

Self-Assembly of Amphiphilic Block Copolymers in Selective Solvents

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Abstract For the last decades, amphiphilic block copolymers have been at the focus of extensive scientific interest, due to their unique properties and numerous potential applications. Their technological potential evolves from their ability to self-assemble into a plethora of morphologically diverse nanostructures such as micelles, polymersomes, cylinders and others. In this chapter, we discuss the basic principles governing amphiphilic block copolymer self-organisation in solutions and the variety of morphologies observed so far, as well as the experimental techniques available for characterising such nanostructures. Some representative examples of self-assembly from nonionic and ionic amphiphilic block copolymers of different macromolecular architectures are also presented.

Keywords Amphiphilic block copolymer • Nanostructures • Micelles • Polymersomes • Morphology • Macromolecular architecture

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Abbreviations

AFM	Atomic force microscopy
AUC	Analytical ultracentrifugation
cmc	Critical micelle concentration
(cryo-)TEM	(cryogenic) Transmission electron microscopy
DLS	Dynamic light scattering
DMF	Dimethylformamide
NMR	Nuclear magnetic resonance
P2VP	Poly(2-vinylpyridine)
P4VP	Poly(4-vinylpyridine)
P4VPDecI	Poly(4-vinylpyridine decyliodide)
P4VPMel	Poly(4-vinylpyridine methyl iodide)
PAA	Poly(acrylic acid)
PAI	Poly(5-(<i>NN</i> -diethylaminoisoprene))
PBD	Polybutadiene
PBO	Poly(butylene oxide)
PCL	Poly(ϵ -caprolactone)
PDEAEMA	Poly(<i>N,N</i> -diethylaminoethyl methacrylate)
PDMAEMA	Poly(<i>N,N</i> -dimethylaminoethyl methacrylate)
PDMS	Poly(dimethylsiloxane)
PEE	Poly(ethylethylene)
PEG	Poly(ethylene glycol)
PEHA	Poly(2-ethylhexyl acrylate)
PEO	Poly(ethylene oxide)
PEP	Poly(ethylene- <i>alt</i> -propylene)
PSGMA	Poly(sulfonated glycidyl methacrylate)
PI	Polyisoprene
PIB	Poly(isobutylene)
PISC	Poly((sulfamate-carboxylate)isoprene)
PMA	Poly(methyl acrylate)
PMAA	Poly(methacrylic acid)
PMMA	Poly(methyl methacrylate)
PMOXA	Poly(2-methyloxazoline)
P _n BA	Poly(<i>n</i> -butyl acrylate)
P _n BMA	Poly(<i>n</i> -butyl methacrylate)
PPO	Poly(propylene oxide)
PS	Polystyrene
PSS	Poly(styrene sulfonate)
PSSH	Poly(styrene sulfonic acid)
PSSNa	Poly(sodium styrene sulfonate)
P _t BA	Poly(<i>tert</i> -butyl acrylate)
P _t BMA	Poly(<i>tert</i> -butyl methacrylate)
SANS	Small-angle neutron scattering

SAXS	Small-angle X-ray scattering
SEC	Size exclusion chromatography
SEM	Scanning electron microscopy
SLS	Static light scattering
THF	Tetrahydrofuran

1 Introduction

During the last decades, amphiphilic block copolymers have been at the focus of extensive scientific interest, both from an experimental and a theoretical point of view, owing to their unique properties and numerous potential applications involving medicine, biology, biomaterials, microelectronics, photoelectric materials, catalysts, etc. Their most important feature is the ability to self-assemble in solution giving rise to a plethora of resulting morphologies including spherical micelles, cylindrical micelles, lamellae and vesicles and bicontinuous structures, among others. A major contribution to this respect has been the recent development in the synthetic techniques, especially ionic and living radical polymerisation methods, which facilitate the preparation of block copolymers with well-defined compositions, molecular weights, and elaborate architectures. The growing range of available block copolymer architectures includes linear block copolymers, graft copolymers, dendritic polymers, starlike polymers, cyclic polymers and so on, which can self-organise into aggregates of diverse morphologies under certain conditions [1–3].

Among these, the most common and extensively studied systems are those of linear amphiphilic block copolymers which are generally defined as macromolecules consisting of two or more chemically distinct and frequently immiscible blocks linked together by covalent bonds. This immiscibility results in their self-assembly in solutions of a selective solvent of one of the blocks. In particular, when a block copolymer is dissolved in a liquid that is a thermodynamically good solvent for one block and at the same time a precipitant for the other, the copolymer chains associate reversibly thus forming micellar aggregates of nanoscopic dimensions and of various shapes, similar to those obtained from low molecular weight surfactants. The resulting micelles consist of a more or less swollen core of the insoluble blocks surrounded by a flexible corona of the soluble blocks. As far as the micellar morphology is concerned, when the soluble block is predominant, the insoluble block aggregates to form spherical micelles, while cylindrical micelles or vesicles are formed as the length of the soluble block decreases relatively to that of the insoluble block. Nevertheless, for a given copolymer, unusual micelles differing from the spherical morphology can be produced depending on the specific solution conditions [1–3].

As can be expected, the number of studies, both experimental and theoretical, on copolymer self-assembly is vast, and their results have been thoroughly reviewed by various authors including Price [4], Tuzar and Kratochvil [5], Webber et al. [6],

Hamley [7], Alexandridis and Lindman [8], Riess and co-workers [1, 9], Gohy [2], Quémener et al. [10] and Eisenberg et al. [3], to name but a few. In the following, we intend to present a brief overview on the main aspects of micelle formation and morphology, the experimental methods used for their characterisation, as well as theoretical and computer simulation predictions of their structural parameters. Furthermore, representative examples of the main classes of different amphiphilic copolymer-selective solvent systems will be presented, along with possible applications of such systems.

2 Amphiphilic Block Copolymer Micelles

2.1 General Features

It is well established that when an amphiphilic block copolymer is dissolved in a selective solvent at a fixed temperature, above a specific concentration called the critical micelle concentration (cmc), micellisation occurs. Below the cmc, only molecularly dissolved copolymer chains (unimers) are present in the solution, while above the cmc multimolecular micelles are in thermodynamic equilibrium with the unimers. This process is in analogy to classical low molecular weight surfactants, differing in that the cmc is much lower in the case of block copolymers macrosurfactants. The self-assembly arises from the need of the copolymer chains to minimise energetically unfavourable solvophobic interactions. Therefore, micelle formation is dictated by two opposite forces, the attractive force between the insoluble blocks, which leads to aggregation, and the repulsive one between the soluble blocks preventing unlimited growth of the micelle. At the same time, the interaction of the soluble blocks and the solvent is responsible for the stabilisation of the micelles [1, 10].

The morphology of the resulting micellar aggregates is primarily a result of the inherent molecular curvature arising from the relative sizes of the soluble and insoluble domains, and of the way, this influences the packing of the copolymer chains within the aggregates. The dimensionless packing parameter, p , can be used to define the relative size of the insoluble region of a copolymer. The balance between solvophobic and solvophilic interactions gives rise to an optimal surface area, a_0 , of the insoluble block at the interface between the soluble and insoluble blocks. This area together with the length, l_c , and the volume, v , of the insoluble block contributes to the packing parameter, which is defined as:

$$p = \frac{v}{a_0 l_c} \quad (1)$$

The packing parameter expresses the ratio of the insoluble chain molecular volume to the volume actually occupied by the copolymer in the assembly, thus usually dictating the most likely self-assembled morphology. As a general rule,

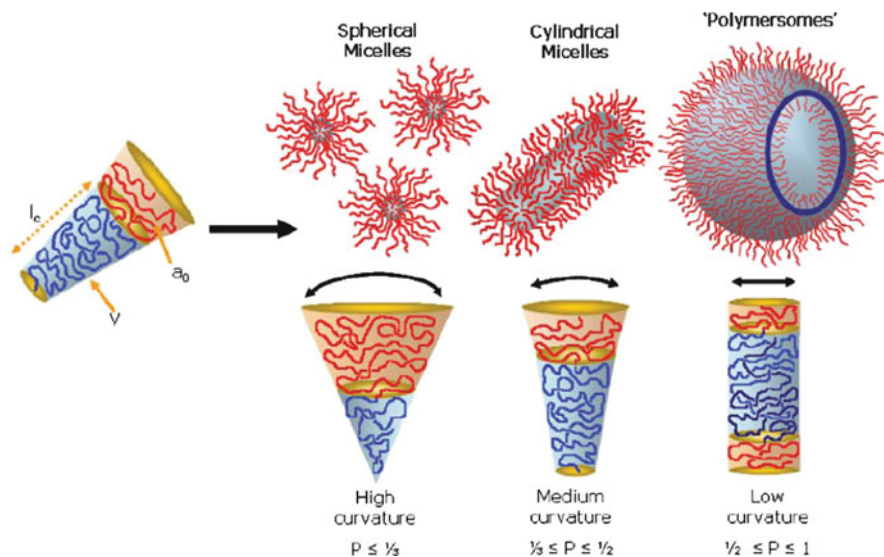


Fig. 1 Various self-assembled structures formed by amphiphilic block copolymers in a block-selective solvent. The type of structure formed is due to the inherent curvature of the molecule, which can be estimated through calculation of its dimensionless packing parameter, p . Reproduced with permission from [12]. Copyright (2009) WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

spherical micelles are formed when $p \leq 1/3$, cylindrical micelles are formed when $1/3 < p \leq 1/2$ and enclosed membrane structures (vesicles, a.k.a. polymersomes) arise when $1/2 \leq p \leq 1$ [11, 12], as depicted schematically in Fig. 1.

