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DOI:

[10.1016/j.jcis.2020.03.067](https://doi.org/10.1016/j.jcis.2020.03.067)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Campos Villalobos, G. D. J., Siperstein, F., Charles, A., & Patti, A. (2020). Solvent-induced morphological transitions in methacrylate-based block-copolymer aggregates. *Journal of Colloid and Interface Science*. <https://doi.org/10.1016/j.jcis.2020.03.067>

Published in:

Journal of Colloid and Interface Science

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Solvent-induced morphological transitions in methacrylate-based block-copolymer aggregates

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Abstract

Poly(ethylene oxide)-*b*-poly(butylmethacrylate) (PEO-*b*-PBMA) copolymers have recently been identified as excellent building blocks for the synthesis of hierarchical nanoporous materials. Nevertheless, while experiments have unveiled their potential to form bicontinuous phases and vesicles, a general picture of their phase and aggregation behavior is still missing. By performing Molecular Dynamics simulations, we here apply our recent coarse-grained model of PEO-*b*-PBMA to investigate its self-assembly in water and tetrahydrofuran (THF) and unveil the occurrence of a wide spectrum of mesophases. In particular, we find that the morphological phase diagram of this ternary system incorporates bicontinuous and lamellar phases at high copolymer concentrations, and finite-size aggregates, such as dispersed sheets or disk-like aggregates, spherical vesicles and rod-like vesicles, at low copolymer concentrations. The morphology of these mesophases can be controlled by tuning the THF/water relative content, which has a striking effect on the kinetics of self-assembly as well as on the resulting equilibrium structures. Our results disclose the fascinating potential of PEO-*b*-PBMA copolymers for the templated synthesis of nanostructured materials and offer a guideline to fine-tune their properties by accurately selecting the THF/water ratio.

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Keywords: Block-Copolymers, Self-Assembly, Molecular Dynamics,
Coarse-Grained, Morphological Transitions, Binary Solvents

1. Introduction

In the early 1900's, the pioneering experiments by McBain [1] and Hartley [2] disclosed a realm of intriguing morphologies resulting from the spontaneous self-assembly, in selective solvents, of a particular family of molecules. These
5 molecules, consisting of a solvophilic and a solvophobic domain, are generally referred to as amphiphiles, from the Greek $\alpha\mu\phi\iota\varsigma$ (both) and $\phi\iota\lambda\iota\alpha$ (love). The technological implications of these observations have become clearer and clearer over the last few decades, with the development of synthesis techniques transforming relatively simple molecular building blocks into structured supramolec-
10 ular aggregates and these into *ad hoc* templates for highly ordered nanoporous materials [3]. Unveiling the physico-chemical principles underpinning the microstructural transitions that occur in micellar solutions, dating back to Debye [4], has been crucial to identify the key factors controlling the formation of equilibrium aggregates: amphiphile's architecture and concentration, pH, tem-
15 perature, solvent and additives [5]. The coordinated action of these factors can be concisely summarized by the so-called packing parameter, $p = \nu/al$, where ν and l are the volume and effective length of the solvophobic block, respectively, while a is the area per solvophilic head group. In particular, lamellae and vesicles are expected at $1/2 < p \leq 1$, whereas rod-like and spherical micelles at
20 $1/3 < p \leq 1/2$ and $p \leq 1/3$, respectively [6].

In particular, when diblock-copolymers are added to a solvent that has a selective affinity for one of the blocks, the self-assembly of the other block sparks the formation of colloidal clusters or micelles. In the most general case, these aggregates consist of a solvophobic core (hydrophobic, in aqueous solutions) and
25 a solvophilic (hydrophilic) corona, but more complex copolymer's architectures, comprising three or more blocks, can form aggregates with more than just two separate domains. If the volume occupied by the corona is significantly larger

than that occupied by the core, then the resulting aggregates are generally referred to as "star-like" micelles. By contrast, aggregates with a bulky core and a thin corona are defined as "crew-cut" micelles [7]. Today, more than 20 stable morphologies obtained via self-assembly of block-copolymers (BCPs) have been reported [8], approximately three times more than those firstly identified almost 25 years ago by Zhang and Eisenberg [9]. Some morphologies, such as spherical or rod-like micelles, are more frequently observed, while others - hexagonally packed hollow hoops [10], helical micelles [11], disk-like micelles (also called "hamburger micelles") [12] and multilamellar vesicles [13] - are more exotic. In general, the BCP assemblies exhibit a higher stability and longevity compared to those formed by small surfactants and consequently have attracted considerable attention as drug-delivery systems in biomedicine [14, 15, 16], templates for fabricating capacitors with increased charge storage capacity in microelectronics [17, 18] and nanoreactors and multiple stimuli-responsive biomaterials [19, 20].

