complex micelles<sup>116</sup>. The same concept is repeated in polyion complex micelles, where ionic and nonionic blocks play a crucial role for the final encapsulation and delivery of biological macromolecules such as DNA<sup>117–121</sup>.

## Nanocomposites

The ability of block copolymers to form well-defined nanostructures has been exploited in the generation of nanocomposites by combining the copolymers with other nanoparticles that would not normally form nanostructures<sup>122,123</sup>, for example silica<sup>124,125</sup>, metals<sup>126</sup>, or proteins<sup>125</sup>. This allows the controlled preparation of multifunctional materials with customized properties, such as catalytic activity, optoelectrical, and magnetic properties. Recently the combination of nanoscopic clay with polyurethane in a selective solvent condition has led to the development of a high performance elastomer<sup>127</sup>.

As well as nanotemplating, block copolymer structures have been observed to act as toughening agents when they assemble in thermosets<sup>128–130</sup>. The modified thermosets experience an improvement in their mechanical properties because of toughening.

This depends on the morphology adopted by the copolymers<sup>131–134</sup>. Over moderate-to-high polymer concentrations the system behaves as expected for block copolymers placed in a solvent that is selective for one block<sup>135</sup>.

The formation of nanostructured systems in cured blends of epoxy resin and a diblock copolymer was first reported by Hillmyer *et al.* in 1997<sup>136</sup>. Since that initial report, extensive investigation has been carried out by numerous research groups into epoxy/block copolymer blend systems. Two types of copolymers have been studied: unreactive and reactive modifiers. In the unreactive case, the nanoscale structures are formed in solution and fixed during cure. In this way a block copolymer self-assembles in the pre-cure stage via a block copolymer core (resinophobe) and a corona (resinophile) that are immiscible and miscible with the resin, respectively. As with block copolymers in aqueous solution, the self assembly in the pre-cured phase yields morphologies such as micelles and vesicles. The polymerization of the resin (typically an epoxy resin but the principles apply universally) causes the high molecular weight cross-linking mixture to become a poorer solvent. This can cause macrophase separation or a change in the particle morphology. If the solubilities are selected correctly, then the crosslinking of the resin causes debonding between the micelles and thermoset and this yields optimum toughness.

In the reactive scenario the epoxy miscible block is reactive towards the resin or the curing agent. Chemical linking through reactive corona molecules only increases the toughness of the materials if they remain brittle; that is, they have not reached a sufficiently high number density. Dean *et al.*<sup>132</sup> studied the effect of poly(ethylene oxide)-*b*-poly(ethylene-*alt*-propylene), PEO-PEP block copolymers at low concentration on a Bisphenol A diglycidyl ether (BADGE) resin cured with methylene dianiline MDA. Spherical micelles were found to improve fracture toughness  $K_{Ic}$  by 25–35%. A vesicular morphology increased  $K_{Ic}$  by 45% even at half the concentration of the micelle forming systems. In a further paper<sup>131</sup> unreactive poly(ethylene oxide)-*b*-poly(butadiene) PEO-PB copolymers are compared with epoxidised poly(isoprene)-*b*-poly(butadiene) ePI-PB and polymers with a reactive poly(methylacrylate-*co*-glycidyl methacrylate) P(MA-*co*-GMA) epoxy miscible block. The ePI-PB and reactive epoxy miscible P(MA-*co*-GMA) block copolymers form nanoscale structures which are chemically bonded to the resin after and before gelation of the epoxy resin, respectively. Once more, vesicles are the best at improving fracture mechanics. The vesicles in which the resinophilic block reacts with the resin after gelation provide higher toughness than unreactive vesicles. Differing findings have been obtained in a study using PEO-PEP and reactive block copolymers in partially brominated BADGE resins cured with phenol novolac<sup>133</sup>. Spherical micelles were found to give considerably superior improvements in toughness than vesicles. Even greater enhancement has been found when wormlike micelles form (~ 4x improvement in  $K_{Ic}$ ; ~ 3x with spherical micelles). Wu *et al.*<sup>137</sup> observed similar behavior when they

studied PEO-PBO diblock copolymers in non-brominated BADGE + phenol novolac. Again, wormlike micelles show the greatest improvement in  $K_{Ic}$  (~ 4x), followed by spherical micelles (~ 2.5x) and vesicles (~ 1.8x). It is suggested that the toughening observed with micelles may be due to cavitation processes. With wormlike micelles, scanning electron microscopy (SEM) indicates that worms bridging the crack are 'pulled-out'.