2.2 Micelle Preparation

The preparation of amphiphilic block copolymer micelles is usually achieved by one of the two following methods [1, 2, 5, 13]. The first method is the most straightforward way to prepare a block copolymer micellar solution and consists in the direct dissolution of the bulk sample in a selective solvent for one of the blocks. However, it should be noted that this method is generally suitable for block copolymers with relatively low molecular weight, M_w , and rather short length of the insoluble block. The solubility can be improved by a subsequent annealing processes of the solution such as standing, prolonged stirring, thermal or ultrasound treatments. The main disadvantage of these techniques is that depending on the block copolymer system, an equilibrium situation is not necessarily reached, especially when the insoluble, core-forming block is characterised by a high glass transition temperature (T_g), for example, PS. In this case, the so-called frozen micelles are formed, meaning that a unimer-micelle exchange does not take place

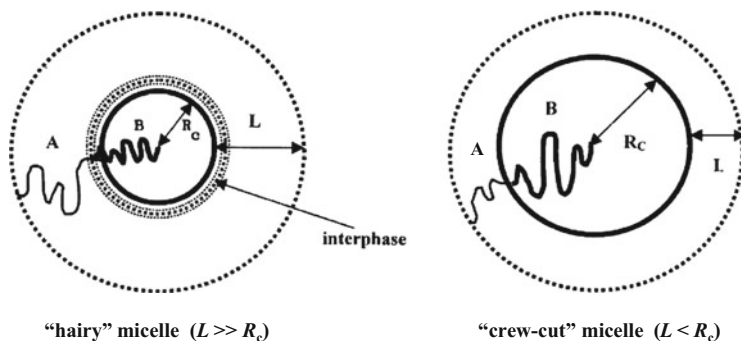


Fig. 2 Schematic representation of AB diblock copolymer micelles in a selective solvent of the A block. R_c , core radius; L , shell (corona) thickness. Adapted from [1]. Copyright (2003) Elsevier

in the solution. The features of these micelles usually depend on the two-phase morphology of the bulk block copolymer sample, as well as on the interactions of the selective solvent and the polymer microphases.

The second method is based on the dissolution of the copolymer in a nonselective solvent, i.e. a common good solvent for both blocks, thus forming molecularly dissolved chains. In order to induce micelle formation, the properties of the solvent are then changed, either by stepwise addition of a selective solvent for one block and precipitant for the other or by changing the temperature or pH of the solution, thus forming stimulus-responsive micelles. In the former case, the initial common solvent can be further eliminated by evaporation or gradually replaced by the selective solvent via a dialysis process. This technique is generally considered the preferred preparation method for micellar systems, mainly in aqueous solutions, since it prevents the formation of large aggregates and allows the formation of micelles from highly asymmetric block copolymers with a large insoluble block. However, it does not always avoid the production of “frozen micelles”, due to the formation of a glassy micellar core at a given temperature and/or at a specific common/selective solvent composition. Moreover, if the starting copolymer sample has a polydispersity in composition or M_w , the dialysis process can generate polydisperse micelles regarding to their characteristics.

2.3 Micellar Morphology

2.3.1 Spherical Micelles

The most abundant micellar morphology is that of spherical micelles [1, 10]. The self-assembly of a classical amphiphilic diblock copolymer AB (A and B denote the two different blocks) leads to two different micellar structures, depending on the relative length of the blocks. These two types of spherical micelles are schematically presented in Fig. 2. When the soluble block A is larger than the insoluble

block B, the resulting micelles consist of a small dense core and a very large corona, i.e. the core radius, R_c , is much smaller than the corona thickness, L . These micelles are usually called “hairy”, “starlike” or “core-shell” micelles. In the other extremity, if the insoluble block B is larger than the soluble block A, the micelles that are formed are characterised by a large dense core and a rather short highly stretched corona, with $L > R_c$, and the term “crew-cut” micelles is usually used to describe them.

Apart from the core radius and the corona thickness, other characteristic parameters of a micellar system are the aggregation number, N_{agg} , which denotes the average number of polymer chains in a micelle, the radius of gyration, R_g , and the hydrodynamic radius, R_h , of the micelle, as well as the distance between neighbouring blocks at the core/corona interface, called the grafting distance b , with b^2 expressing the area per corona chain on the core surface. These parameters are mainly controlled by the degree of polymerisation of the two blocks, N_A and N_B , and the Flory-Huggins interaction parameter χ . Moreover, the interfacial energy of the core/corona interface, the stretching energy of the block copolymer chains and the repulsion among coronal chains determine the total free energy of the micelle, which must be minimised in order to obtain an equilibrium micellar structure [2].

It is quite evident that both micellar structures can be obtained by the same amphiphilic diblock copolymer system only by changing the structural parameters of the AB copolymer. The relative lengths of the two blocks and the total M_w of the copolymer not only dictate the morphology of the resulting micelles (“hairy” vs. “crew-cut”) but also determine the rest of the micellar characteristics (N_{agg} , R_c , b , etc.). Numerous experimental studies have been dedicated to the investigation of this notion, and most typical examples of the studied diblock copolymer systems include PS-PEO, PS-PI, PS-PAA and PPO-PEO among others [1, 2, 10].

Spherical micelles can also result from the self-assembly of triblock copolymers of the ABA type. When these copolymers are dissolved in a selective solvent for the outer A blocks, they form “starlike” micelles, as seen in Fig. 3a. The situation is more complex for the micellisation of ABA copolymers in a selective solvent of the middle B block. If the concentration of the copolymer is low and/or the A blocks have a relatively small M_w , isolated “flower-like” micelles can be assembled, where the B block is looped and the A blocks participate in the same micellar core (Fig. 3b). However, an increase in the concentration of the copolymer or the M_w of the A blocks could lead to micelle association into larger aggregates due to partial conversion from loops to bridges, i.e. the A blocks of the copolymer chain can be located in two different micellar cores (Fig. 3c). Both theoretical [14] and experimental investigations of the self-assembly of ABA triblock copolymers have been carried out, e.g. studies on PAI-PS-PAI copolymers dissolved in DMF [15], as well as PBO-PEO-PBO in water [16, 17].

The introduction of a third block leads to another intriguing class of triblock copolymers that of the ABC type, since it can provide interesting new functionalities and higher diversity of micellar organisations. Depending on the selective solvent, one or two of the triblock copolymer blocks can be insoluble. In the first case, micelles with a compartmentalised corona are formed, while in the second

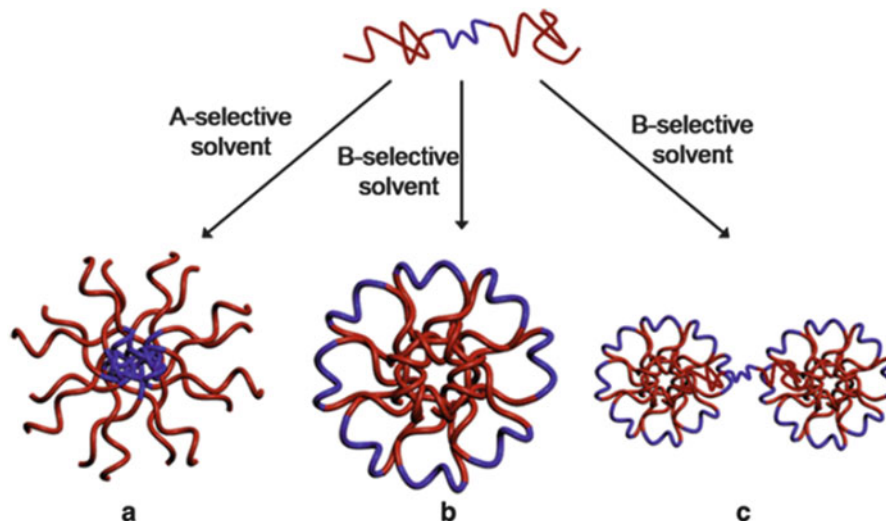


Fig. 3 Self-assembly of ABA triblock copolymers under different conditions. (a) “Starlike” micelles. (b) “Flower-like” micelles. (c) Micelle assembly. Reproduced with permission from [10]. Copyright (2011) Springer-Verlag

case, a compartmentalisation of the core is observed. More specifically, ABC copolymers in a selective solvent for the C block (or equivalently the A block) self-assemble into micelles where the first insoluble A block forms the core, the second insoluble B block is located around the core and the third soluble block C extends in the solution, thus forming the micellar corona. This type of micelles is called “onion”, “three-layer” or “core-shell-corona” micelles. When one of the three blocks is insoluble in the specific solvent, the block sequence, i.e. the copolymer architecture, influences the resulting micellar structure. If the insoluble block is located at one extremity of the triblock (A or C block), “core-shell-corona” micelles with a compartmentalised (two-layer) corona are assembled, while when the insoluble block is located between the two soluble ones (B block), “core-corona” micelles are formed. The latter can be further distinguished into two categories: micelles that have a mixed corona and micelles with a laterally compartmentalised corona known as “Janus” micelles. This segregation of the corona in “Janus” micelles usually occurs due to high incompatibility of the two soluble blocks. All the above-mentioned types of micelles are schematically presented in Fig. 4. Characteristic examples of ABC triblock copolymer micellar systems can be found in the review of Gohy et al. [18], including studies of PEHA-PMMA-PAA, PS-P2VP-PEO, PI-P2VP-PEO, PS-PMMA-PAA and so on triblock copolymers in various selective solvents.

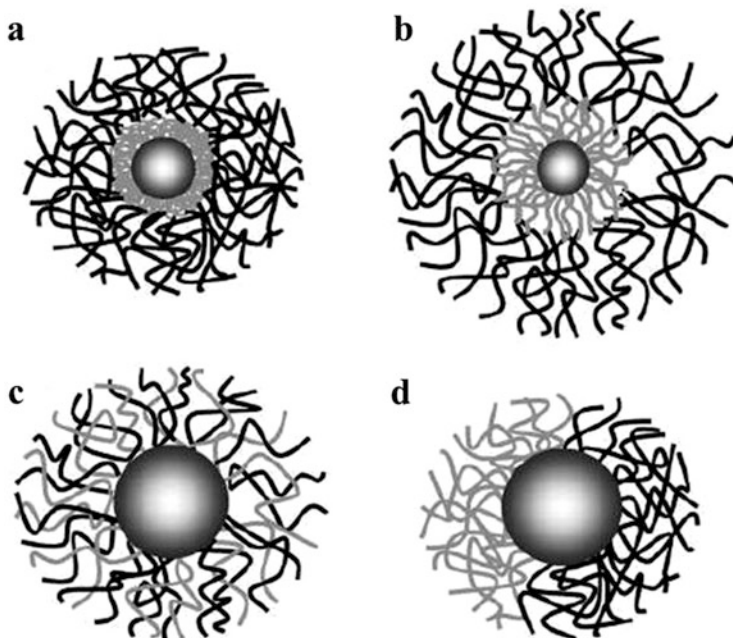


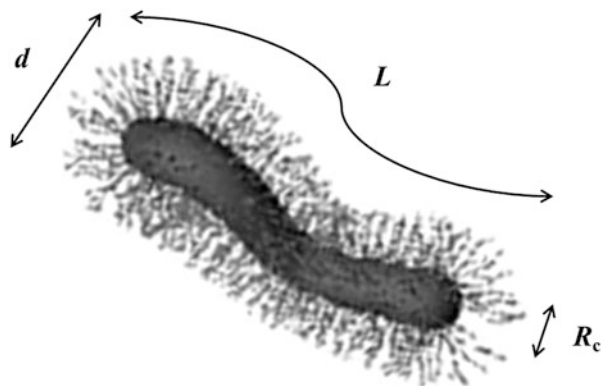
Fig. 4 Schematic representation of different types of micelles formed by ABC triblock copolymers. (a) “Core-shell-corona” micelles with insoluble core and shell, (b) “core-shell-corona” micelles with radially compartmentalised corona, (c) “core-corona” micelles with mixed corona and (d) “Janus” micelles with laterally compartmentalised corona. Adapted from [18]. Copyright (2005) Springer-Verlag

2.3.2 Cylindrical Micelles

The second of the three basic micellar morphologies is that of cylindrical micelles, which are often referred to as “worm-like”, “rod-like” or even “thread-like” micelles. The fact that this morphology corresponds to the smallest range of packing parameter values ($1/3 < p \leq 1/2$) explains why “worm-like” aggregates are less frequently observed, compared to spherical micelles and polymersomes [19]. A schematic representation of a “worm-like” micelle, along with its characteristic dimensions, i.e. total length L , overall diameter d and core radius R_c , is given in Fig. 5.

In general “worm-like” micelles are classical one-dimensional structures for which the length is several times greater than their cross-sectional diameter. However, they exhibit rich structural polymorphism, in the sense that they can be relatively short (finite length) or very long (reaching the micrometre length scale), while at the same time they can either be rigid or thin and flexible. Thus, relatively short and rigid micelles are usually termed as cylindrical or “rod-like”, whereas the ones that are long and thin are called “thread-like” micelles.

Fig. 5 Schematic representation of a “worm-like” micelle. The characteristic dimensions including total length L , overall diameter d and core radius R_c are shown. Reproduced in part with permission from [20]. Copyright (2003) The Royal Society of Chemistry



From an energetic point of view, infinitely long cylinders are more favourable than shortened cylinders with incorporated end defects, since these structures allow uniform curvature across the entire aggregate. Nevertheless, entropic demands and molecular frustration result in the formation of defects such as end caps and branch points, which are respectively more or less energetically favourable [12, 19, 21]. As a result, a great variety of cylindrical micellar morphologies have been observed, including giant [22] and short [23, 24] “worms”, y-junction and end cap defects [25, 26], networks [27, 28] or even toroidal/ring-shaped micelles [29–31], which result when cylindrical structures bend and close up their ends. From these studies, it is evident that all previously mentioned types of amphiphilic copolymers, AB, ABA and ABC, can self-assemble into “worm-like” aggregates, depending on their composition. Finally, because of the cylindrical shape, these micelles provide particularly interesting potential applications in nanotechnology and medicine. For example, a great enhancement of the toughness of epoxy resins was facilitated by the incorporation of PEO-PEP cylinders [32]. In the same manner, cylindrical micelles can orient and stretch in a flowing stream, a fact that makes them ideal for flow-intensive delivery applications such as phage-mimetic drug carriers and micropore delivery agents [33, 34].

2.3.3 Polymersomes

Polymer vesicles or polymersomes constitute an extremely interesting class of macromolecular self-assembly, and since their first observation 20 years ago [35], they have attracted a rapidly increasing degree of scientific attention. This is mainly because of their resemblance to natural cellular membranes, the ability to control their size along with their interactions with the environment, their tailorable membrane properties, as well as their versatile potential applications spanning from (bio-) electronics and catalysis to medical therapy. In the last decade, the

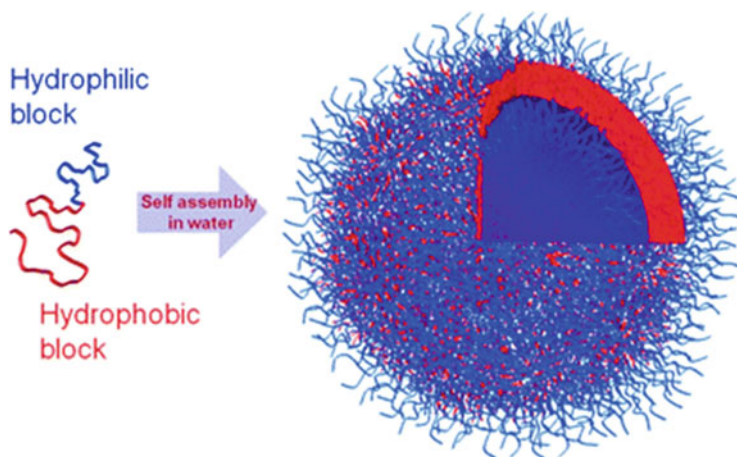


Fig. 6 Schematic representation of a polymer vesicle. Reproduced with permission from [43]. Copyright (2009) The Royal Society of Chemistry

number of studies in this field shows a substantial growth, and a significant amount of reviews on the subject is already available in the literature [12, 36–45].

As mentioned before, if the right hydrophobic/hydrophilic balance is achieved, amphiphilic block copolymers can self-assemble in water into membranes. These membranes usually close, thus forming hollow spheres with an aqueous core, as shown in Fig. 6, with sizes that vary from tens to thousands of nanometres. The resulting structures known as polymer vesicles are commonly referred to as polymersomes in analogy to the lipid-based vesicles which are called liposomes. Contrary to liposomes, polymersomes exhibit enhanced stability and toughness, reduced permeability, restricted chain mobility within the membrane and better resistance to dissolution. These characteristics are attributed to the considerably higher molecular weight of the amphiphilic copolymers compared to that of lipids. Copolymer M_w also determines the vesicular membrane thickness, which can reach up to 50 nm, whereas the liposome bilayer membranes have thicknesses of 3–5 nm. Furthermore, the enhanced mechanical properties of the polymeric vesicle membranes are a consequence of the entanglement and interdigitation that can occur between the hydrophobic chains within the membrane [12, 19].