## Nanoporous membranes

Materials engineered with well-defined porosity and surface properties are essential as they find use in applications such as separation catalysis, water purification, and fuel cell technology. Block copolymer mesophases, such as hexagonally packed cylinders and bicontinuous structures, provide selective transport channels of defined size. Hillmyer and colleagues<sup>138</sup> have shown that diblock copolymers which comprise a nondegradable block (matrix) such as polystyrene (PS) and a chemically-etchable block such as poly(lactic acid) (PLA) can be used to generate nanoporous materials upon removal of the sacrificial component. Upon chemical etching, provided that the PLA assemble into cylinders within a continuous PS phase, the final structures will have high porosity with the potential to align the cylinders/pores using an external field. Furthermore, the nanochannels formed by the PLA can be also be functionalized with specific groups either by mixing the PS-PLA copolymers with a fully inert copolymer such as PS-PEO<sup>139</sup> or even more efficiently by forming a ABC copolymer where the C block is the sacrificial component<sup>140</sup>. By doing so, the surface chemistry of the channel can be effectively controlled by the B block. Similarly, Mayes and colleagues<sup>141,142</sup> have reported a thin film membrane made of a poly(vinylidene fluoride) (PVDF) backbone and poly(oxyethylene methacrylate) (POEM) side chains. These copolymers assemble into bicontinuous phases that can selectively separate small molecules. Here, however, effective separation demands materials with few imperfections in the assembly, and often, time-consuming steps are required in order to achieve sufficient long-range order. Recently, the combination of industrially well-established membrane formation methods with the self-assembly of a block copolymer has led to the development of well-organized asymmetric membranes exploiting the natural de-wetting of copolymers at the air-liquid interface<sup>143</sup>.

More examples of block copolymer membranes are finding applications in fuel technology<sup>144,145</sup>. Fuel cells require the use of membranes with high and low permeability to protons and water, respectively. The potential ability to modify block copolymer membranes almost infinitely to give the desired characteristics makes them especially suitable for this use.

## Conclusions and future directions

Research into block copolymer nanoparticles and nanostructures is a relatively new area, but has created a vast amount of interest due to their versatility. Block copolymer nanoparticles and

nanostructures have become so popular because their size, structure, properties, and surface chemistry can all be designed to suit the intended purpose.


The ability to generate compartmentalized volumes at the nanometer level is one of the fundamental motifs used by cells in synthesizing biomolecules and performing the biochemical processes necessary for their function. This motif has been recently reassembled using block copolymer micelles and vesicles as nanoreactors<sup>146</sup>.

Nanoreactors have been prepared by the incorporation of a channel protein into the membrane of block copolymer vesicles<sup>147–149</sup>. Similarly Montemagno and colleagues<sup>150–152</sup> have reported the design of hybrid nanoreactors that comprise membrane proteins stabilized with block copolymer membrane for energy conversion applications. Recently, Vriezema *et al.*<sup>153</sup> have demonstrated that block copolymer vesicles containing enzymes can be used to perform one-pot multi step reactions. Block copolymer vesicles containing enzymes, one in the aqueous inner compartment and one in the bilayer, have also been used for enzymatic ring-opening polymerization of lactones in water<sup>145</sup>.

It has been shown that this approach can be readily expanded into nonaqueous solvent. In particular, the recent reports of block

copolymer nanostructures in ionic liquid<sup>154</sup> and the ability of micelles to shuttle from an aqueous solvent to an ionic liquid as a function of temperature<sup>155</sup>, link block copolymer technology with more sophisticated synthetic routes.