The chain architecture and chemical composition of the polymersome-forming amphiphilic block copolymers can be either simple or rather complex giving the corresponding polymersomes their peculiar properties. The AB copolymer type, where A and B, respectively, denote the hydrophilic and hydrophobic blocks, is the simplest possible chain architecture, and the majority of polymer vesicles are produced by such copolymers, including PEO-PPO, PS-PAA, PS-PEO, PBD-PAA, PB-PEO and P2VP-PEO among others. Even so, copolymers of more complex linear architecture such as ABA, BAB, ABABA, ABC and ABCA (with C being either hydrophilic or hydrophobic) have also been reported to assemble into polymersomes [43]. A very comprehensive representation of the various membrane

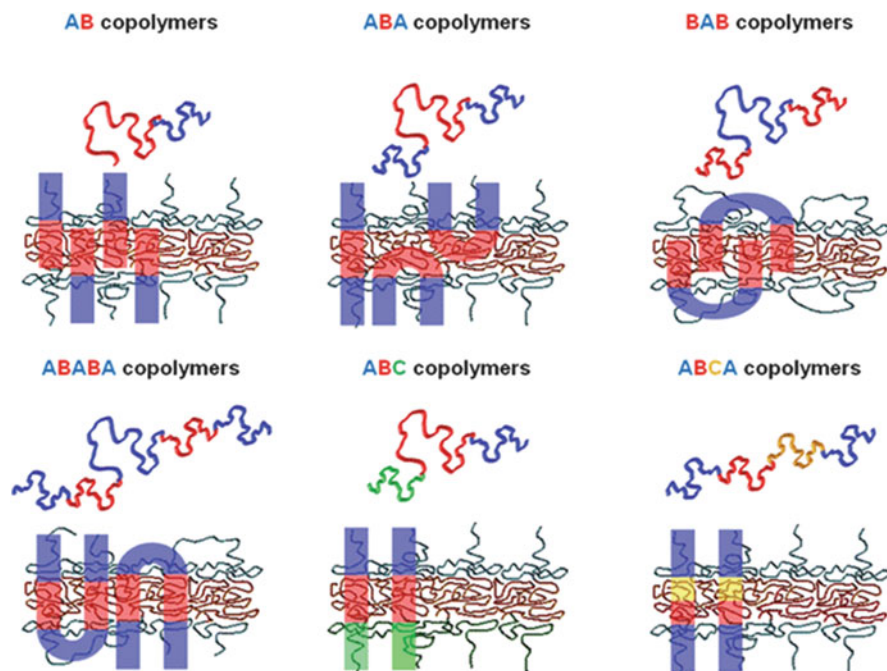


Fig. 7 Membrane conformation of polymersomes formed by diblock, triblock and multiblock copolymers. Reproduced with permission from [43]. Copyright (2009) The Royal Society of Chemistry

conformations of polymersomes formed by diblock, triblock and multiblock amphiphilic copolymers is given in Fig. 7.

Only one membrane conformation is possible for AB copolymers, where the B blocks constitute the hydrophobic layer and the A blocks extend outwards on both sides of the membrane. In the case of the ABA triblocks, the hydrophobic B block either can form a loop so as the hydrophilic A chains are on the same side of the membrane (U shape) or can stretch forming a monolayer with the two A blocks at the opposite sides of the membrane (I shape), while for the BAB type only, the U-shaped conformation is possible since the hydrophobic B chain ends must assemble into a membrane and the hydrophilic A blocks must form a loop. Similar conformations can be anticipated for ABABA pentablock copolymers. The same general rules apply when a third chemically different block is added, and although the overall geometry is the same, multiblock copolymers have an extra level of control over the polymersome structure introduced by the extra interaction between the blocks. Hence, ABC triblock copolymers assemble into asymmetric or “Janus” membranes, and the resulting vesicles are characterised by different external and internal surface chemical properties. Even more interestingly, ABCA tetrablocks (where A is hydrophilic and B and C are both hydrophobic) have been shown to

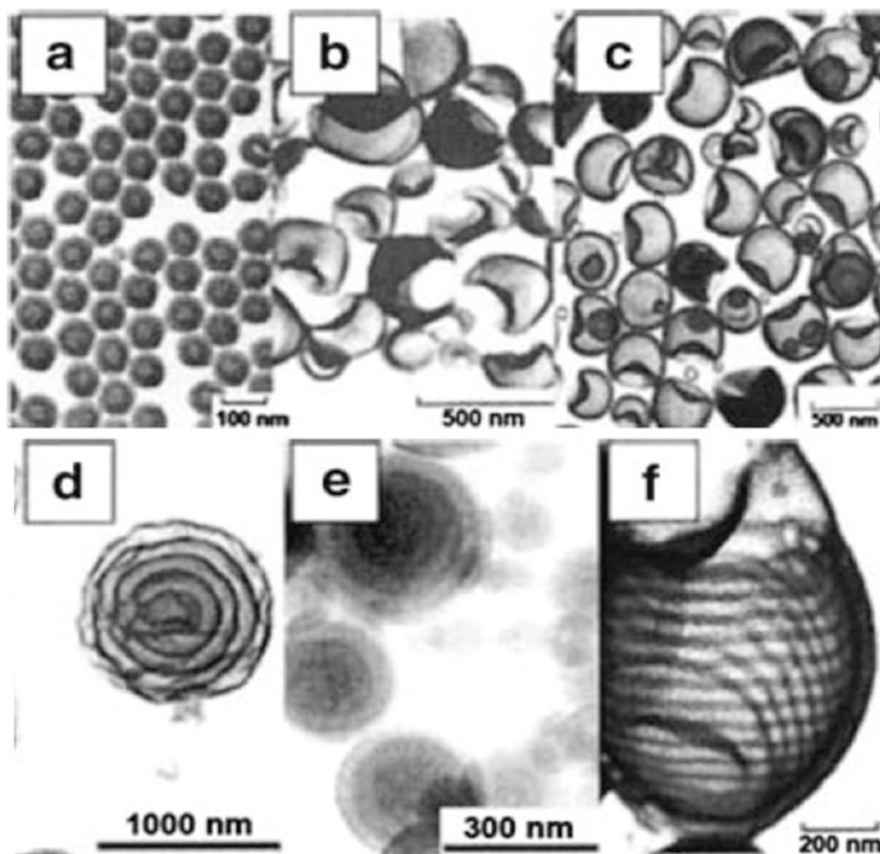


Fig. 8 Micrographs of vesicles with complex morphology. (a) Small uniform vesicles, (b) large polydisperse vesicles, (c) entrapped vesicles, (d) hollow concentric vesicles, (e) “onion-like” vesicles and (f) vesicles with tubes in the wall. Reproduced with permission from [36]. Copyright (2001) WILEY-VCH Verlag GmbH, Weinheim, Fed. Rep. of Germany

form vesicles whose membrane has an internal morphology that changes from lamellae to cylinders upon changing the volume fraction between B and C [46].

Contrary to the ideal notion that polymer vesicles are unilamellar spherical objects with uniform size and shape, in practice, a great variety of vesicular morphologies have been observed. Polymersome morphology is critically influenced by a number of factors such as the nature of the copolymers and their constituent blocks; the presence of ionisable groups or groups capable of hydrogen bonding; the solution conditions, e.g. temperature, concentration and pH; the presence of additives (salts, acids, bases, cosolvents, surfactants); as well as the method of preparation. This fact suggests that the great majority of polymersomes are nonequilibrium structures. As characteristically shown in Fig. 8, Eisenberg and co-workers [36] have managed to produce vesicles with multiple complex

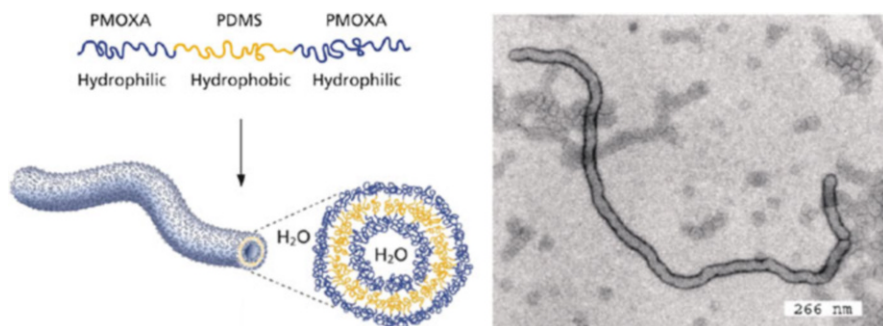


Fig. 9 Self-assembly of ABA triblock copolymers in aqueous solution and TEM image of a polymer nanotube. Reproduced with permission from [47]. Copyright (2004) The Royal Society of Chemistry

morphologies such as small uniform vesicles, large polydisperse vesicles, entrapped vesicles, hollow concentric vesicles, “onion-like” vesicles and vesicles with tubes in the wall, using six different types of polymers (PS-PAA, PS-PEO, PBD-PAA, PS-P4VPMeI, PS-P4VPDecI and PS-PMMA-PAA), only by changing parameters like the copolymer concentration and relative block lengths, the solvent composition, the temperature and the addition of ions to the system. Another interesting morphology is that observed by Grumelard et al. [47] from the self-assembly of an amphiphilic ABA copolymer (PMOXA-PDMS-PMOXA) in water, which led to the formation of a vesicular nanotube seen in Fig. 9.

Apart from their morphological diversity, polymer vesicles have been at the focus of extensive research also because of their potential applications, especially in medical fields. These kinds of applications usually exploit the unique ability of polymersomes to encapsulate hydrophilic compounds within the core and, at the same time, hydrophobic and amphiphilic molecules within the membrane. This feature combined with the enhanced mechanical properties of polymeric membranes renders them ideal delivery devices. As a result, polymer vesicles have been extensively utilised in drug delivery, gene therapy, protein delivery, medical imaging, cancer diagnosis and therapy, etc. [48–54].

2.3.4 Other Morphologies

Although spherical and cylindrical micelles, as well as polymersomes, constitute the majority of structures formed through the self-assembly of amphiphilic copolymers, lately there has been a substantial effort to create new intriguing morphologies, including multicompartiment, “disc-like” and bicontinuous micelles. These classes of novel micellar morphology have been recently reviewed by Holder and Sommerdijk [55].