Block copolymer structures can also be used to mimic the ability of biomolecules to convert chemical energy into mechanical energy. Howse *et al.*<sup>156</sup> have demonstrated that an ABA copolymer, where the B block is pH sensitive, assembles into cubic micellar phases whose d-spacing and hence, the size of the whole gel can be tuned by a chemical oscillator. More recently Topham *et al.*<sup>157</sup> exploited phase separation in a pH sensitive triblock copolymer to create an antagonistic swelling gel. Powered by pH oscillations, this system uses a poly(acid) gel attached to a poly(base) gel where as one swells the other contracts, creating a force in the same fashion that muscles work antagonistically in the body<sup>158</sup>.

Possible applications for the block copolymer nanostructures encompass many areas, from delivery vectors, tissue engineering scaffolds, artificial muscles and nanoreactors, to fuel cells and water purification systems. However, despite all the research conducted so far, there is still a great deal left to explore, with the only limitation being our creativity. 

## REFERENCES

- Hawker, C. J., and Wooley, K. L. *Science* (2005) **309**, 1200
- Beylen, M. V., *et al.*, *Adv. Polym. Sci.* (1988) 86
- Matyjaszewski, K., and Spanswick, J., *Materials. Today* (2005) **8**, (3), 26
- Leibler, L., *Macromolecules* (1980) **13**, 1602
- Bates, F. S., and Fredrickson, G. H. *Annu. Rev. Phys. Chem.* (1990) **41**, 525
- Hamley, I. W., *The Physics of Block Copolymers*. Oxford University Press: Oxford, (1998)
- Hamley, I. W., *Developments in Block Copolymer Science and Technology*. John Wiley and Sons: (2004) 380
- Klok, H.-A., and Lecommandoux, S., *Adv. Mater.* (2001) **13**, 1217
- Förster, S., and Plantenberg, T. *Angew. Chem. Int. Ed* (2002) **41**, 688
- Ruzette, A.-V., and Leibler, L., *Nat. Mater.* (2005) **4**, 19
- Tanford, C., *Hydrophobic Effect: Formation of Micelles and Biological Membranes*. 1st ed.; John Wiley & Sons Inc: (1973) 208
- Meyer, E. E., *et al.*, *Proc. Natl. Acad. Sci. USA* (2006) **103**, 15739
- Pratt, L. R., *Theory of Hydrophobic Effects*, (1985) 433
- Israelachvili, J. N., *Intermolecular & Surface Forces*. 9th ed.; Elsevier Science Imprint: London, (2002) 450
- Israelachvili, J. N., *et al.*, *J. Chem. Soc. Faraday Trans. 1* (1975) **72**, 1525
- Israelachvili, J. N., *et al.*, *Biochim. Biophys. Acta* (1977), **470**, 185
- Paschalis, A., and Bjorn, L., *Amphiphilic Block Copolymers: Self-Assembly and Applications*; Elsevier, (2000)
- Alexandridis, P., and Spontak, R. J., *Curr. Opin. Colloid In.* (1999) **4**, 130
- Nagarajan, R., Ganesh, K. J. *Chem. Phys.* (1989) **90**, 5843
- Nagarajan, R., *Langmuir* (2002) **18**, 31
- Bourov, G. K., and Bhattacharya, A., *J. Chem. Phys.* (2007) **127**, 24
- Jones, R. A. L., *Soft Condensed Matter*. Oxford University Press, Oxford, (2004)
- Castelletto, V., *et al.*, *Langmuir* (2007) **23**, 6896
- Won, Y.-Y., *et al.*, *Science* (1999) **283**, 960
- Jain, S., and Bates, F. S., *Science* (2003) **300**, 460
- Jain, S., and Bates, F. S., *Macromolecules* (2003) **37**, 1511
- Förster, S., *et al.*, *J. Phys. Chem. B* (1999) **103**, 6657
- Pochan, D. J., *et al.*, *Science* (2004) **306**, 94
- Cui, H., *et al.*, *Science* (2007) **317**, 647
- Cui, H., *et al.*, *Macromolecules* (2006) **39**, 6599
- Zhong, S., *et al.*, *Soft Matter* (2008) **4**, 90
- Erhardt, R., *et al.*, *J. Am. Chem. Soc.* (2003) **125**, 3260
- Butun, V., *et al.*, *Macromolecules* (2000) **33**, 1
- Ritzenthaler, S., *et al.*, *Macromolecules* (2003) **36**, 118
- Liu, Y., *et al.*, *Macromolecules* (2003) **36**, 7894
- Stewart, S., and Liu, G., *Angew. Chem. Int. Ed.* (2000) **39**, 340
- Stoenescu, R., *et al.*, *Macromol. Biosci.* (2004) **4**, 930
- Li, Z., *et al.*, *Nano Lett.* (2006) **6**, 1245
- Battaglia, G., and Ryan, A. J., *J. Am. Chem. Soc.* (2005) **127**, 8757
- Napoli, A., *et al.*, *Langmuir* (2002) **18**, 8324
- Sommerdijk, N. A. J. M., *et al.*, *Macromolecules* (2000) **33**, 8289
- Read, E. S., and Armes, S. P., *Chem. Commun.* (2007) 3021
- Zhu, J., and Jiang, W., *Macromolecules* (2005) **38**, 9315
- Walther, A., and Muller, A. H. E., *Soft Matter* (2008) **4**, 663
- Erhardt, R., *et al.*, *Macromolecules* (2001) **34**, 1069
- Ma, Q., *et al.*, *Proc. Natl. Acad. Sci.* (2002) **99**, 5058
- Ritzenthaler, S., *et al.*, *Macromolecules* (2002) **35**, 6245
- Li, Z., *et al.*, *Science* (2004) **306**, 98
- Brannan, A. K., Bates, F. S., *Macromolecules* (2004) **37**, 8816
- Malmsten, M., and Lindman, B., *Macromolecules* (1992) **25**, 5440



51. Jain, S., et al., *Phys. Rev. Lett.* (2006) **96**, 138304
52. Lipic, P. M., et al., *J. Am. Chem. Soc.* (1998) **120**, 8963
53. Förster, S., et al., *Macromolecules* (2001) **34**, 4610
54. Hillmyer, M. A., et al., *J. Am. Chem. Soc.* (1997) **119**, 2749
55. Battaglia, G., and Ryan, A. J., *Nat. Mater.* (2005) **4**, 869
56. Battaglia, G., and Ryan, A. J., *Macromolecules* (2006) **39**, 798
57. Bermudez, H., et al., *Macromolecules* (2002) **35**, 8203
58. Förster, S., et al., *Nat. Mater.* (2007) **6**, 888
59. Liu, T., et al., *Prog. Polym. Sci.* (2003) **28**, 5
60. Battaglia, G., and Ryan, A. J., *J. Phys. Chem. B* (2006) **110**, 10272
61. Zhang, L., and Eisenberg, A., *Science* (1995) **268**, 1728
62. Zhang, L., et al., *Science* (1996) **272**, 1777
63. Zhang, L., et al., *Phys. Rev. Lett.* (1997) **79**, 5034
64. Battaglia, G., et al., *Soft Matter* (2007) **1**, 470
65. Battaglia, G., and Ryan, A. J., *Angew. Chem. Int. Ed.* (2007) **45**, 2052
66. Schmolka, R., Poloxamers in the Pharmaceutical Industry. In *Polymers for Controlled Drug Delivery*, Tarcha, P. J., (ed.) CRC Press, (1991) 189
67. Jeong, B., et al., *Adv. Drug Deliv. Rev.* (2002) **54**, 37
68. Jeong, B., et al., *Nature* (1997) **388**, 860
69. Bae, Y. H., et al., *Macromol. Chem. Rapid Commun.* (1987) **8**, 481
70. Drury, J. L., and Mooney, D. J., *Biomaterials* (2003) **24**, 4337
71. Mann, B., *Clin. Plastic Surg.* (2003) **30**, 601
72. Saito, N., et al., *Nature Biotech.* (2001) **19**, 332
73. Hartgerink, J. D., et al., *Science* (2001) **294**, 1684
74. Hartgerink, J. D., et al., *Proc. Natl. Acad. Sci.* (2002) **99**, 5133.
75. Hwang, J. J., et al., *Proc. Natl. Acad. Sci.* (2002) **99**, 9662
76. Beniash, E., et al., *Acta Biomaterialia* (2005) **1**, 387
77. Letchford, K., and Burt, H., *Eur. J. Pharm. and Biopharm.* (2007) **65**, 259
78. Torchilin, V. P., *Annu. Rev. Biomed. Eng.* (2006) **8**, 343
79. Maeda, H., et al., *J. Controlled Release* (2000) **65**, 271
80. Matsumura, Y., and Maeda, H., *Cancer Res.* (1986) **46**, 6387
81. Kataoka, K., et al., *Adv. Drug Deliv. Rev.* (2001) **47**, 113
82. Lawrence, M. J., *Chem. Soc. Rev.* (1994) **23**, 417
83. Uchegbu, I. F., and Vyas, S. P., *Int. J. Pharm.* (1998) **172**, 33
84. Lasic, D. D., and Papahadjopoulos, D., *Medical Applications of Liposomes*, Elsevier, (1998) 794
85. Battaglia, G., et al., *Langmuir* (2006) **22**, 4910
86. Discher, B. M., et al., *Science* (1999) **284**, 1143