The term multicompartiment micelles is used to describe micelles with water-soluble shells and internally segmented cores, where two (or more) separate types

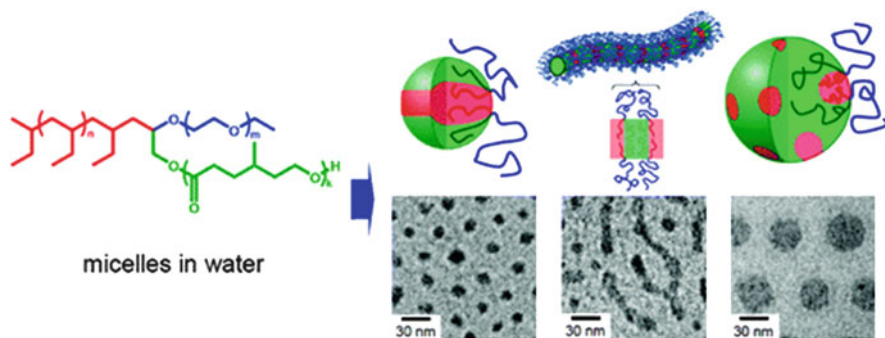


Fig. 10 Structure of a μ -((PEE)-(PEO)-(poly(γ -methyl- ϵ -caprolactone))) miktoarm block terpolymer, along with schematic representations and cryo-TEM micrographs of the resulting self-assembled micellar structures: “hamburger”, segmented “worm-like” and “raspberry” micelles (from left to right). Reproduced with permission from [56]. Copyright (2008) American Chemical Society

of hydrophobic regions exist. Obviously, this kind of structure provides the advantage of storing two or more incompatible compounds in the different nanocompartments of the core, and it can thus be used in the simultaneous delivery of different types of pharmaceutical and/or bioactive agents which are otherwise incompatible. The overall morphology of such micelles is similar to that of spherical, “worm-like” or even vesicular structures previously discussed, while for their preparation, usually ABC-type copolymers with linear and non-linear (e.g. miktoarm star) chain architecture are used. A characteristic example is that of the self-assembly of a miktoarm star terpolymer with PEE, PEO and poly(γ -methyl- ϵ -caprolactone) arms (μ -EOC) studied by Lodge, Hillmyer, et al. [56]. Depending on the initial composition of the μ -EOC copolymer, different types of resulting structures with distinct hydrophobic core regions were found, i.e. “hamburger” (where a lamellar region is sandwiched between two other regions), segmented “worm-like” (where the hydrophobic regions alternate along the length of the micelles) or “raspberry” (where one region adopts spherical shapes embedded in the matrix of the other) micelles. A schematic representation of these structures is shown in Fig. 10. Another similar example is that of the multicompartment micelles formed by a linear PISC-PS-PEO triblock terpolymer, where the micellar structure is dictated by the random architecture of the PISC block, which includes hydrophilic and hydrophobic segments [57].

“Disc-like” micelles are relatively rarely observed [58–63], and they are not considered stable equilibrium morphologies, but rather transient intermediate structures which occur under specific circumstances. The latter include (a) extremely strong interfacial tension between the amphiphilic blocks typically manifested by fluoro-containing copolymers, (b) alteration of the interfacial curvature by manipulating the volumes of the core and/or corona regions (usually via the addition of organic or inorganic substances), (c) the presence of “rod-like” corona- and/or core-forming blocks thus leading to parallel arrangement of the chains in the corona/core interface or (d) the presence of crystallisable core-forming blocks which can develop closely packed flat structures [19].

Finally, in limited occasions, self-assembled aggregates with a bicontinuous structure have been reported. For example, in the case of a PS-PAA diblock copolymer in a water/DMF mixture [64], of PEO-PPO-PEO triblock copolymers in water or water/oil mixtures [65–67] and PAA-PMA-PS in water/THF mixture [68], or more complex chain architectures, like a linear-comb [69] and a comb-comb [70] diblock copolymer, are considered.

2.4 *Micelle Characterisation: Experimental Techniques*

Several experimental techniques are available for the investigation of micellar systems, capable of elucidating different aspects of the micellisation process, as well as the micellar structure and morphology. In a first approach, these techniques can be categorised in three subclasses: microscopy, scattering and spectroscopic techniques. Extensive reviews on the various experimental methods suitable for block copolymer micelle characterisation have been provided [6–8]. Therefore, in this section, our aim is to briefly outline the different methods used and the information they provide, along with some of their main advantages and limitations [1, 2, 71].

2.4.1 Microscopy Techniques

Atomic force, scanning and transmission electron microscopies (AFM, SEM and TEM) have been widely used for the direct visualisation of block copolymer micelles and the determination of micellar size, shape, size distribution and internal structure. All three techniques require deposition of the micelles on a flat substrate and subsequent evaporation of the solvent, while additional coating or staining of the dried samples is usually necessary for SEM or TEM imaging, respectively. Thus, one could argue that the obtained information, especially about the size of the micelles, does not correspond to that in the initial micellar solution, since the surface deposition perturbs in some extent the original micellar size. The more lately developed cryo-TEM technique overcomes these limitations, since the micellar solution is rapidly frozen by liquid nitrogen and the micelles are observed unperturbed in a glassy water phase. This comparative advantage of cryo-TEM has increased its popularity as a standard characterisation technique of macromolecular self-assembly, as highlighted in the recent review of Zhong and Pochan [72].

2.4.2 Scattering Techniques

This subcategory includes static and dynamic light scattering (SLS and DLS), along with small-angle X-ray and neutron scattering (SAXS and SANS) techniques,

which provide information on micellar morphology with the advantage of giving a mean value calculated over a large number of micelles. These are also in situ techniques that produce minimal perturbation in the state of the micelles in solution. Light scattering is a very common technique used for micelle characterisation. SLS allows for the determination of the weight average M_w and thus N_{agg} of the micelles, as well as their R_g , while information about the quality of the solvent for the coronal chains can be obtained through the estimated second virial coefficient, A_2 . Moreover, due to its greater sensitivity in larger particles, SLS can be used for the measurement of cmc. The R_h of the micelles can be calculated from their diffusion coefficient obtained through DLS measurements, while at the same time information on the size distribution of the micelles and the relative amounts of individual species in the initial copolymer solution can be extracted. It should also be noted that from the combination of these two techniques, the characteristic ratio $\rho = R_g/R_h$ can be derived, which provides valuable insight on micellar morphology [73].

Small-angle scattering methods rely on the assumption of suitable models for the analysis of scattering data and have been proven very well suited for studying the structure of block copolymer micelles, as well as their interactions or ordering [74]. One of their most important features is that they allow for the independent study of the core or the corona of the micelles. More specifically, SAXS measurements yield parameters like the molecular weight, the overall size and the internal structure of the micelles, while through the appropriate model fitting, additional information on the individual dimensions of the micellar core and corona, as well as on the core/corona interface sharpness, can be acquired. In a similar manner, SANS experiments are usually conducted in deuterated solvents and/or with partially deuterated copolymers, in order to generate a sufficient scattering contrast between the core and the corona of the micelles, thus making possible the determination of their respective dimensions. Of course, the overall micellar characteristics can also be estimated in analogy to SAXS measurements.

2.4.3 Spectroscopic Techniques

From the various available spectroscopic techniques, fluorescence [75, 76] and nuclear magnetic resonance (NMR) [182] spectroscopy have been employed in the study of micellar solutions and are considered especially helpful in the investigation of local phenomena within the micelles. In fluorescence spectroscopy, probe molecules are usually utilised, which either are attached by covalent bonds to specific sites of the copolymer chain or can be easily distributed within the micelle core or corona. Energy transfer, fluorescence quenching and time-dependent fluorescence depolarisation techniques allow for the inspection of the micellar microenvironment. Owing to this local sensitivity determination of very small cmc values, probing the internal viscosity of the micelle core, as well as observation of the solubilisation of low M_w substances into the micelles, is possible. Unimer-micelle equilibrium or chain exchange between micelles can also be studied, by the use of copolymers suitably labelled with fluorophore groups.

Additional information on potential alterations of chain conformations or core/corona interface due to micellisation can also be gained. Similarly, the application of NMR spectroscopy for the study of chain dynamics in micellar systems is based mainly on the fact that block copolymer segment mobility is directly correlated to the intensity of respective NMR spectrum peaks. Thus, when the core of the micelles is formed and the mobility of the insoluble blocks is significantly reduced, the intensity of the corresponding NMR peaks is reduced accordingly.

2.4.4 Other Techniques

Other more or less commonly used experimental methods include analytical ultracentrifugation (AUC), size exclusion chromatography (SEC), viscometry and stop-flow techniques. AUC measures the velocity at which each species in solution is displaced under the influence of a strong centrifugal force [77]. Since the sedimentation velocity depends on the size, M_w and density of the species, as well as on the frictional forces developed by the solvent, information regarding these parameters can be extracted. Furthermore, this method allows for the determination of the weight fraction of micelles and unimers in the solution or even other species such as micelle aggregates. Likewise, SEC has been used to characterise the unimer/micelle distribution in the solution, along with the corresponding hydrodynamic sizes. Nevertheless, it should be noted that perturbation of the unimer-micelle equilibrium is possible during SEC experiments, so this technique is more suited for concentrations far away from the cmc or block copolymer systems that form “frozen” micelles. Viscometry is an extensively used method for the investigation of the hydrodynamic properties of block copolymer micellar solutions, providing information on the hydrodynamic size and the intrinsic viscosity of the micelles, together with an approximate estimation of their compactness. Finally, various stop-flow techniques have been employed in order to investigate the kinetics of micelle formation and dissociation.