87. Won, Y.-Y., et al., *Macromolecules* (2003) **36**, 953
88. Xia, W. J., and Onyuksel, H., *Pharm. Res.* (2000) **17**, 612
89. Kabanov, A. V., et al., *Control. Release* (2005) **101**, 259
90. Torchilin, V. P., et al., *Proc. Natl. Acad. Sci.* (2003) **100**, 6039
91. Licciardi, M., et al., *Polymer* (2006) **47**, 2946
92. Dalhaimer, P., et al., *Biomacromolecules* (2004) **5**, 1714
93. Lin, J. J., et al., *Langmuir* (2006) **22**, 3975
94. Broz, P., et al., *J. Controlled Release* (2005) **102**, 475
95. Alcantar, N. A., et al., *J. Biomed. Mater. Res.* (2000) **51**, 343
96. Vonarbourg, A., et al., *Biomaterials* (2006) **27**, 4356
97. Chen, S., et al., *J. Am. Chem. Soc.* (2005) **127**, 14473
98. Lewis, A. L., *J. Colloids Surf. B* (2000) **18**, 261
99. Torchilin, V. P., *Adv. Drug Deliv. Rev.* (2002) **54**, 235
100. Photos, P. J., et al., *J. Controlled Release* (2003) **90**, 323
101. Kwon, G. S., and Kataoka, K., *Adv. Drug Deliv. Rev.* (1995) **16**, 295
102. Geng, Y., et al., *Nature Nanotech.* (2007) **2**, 249
103. Du, J., et al., *J. Am. Chem. Soc.* (2005) **127**, 17982
104. Giacomelli, C., et al., *Biomacromolecules* (2006) **7**, 817
105. Borchert, U., et al., *Langmuir* (2006) **22**, 5843
106. Napoli, A., et al., *Nature Mat.* (2004) **3**, 183
107. Qin, S., et al., *Adv. Mat.* (2004) **18**, 2905
108. Topp, M. D. C., et al., *Macromolecules* (1997) **30**, 8518
109. Gaucher, G., et al., *J. Control. Release* (2005) **109**, 169
110. Ahmed, F., and Discher, D. E. J., *Control. Release* (2004) **96**, 37
111. Jeonga, B., et al., *J. Control. Release* (1999) **62**, 109
112. Ahmed, F., et al., *Mol. Pharm.* (2006) **3**, 340
113. Ghoroghchian, P. P., et al., *Proc. Natl. Acad. Sci. USA* (2005) **102**, 2922
114. Lomas, H. et al., *Adv. Mater.* (2007) **19**, 4238
115. Lomas, H., et al., *Faraday Discuss.* (2008) in press
116. Nishiyama, N., et al., *Cancer Res.* (2003) **63**, 8977
117. Chim, Y. T. A., et al., *Langmuir* (2005) **21**, 3591
118. Lam, J. K. W., et al., *Control. Release* (2004) **100**, 293
119. Licciardi, M., et al., *Biomacromolecules* (2005) **6**, 1085
120. Toncheva, V., et al., *Biochim. Biophys. Acta* (1998) **1380**, 354
121. Kakizawa, Y., and Kataoka, K., *Adv. Drug Deliv. Rev.* (2002) **54**, 203
122. Förster, S., and Antonietti, M., *Adv. Mater.* (1999) **10**, 195
123. Haryono, A., and Binder, W. H., *Small* (2006) **2**, 600