2.5 Theoretical Aspects of Micellisation

Numerous theories, models and mathematical approaches have been developed over the years in order to describe the micellisation process and the dependence of fundamental structural parameters of the micelles, like cmc, aggregation number (N_{agg}), overall size (R_m), core radius (R_c) and corona thickness (L), on the molecular characteristics of the block copolymer, with respect to the degrees of polymerisation of the constituent blocks (N_A and N_B), as well as the Flory-Huggins interaction parameters χ between the blocks and between the blocks and the solvent. Some of these approaches use the minimisation of the total free energy of the micellar system so as to extract relations between the copolymer and micelle features, while others are based on the scaling concept of Alexander-de Gennes and

on the proposed mean-field theories [78–81]. Thorough overviews on the thermodynamic background and the different theoretical approaches have been presented by Tuzar and Kratochvil [5], Hamley [7], Linse [82], Riess [1] and Zhulina and Borisov [83].

In scaling theories, two limiting cases have to be considered for a monodisperse AB diblock copolymer in a selective solvent for the A block [82]. These are the “hairy” or “starlike” micelles, with $N_A \gg N_B$ and accordingly $L > R_c$, and the “crew-cut” micelles for which $N_B \gg N_A$ and $R_c > L$ (see Fig. 2). For the case of “hairy” micelles, based on the star polymer theory of Daoud and Cotton [84], the following scaling relations for N_{agg} and L have been derived:

$$N_{\text{agg}} \sim N_B^{4/5} \quad (2)$$

$$L \sim N_{\text{agg}}^{1/5} N_A^{3/5} \quad (3)$$

Zhulina and Birshtein [85] and Halperin [183] have obtained similar results for N_{agg} , while the corresponding scaling relations for R_c ($\sim N_B^{3/5}$) and L ($\sim N_A^{3/5} N_B^{6/25}$) are in agreement with the ones of Daoud and Cotton. For the total micellar radius, R_m , Halperin found:

$$R_m \sim N_A^{3/5} N_B^{4/25} \quad (4)$$

that demonstrates the predominant contribution of the coronal chains (A block) to the total micelle size.

For “crew-cut” micelles, the theories of Alexander and de Gennes for polymer brushes have been used, assuming micelles with uniformly stretched chains in the core and the corresponding scaling relations are:

$$R_c \sim \gamma^{1/3} N_B^{2/3} \alpha \quad (5)$$

$$N_{\text{agg}} \sim \gamma N_B \quad (6)$$

where γ is the interfacial tension between the A and B blocks and α is the segment length. These relations demonstrate that in this case, the dependence of the micellar parameters on N_A disappears.

However, scaling theories are not able to predict finite chain effects and polymer-solvent interactions, since they are restricted to long polymer chains in good solvents. More detailed mean-field calculations and molecular simulations are needed in order to complement these models.

Regarding semianalytical mean-field theories, Noolandi and Hong [78] and Leibler et al. [79] derived the micellar characteristics by minimising the free energy of both isolated micelles and the whole micellar system. A further development was achieved by Nagarajan and Ganesh [80], who took into account the molar volumes of the solvent and blocks A and B, the interfacial tension between the B block and the solvent and the interaction parameter between the A block and the solvent. This

way they acquired scaling relations for PPO-PEO micelles in water, which show the strong influence of the coronal block on the micellar characteristics. Specifically:

$$R_c \sim N_A^{-0.17} N_B^{0.73} \quad (7)$$

$$L \sim N_A^{0.74} N_B^{0.06} \quad (8)$$

$$N_{agg} \sim N_A^{-0.51} N_B^{1.19} \quad (9)$$

In a similar manner, the lattice self-consistent mean-field theory has been used to calculate the effects of the copolymer architecture on the self-assembly behaviour of nonionic and ionic copolymers [82, 86, 87].

Also complementary to the study of block copolymer self-assembly are analytical theories and computational simulations, mainly Monte Carlo-type simulations, as demonstrated by Mattice and Halilöğlu [88] and by Binder et al. [89]. Detailed revisions of simulation studies, along with the background of these techniques, can be found in the reviews of Binder and Muller [90] and Shelley and Shelley [91]. The main advantage of computer simulations is that they are generally straightforward methods with relatively few approximations and without any presumptions of micelle geometry or chain conformation. Moreover, they also provide the possibility to vary intermolecular forces at will in a well-controlled manner. Several aspects of the self-assembly process and basic characteristics of micelles formed by amphiphilic copolymers with different chain architectures, such as AB, ABA, BAB linear and A_2B_2 miktoarm star, have been established and compared [82, 92, 93]. Other aspects including chain-length dependence [89], dynamics of chain exchange [88], formation of surface micelles [94], solubilisation of low molecular weight substances [95, 96], chain density profiles and thickness of the interfacial region [82] have also been considered.

As a closing remark, the universality of the self-assembly mechanism should be noted. Based on experimental results from a series of PS-P4VP block copolymers in toluene, a selective solvent for PS, Förster et al. [97] obtained the following general scaling relation for N_{agg} :

$$N_{agg} = N_{agg,0} N_A^{-0.8} N_B^2 \quad (10)$$

When plotted as $N_{agg} N_A^{0.8} / N_{agg,0}$ versus N_B , a master curve (spanning the range of three orders of magnitude for N_B) is produced, which includes data of various diblock, triblock, graft and miktoarm star amphiphilic block copolymers, as well as low molecular weight ionic and nonionic surfactants. Most importantly, $N_{agg,0}$ is related to the surfactant packing parameter and is known for many block copolymer systems, thus allowing tuning of the aggregation number by variations in the molecular masses of the constituent blocks.

3 Representative Amphiphilic Block Copolymer-Selective Solvent Systems

As already mentioned, there has been an extensive amount of studies on the self-assembly of amphiphilic block copolymers in selective solvents over the years. In this section, we will try to give representative examples of these studies divided into two main categories regarding the solvation medium, i.e. amphiphilic copolymers in organic solvents or in aqueous solutions. The latter can be further distinguished in nonionic or ionic containing copolymers. These examples will be limited to the more commonly studied di- and triblock linear copolymers, but concise reviews on the self-assembly of amphiphilic copolymers with more complex non-linear chain architectures can be found elsewhere [98–100].

3.1 *Amphiphilic Copolymers in Organic Solvents*

Detailed overviews on the micellisation of amphiphilic copolymers in organic solvents are provided in the reviews of Riess [1], Gohy [2], Hamley [7] and Chu et al. [101]. Apparently, a wide range of styrene, acrylate or methacrylate and diene-based block copolymers have been investigated, while AB diblock and ABA triblock architectures have been systematically compared. One of the main conclusions is that the formation of micelles in organic solvents can generally be considered as an entropy-driven process.

Micellisation in organic media leads to the formation of the so-called reverse micelles. These micelles usually contain a polar core formed from PEO, PAA, PMMA or P2VP blocks, surrounded by a less polar corona consisting of PS, PB or PPO chains. Among the most characteristic of such systems are PEO-based di- and triblock copolymers, which have attracted considerable attention. Exemplary studies on the self-assembly of PEO-PPO and PEO-PPO-PEO copolymers in organic solvents, such as formamides, have been conducted by Lindman et al. [102, 103] and Alexandridis and Yang [104, 105]. Due to the ability of PEO to crystallise, the formation of reverse micelles in organic solvents from PEO-based block copolymers is considered in general a more complex process.

This interesting feature of PEO crystallisation has been studied for PS-PEO and PB-PEO micelles by Gervais and Gallot [106] and Gast et al. [107–109], while Wu and Chu [110] and Guo et al. [111] investigated this effect in the case of PEO-PPO-PEO copolymers. These authors have clearly demonstrated that one of the most important parameters in the crystallisation of PEO is the amount of residual water. For instance, Gast et al. [107] showed that PS-PEO copolymers in cyclopentane form micelles with N_{agg} between 17 and 100 depending on the copolymer concentration and on the water content. However, in the absence of water, the chain-folding crystallisation of PEO leads to the formation of lamellar microcrystals or

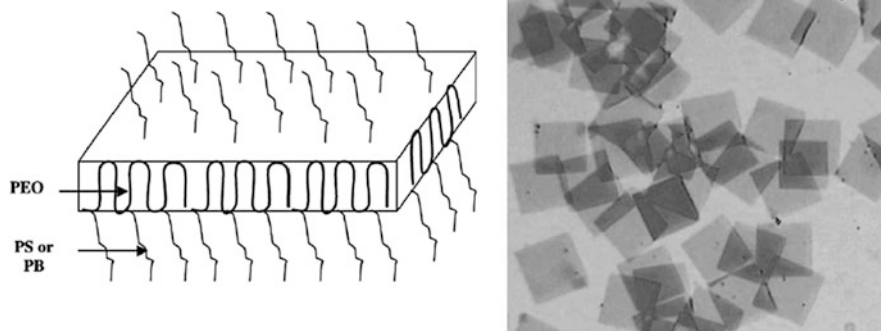


Fig. 11 Schematic structure of lamellar microcrystals or “platelets” formed by the crystallisation of PS-PEO or PB-PEO copolymer micelles in organic solvents, along with a typical micrograph of “platelets” from a PS₁₀₀-PEO₂₅₀₀ copolymer in methylcyclohexane. Reproduced with permission from [1]. Copyright (2003) Elsevier

“shish-kebab” structures. The resulting micelles are known as “platelets” and have an unusual lamellar morphology, as shown in Fig. 11.