124. Finnefrock, A. C., et al., *J. Am. Chem. Soc.* (2003) **125**, 13084
125. Pozzo, D. C., and Walker, L. M., *Macromolecules* (2007) **40**, 5801
126. Ciebien, J. F., et al., *New J. Chem.* (1998) **22**, 685
127. Liff, S. M., et al., *Nat. Mater.* (2007) **6**, 76
128. Guo, Q., et al., *J. Polym. Sci. Part B: Polym. Phys.* (2003) **41**, 1994
129. Hadjichristidis, N., et al., *Block Copolymers : Synthetic Strategies, Physical Properties, and Applications*, Wiley, New York, (2003)
130. Grubbs, R. B., et al., *Macromolecules* (2000) **33**, 9522
131. Dean, J. M., et al., *J. Polym. Sci., Part B: Polym. Phys.* (2003) **41**, 2444
132. Dean, J. M., et al., *J. Polym. Sci., Part B: Polymer Physics* (2001) **39**, 2996
133. Dean, J. M., et al., *Macromolecules* (2003) **36**, 9267
134. Discher, D. E., Eisenberg, A., *Science* (2002) **297**, 967
135. Alexandridis, P., and Lindman, B. R., *Amphiphilic Block Copolymers : Self-Assembly and Applications*, Elsevier, (2000) 435
136. Hillmyer, M. A., et al., *J. Am. Chem. Soc.* (1997) **119**, 2749
137. Wu, J., et al., *J. Polym. Sci. Part B: Polym Phys* (2005) **43**, 1950
138. Chen, L., et al., *J. Am. Chem. Soc.* (2007) **129**, 13786
139. Mao, H., et al., *Faraday Discuss.* (2005) **128**, 149
140. Rzaev, J., and Hillmyer, M. A., *J. Am. Chem. Soc.* (2005) **127**, 13373
141. Asatekin, A., et al., *M. J. Membrane Sci.* (2006) **285**, 81
142. Akthakul, A., et al., *Macromolecules* (2004) **37**, 7663
143. Peinemann, K.-V., et al., *Nat. Mater.* (2007) **6**, 992
144. Cho, C. G., et al., *J. Membr. Sci.* (2008) **308**, 96
145. Feng, S. G., et al., *Progr. Chem.* (2008) **20**, 117
146. Vriezema, D. M., et al., *Chem. Rev.* (2005) **36**, 1445
147. Nardin, C., et al., *Chem. Commun.* (2000) 1433
148. Sauer, M., et al., *Chem. Commun.* (2001) 2452
149. Stoianescu, R., and Meier, W., *Chem. Commun.* (2002) **24**, 3016
150. Choi, H.-J., et al., *Nanotechnology* (2005) **16**, S143
151. Ho, D., et al., *Nanotechnology* (2005) **16**, 3120
152. Choi, H.-J. and Montemagno, C. D., *Nano Lett.* (2005) **5**, 2538
153. Vriezema, D. M., et al., *Angew. Chem. Int. Ed* (2007) **46**, 7378
154. He, Y., et al., *J. Am. Chem. Soc.* (2006) **128**, 2745
155. He, Y., and Lodge, T. P. J., *Am. Chem. Soc.* (2006) **128**, 12666
156. Howse, J. R., et al., *Nano Lett.* (2007) **6**, 73
157. Topham, P. D., et al., *Macromolecules* (2007) **40**, 4393
158. Mirfakhrai, T., et al., *Materials Today* (2007) **10**, (4), 30