Another intriguing study is that of Lodge et al. [24] for an asymmetric PS-PI copolymer in a series of organic solvents. By varying the solvent selectivity for PS, these authors documented the morphological transition of the resulting micelles from spheres to cylinders to vesicles. The various micellar structures were characterised in detail by means of SAXS and cryo-TEM measurements.

Although the majority of the investigations on amphiphilic block copolymers with an ionic block are usually considered in aqueous solutions, some studies of their self-assembly in organic solvents have also been performed. For example, diblock copolymers with a major PS block linked to ionic PAA or PMAA segments have been extensively studied by Eisenberg et al. [112, 113]. In organic solvents, such as toluene, these copolymers formed stable spherical “reverse micelles”, consisting of an ionic core and a PS corona. Their characteristic size was systematically investigated by a combination of experimental techniques including TEM, SAXS, DLS and SLS. Similarly, Förster et al. [97] have conducted detailed investigations for PS-P4VP copolymers in toluene, as mentioned in Sect. 2.5. In general, PS-P2VP and PS-P4VP micelles in organic solvents have been widely used as templates for the synthesis of metallic nanoparticles [114–117].

Finally, very few studies have been devoted on the self-assembly of ABC-type amphiphilic triblock copolymers in organic solvents, especially when compared to the corresponding in aqueous media. Tsitsilianis and Sfika [118] studied the formation of spherical micelles from PS-P2VP-PMMA triblocks in toluene, a bad solvent for P2VP, by light scattering, viscometry and TEM. Mixed corona micelles were formed, with their aggregation number and size depending mainly on the molecular characteristics of the three blocks. Comparison with micelles formed from PS-P2VP diblock copolymer of similar composition revealed that the

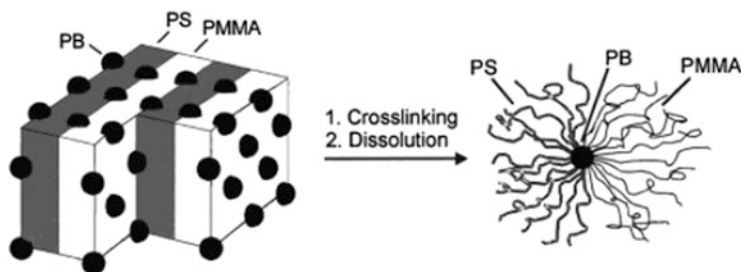


Fig. 12 Schematic representation of the bulk morphology of a PS-PB-PMMA triblock copolymer, along with the resulting “Janus” micelles after PB cross-linking and solubilisation. Reproduced with permission from [120]. Copyright (2001) American Chemical Society

terpolymers form micelles of lower N_{agg} due to the presence of the second end block. In a similar manner, the effect of solvent selectivity on the micellar characteristics of PS-PI-PMMA triblock terpolymers was investigated by Fernyhough et al. [119]. Light scattering and viscosity experiments revealed the formation of spherical mixed corona micelles with high N_{agg} and increased compactness in DMF (a nonselective solvent for PI). The size of the micelles was controlled mainly by the molecular characteristics of the soluble PS and PMMA blocks, but the molecular weight and content of the insoluble PI block also played a role. Another interesting case is that of the formation of “Janus” micelles by cross-linking the PB domains of a PS-PB-PMMA triblock copolymer in the solid state, as seen in the study of Abetz, Müller et al. [120]. The bulk morphology of this copolymer consists of lamellae of the outer PS and PMMA blocks embedding spherical domains of the PB middle block (the so-called lamellae-sphere morphology). When the PB spherical domains are cross-linked and the bulk phase is dissolved in THF, a good solvent for the outer blocks, spherical micelles with two distinct coronal hemispheres of PS and PMMA chains are formed. A schematic representation of the bulk morphology, as well as the resulting “Janus” micelles, is given in Fig. 12.

3.2 Amphiphilic Block Copolymers in Aqueous Solutions

The self-assembly of amphiphilic block copolymers in aqueous solutions has attracted considerable interest not only because of their unique properties but also due to their widespread application possibilities in technical and especially biomedical areas. As far as representative examples of such systems are concerned, a categorisation into nonionic and ionic containing copolymers is feasible.

3.2.1 Nonionic Amphiphilic Block Copolymers

This class of amphiphilic block copolymers typically includes copolymers with a PEO hydrophilic block linked to various hydrophobic blocks like PPO, PBO, PS, PMMA, etc. One of the main advantages of PEO is its non-toxic and non-immunogenic properties, which are the requirements for biomedical use.

The most extensively studied systems are apparently those of PEO-PPO and PEO-PBO di- and triblock copolymers in water. Their micellisation behaviour has been summarised in the review articles of Riess [1], Gohy [2], Hamley [7], Almgren et al. [121], Chu and Zhou [122] and Booth et al. [123, 124]. These studies showed that various micellar morphologies or even physical gels can be formed, depending on parameters such as molecular weight, composition, temperature and concentration. A number of techniques including DLS, SLS, SAXS, SANS and NMR have been utilised in order to characterise these micellar systems. A rather detailed picture of the morphology of spherical micelles formed by PEO-PPO-PEO copolymers has been established by Mortensen and Pedersen [125], who showed that the PPO core is surrounded by a dense layer of PEO segments and an outer corona of flexible PEO chains. Other similar investigations include that of Bahadur et al. [126] who examined the role of various additives on the micellisation behaviour, of Booth and co-workers [127] who were mainly interested in PEO-PBO block copolymers with long PEO sequences and of Hamley et al. [128, 129] who used in situ AFM measurements in water to characterise the morphology of PEO-PPO micelles.

Another well-studied family of PEO-based amphiphilic copolymers is that of PS-PEO diblock and PEO-PS-PEO triblock copolymers, as seen in the works of Riess and co-workers [1]. In summary, the N_{agg} for PS-PEO was found to increase as a function of the copolymer M_w at constant composition, while it decreased with PEO content for a given M_w . Moreover, it was shown that PEO-PS-PEO triblocks had lower N_{agg} than the corresponding PS-PEO diblocks. These types of micelles are generally characterised by two interesting features. The first one is that due to the high T_g of the PS blocks, the resulting micelles belong in the special category of “frozen micelles”, i.e. they are nonequilibrium structures with a “glassy” core. Their second feature is that they are prone to secondary aggregation through clustering of the PEO coronal chains, as observed in various cases [130–132]. In the case of highly asymmetric PS-PEO copolymers with short PEO blocks, various “crew-cut” micellar morphologies including spheres, rods, lamellae and vesicles have been observed by Eisenberg et al. [133].

The self-assembly of copolymers containing nonionic hydrophilic PEO blocks and other hydrophobic blocks, such as PI [134] and PB [25], has also been investigated. Of particular interest is the case of PEO-PCL block copolymers, since they are biocompatible and partly biodegradable and they are thus ideal candidates for drug delivery applications [135, 136].

Contrary to AB and ABA type, ABC nonionic amphiphilic copolymers and the corresponding self-assembly studies are rather scarce. One example is that of the

investigation of the micellar properties in water of a PEO-PS-PB copolymer and its fluorinated analogue, which resulted from the selective fluorination of the PB block. The unmodified triblocks formed spherical “core-corona” micelles in aqueous solution, whereas the fluorinated analogues formed “core-shell-corona” oblate elliptical micelles. This behaviour was ascribed to the stronger segregation of the insoluble blocks and the increase in the hydrophobicity of the PB block in the latter case due to fluorination [137].

3.2.2 Ionic Amphiphilic Block Copolymers

Amphiphilic block copolymers with one ionic block constitute an intriguing class of macromolecules, since their self-assembly in aqueous solution usually leads to the formation of spherical micelles with a hydrophobic core and a polyelectrolyte corona. These micelles are particularly interesting because the intrinsic properties of their polyelectrolyte corona are strongly influenced by many parameters like pH, salt concentration, degree of dissociation, polar interactions and so on. Moreover, they can be considered as a model to spherical polyelectrolyte brushes and thus provide a unique opportunity to study polyelectrolyte properties in high concentration conditions. The micellisation behaviour of ionic amphiphilic copolymers has been reviewed by Riess [1], Gohy [2], Eisenberg et al. [112, 113], Förster et al. [138] and Cohen Stuart et al. [139].

Anionic polyelectrolyte block copolymers based on PAA or PMAA ionisable blocks have been extensively studied. Their self-assembly has been examined for a very wide compositional and molecular weight range in aqueous medium, as well as in various water/organic solvent, like dioxane or DMF, mixtures. At high pH, the (meth)acrylic blocks are ionised resulting in stable micelles with extended coronas, due to electrostatic repulsions, which exhibit typical polyelectrolyte behaviour. Characteristic examples of such systems concerning PS-PMAA diblock and PMAA-PS-PMAA triblock copolymers can be found in the studies of Munk, Tuzar, Webber and their co-workers [6, 140–142] and of Procházka et al. [143–146]. Similarly, PS-PAA copolymers have been at the focus of extensive investigations especially by the group of Eisenberg [3, 35, 37, 64, 112, 113], as well as van der Maarel et al. [147–149]. As mentioned before, Eisenberg and co-workers have studied a series of highly asymmetric PS-PAA copolymers with a long PS and a very short PAA block, and their results have been recently reviewed [3]. These copolymers led to the formation of “crew-cut” micelles, whose morphology could be changed from spheres to rods to vesicles and other complex micellar structures by decreasing the PAA/PS ratio in the starting copolymer, by adding salt or by changing the initial common organic solvent. The underlying thermodynamic and kinetic principles explaining the formation of such morphologies have also been thoroughly discussed. Some of the observed intricate morphologies formed from asymmetric PS-PAA copolymers micelles are shown in Fig. 13.

Besides PS, other hydrophobic blocks have been combined with ionic PAA or PMAA sequences as in the cases of *Pn*BA-PAA and PIB-PMAA copolymers

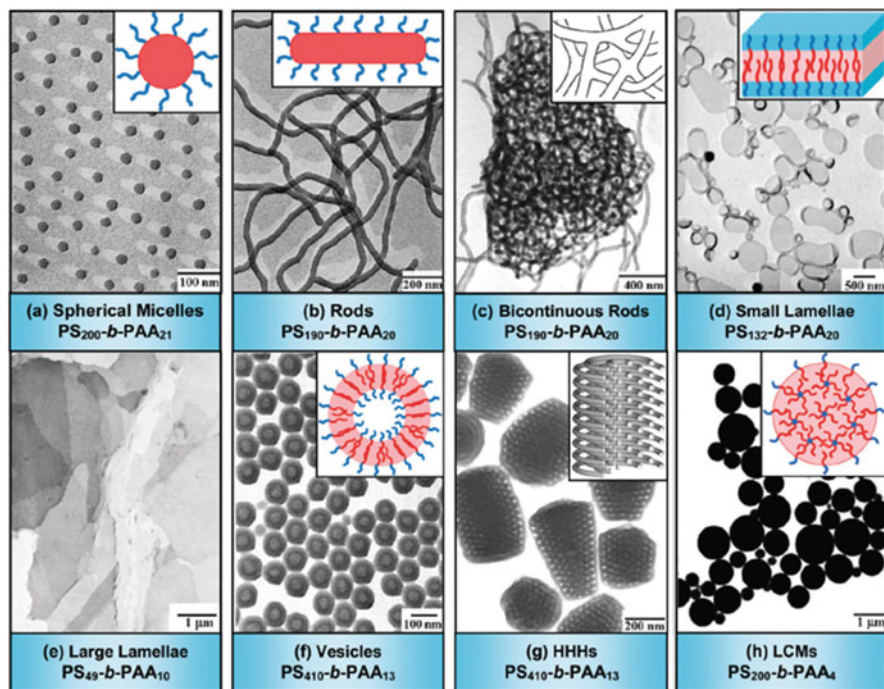


Fig. 13 TEM micrographs and corresponding schematic diagrams of various morphologies formed from amphiphilic PS_m - PAA_n copolymers. *Note:* m and n denote the degrees of polymerisation of PS and PAA, respectively. In the schematic diagrams, red represents hydrophobic PS parts, while blue denotes hydrophilic PAA segments. HHHs, hexagonally packed hollow hoops. LCMs, large compound micelles, in which inverse micelles consist of a PAA core surrounded by PS coronal chains. Reproduced with permission from [3]. Copyright (2012) The Royal Society of Chemistry

studied by Müller et al. [150, 151] or PMMA-PMAA di- and triblocks investigated by Tam et al. [152, 153]. Nevertheless, it should be noted that the ionisation degree of these anionic blocks is strongly dependent on pH and this could be a disadvantage for applications that require pH-independent ionisation behaviour. This drawback can be overcome by the use of anionic polymers derived from strong acids like PSS or PSGMA. PSS-based block copolymer like $PtBS$ -PSSNa or PEE-PSSH have been the subject of studies by Guenoun et al. [154, 155] or Förster et al. [156, 157], respectively. In a similar manner, Gohy et al. [158, 159] have examined the micellisation of PSGMA-containing block copolymers like PMMA-PSGMA or $PtBMA$ -PSGMA.

As far as cationic polyelectrolyte block copolymers are concerned, the number of studies is considerably smaller. The majority of the works in this area are devoted to quaternised P2VP- or P4VP-containing copolymers like the works of Selb and Gallot [160], Riess et al. [1] and Eisenberg and co-workers [36] on PS-P4VP copolymers or those of Förster et al. on PB-P2VP [138] and Procházka et al. on

PrBA-P2VP [161]. Another class of cationic block copolymers is that developed by Armes and co-workers [162–164], who studied the solution properties of various amino-containing poly(methacrylates), such as PDMAEMA and PDEAEMA, which exhibit stimuli responsive properties and were combined together or with other typical hydrophobic blocks.

A significant number of ABC triblock copolymers with at least one ionic block have also been investigated. One of the first examples is that of Patrickios et al. [165–167] who studied a series of triblock copolymers containing mainly PDMAEMA, PMMA and PMAA blocks. By changing the block sequence and the pH of the solution, they observed the formation of either “core-shell-corona” or mixed corona micelles. PEHA-PMMA-PAA and PS-PMMA-PAA triblocks studied by Kříž et al. [168] and Yu and Eisenberg [169], respectively, also formed “core-shell-corona” micelles in water. P2VP-containing ABC triblocks like PS-P2VP-PEO [170–172], PI-P2VP-PEO [173] and PB-P2VP-PEO [1] are the subject of various studies. Gohy and Jérôme [170, 171] showed that an interesting feature of these copolymers is that they form pH-responsive three-layered micelles, with a collapsed ($\text{pH} > 5$) or a swollen ($\text{pH} < 5$) P2VP middle shell, due to the protonation of the pyridine groups.

Less common are the ABC copolymers with one middle polyelectrolyte and two hydrophobic blocks, whose self-assembly in water usually leads to the formation of “flower-like” micelles. Such micelles have been reported by Tsitsilianis et al. in the case of PS-PAA-*Pn*BMA [174] or P2VP-PAA-*Pn*BMA at pH above 5 [31]. Finally, two more examples of the formation of mixed corona micelles are those observed from the micellisation of a PEO-PS-P4VP triblock copolymer studied by Chen et al. [175] or in the case of PEG-*Pn*BA-PDMAEMA triblock investigated by Won et al. [176].

4 Potential Applications and Conclusions

From early on, the unique properties of amphiphilic block copolymers have been exploited in numerous applications, since their surface activity renders them suitable candidates for many industrial and pharmaceutical preparations as dispersants, emulsifiers, wetting agents, foam stabilisers, flocculants, demulsifiers, viscosity modifiers, etc. [1, 8].

Among the various possible utilisations of block copolymers, one of the most important categories is that of biomedical applications, as evidenced by the significantly large number of relative studies and reviews [12, 19, 49, 177–181]. Block copolymers in their colloidal form, i.e. micelles or vesicles, have been extensively used as drug delivery systems and carriers of diagnostic agents and in gene therapy. Especially in drug delivery, three major strategies have been developed concerning (a) micelle-forming conjugates of drugs and block copolymers, where the drug is covalently linked to one of the sequences of the copolymer; (b) drugs non-covalently incorporated into the block copolymer, that is, the formation of

the so-called micellar microcontainers; and (c) polyion complex micelles formed between oppositely charged polyelectrolyte block copolymers. The major interest of block copolymers as drug delivery nanosystems stems from the ability to adjust the chemical nature of the blocks along with the molecular characteristics of the copolymer (molecular weight, composition, presence of functional groups for active targeting), thus optimising the performance of the delivery system. Furthermore, block copolymers offer the advantages of tunable dimensions in the range of 10–100 nm, of relatively high cmc and thus enhanced thermodynamic and kinetic stability of the micelles during dilution occurring in biological fluids, of increased targeting efficiency through suitable corona block end-group functionalisation and finally of adjustable distribution, as well as total amount of solubilised drug.

In a similar manner, several nanoparticles have been produced in the presence of block copolymers in selective solvents so as to form micelles that encapsulate particles such as metal salts. Consequently, these micelles are chemically converted to finely disperse colloidal hybrid polymer/metal particles with interesting catalytic, non-linear optic, semiconductor and magnetic properties [1, 20]. Finally, another area of potential application of amphiphilic block copolymers is that involving surface modification through the adsorption of block copolymer micelles or film formation. The use of a suitable micellar system allows for the alteration of specific surface characteristics, such as wetting and biocompatibility, or even enables the dispersion and stabilisation of solid pigment particles in a liquid or solid phase [1, 178].

In conclusion, the self-assembly of amphiphilic block copolymers in selective solvents constitutes a scientific field of ever increasing interest not only from the fundamental understanding point of view but also due to the variety of practical application possibilities. The virtually countless studies that have been devoted in this area so far have revealed a cornucopia of possible self-aggregated structures, from simple spherical micelles and vesicles to sophisticated multicompartment segregated nano-objects. Nevertheless, as our understanding of the basic intramolecular and intermolecular interactions, which govern the self-assembly process, grows and the synthetic capabilities continue to advance, allowing the preparation of copolymers with remarkably diverse architectures and intriguing functionalities, this field of research will always remain active providing new pathways for exploration.

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