The self-assembly of BCPs in solution is dictated by principles analogue to those valid for small surfactants. Nevertheless, extra elements of complexity are present, such as the long-time relaxation dynamics and higher degree of hydrophobicity of polymeric chains [21, 22]. Consequently, the synthesis method to obtain BCP's mesophases tightly depends on the composition of the copolymer being employed as well as on the size of its two blocks. Usually, aggregates of BCPs with relatively bulky hydrophobic blocks, such as polystyrene-*b*-poly(acrylic acid), which show an especially rich variety of morphologies [9], are prepared via the so-called *solvent switch* or co-solvent method [23]. This method consists in dissolving a small amount of BCP in an organic solvent, such as dioxane, *N,N'*- dimethylformamide (DMF) or tetrahydrofuran (THF), that is a good solvent for both blocks. Subsequently, water, a selective solvent for the hydrophilic block, is slowly added to this solution up to a content (usually between 25 and 50 wt%) that is significantly larger than the water content at which micellization starts [8]. Finally, the so-obtained aggregates are quenched in excess of water in order to freeze all the kinetic processes and morphologies.

Eisenberg and coworkers found that various morphologies could be obtained
60 for a given copolymer architecture and concentration by tuning solely the com-
mon/selective solvent ratio [24], thus offering an alternative path to control the
properties of the nanostructures at equilibrium [25]. In order to exploit the
beneficial implications of such an additional degree of freedom, it becomes es-
sential to understand how altering the medium quality determines the kinetics
65 and thermodynamics of BCP self-assembly. To this end, one needs to gain a
full insight into the nature of the molecular interactions, which is all but trivial
and nevertheless of fundamental importance.

Statistical-mechanical theories and computer simulation, including molec-
ular Dynamics (MD), Dissipative Particle Dynamics (DPD) and Monte Carlo
70 (MC) methods, have proven to be especially effective in addressing this chal-
lenging task and offered a clearer picture of the physico-chemical effects driving
the phase and aggregation behavior of BCPs. Over the last two decades, most of
the computational works have predominantly focused on the self-assembly of low
molecular weight surfactants, lipids and BCPs in water solutions, and on the es-
75 timation of their critical micelle concentration (CMC), aggregation number, ag-
gregate size and solution rheology [26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38].
More recently, mean field theories have been applied to investigate the kinetics
of molecular exchange in micellar solutions [39, 40]. By contrast, only little
attention has been paid to the self-assembly of amphiphiles in solutions of two
80 solvents. In particular, Li and coworkers have recently applied the simulated an-
nealing MC method to investigate the phase behavior of generic amphiphilic AB
diblock copolymers in mixtures of selective and common solvents [41]. The au-
thors observed that by increasing the amount of selective solvent, self-assembled
structures experience a number of morphological transformations that follow a
85 sphere→rod→ring/cage→vesicle sequence.

Most of these studies have been performed by employing oversimplified po-
tential models that neglect important chemical details of amphiphilic BCPs.
Molecular simulations of fully atomistic models remain prohibitively expensive
because the timescale for spontaneous self-assembly is usually too long (mi-

croseconds) and the required system size too large (several hundreds of thousands of atoms) to be systematically investigated using the currently available computational power. An alternative route is based on high-level coarse-grained (CG) potential models that are built via a multiscale simulation approach. More specifically, fully atomistic models of smaller systems are employed to estimate some well-selected properties that are used to identify the most suitable parameters of the CG model’s force field [29, 42, 43]. In this work, we employ our recently developed CG model for methacrylate-based copolymers [44] to investigate the self-assembly of low-molecular weight poly(ethylene oxide)-*b*-poly(butylmethacrylate) (PEO-*b*-PBMA) copolymers in mixtures of water and THF. This ternary system has been recently reported to exhibit a wide variety of self-assembled nanostructures, including bicontinuous polymer nanospheres, dispersed sheets, vesicles and octopus-like assemblies [45, 46]. By MD simulations, we map their phase diagram by mimicking the solvent-switch method and observe a wide spectrum of interesting mesophases at different common/selective solvent ratios. We also discuss the mechanisms driving the kinetics of morphological transitions that are determined by changes in the solvent composition. Our findings highlight the importance of solvent correlations on the intra-aggregate chain structure and resulting equilibrium morphology.

2. Methods

2.1. Model

Classical MD simulations were performed using CG-scale representations of PEO-*b*-PBMA copolymers, water and THF. Two different methacrylate-based BCPs, PEO₆-*b*-PBMA₄ and PEO₁₂-*b*-PBMA₁₀, have been modelled in this work. Their interactions were described via inter- and intra-molecular potentials of the MARTINI force-field family [47]. In particular, we adopted our recently refined parameters, which allow for the reproduction of the structural and thermodynamic properties of the BCPs in melt and solutions [44]. In this scheme, the PBMA monomer is represented by three CG beads, whereas the

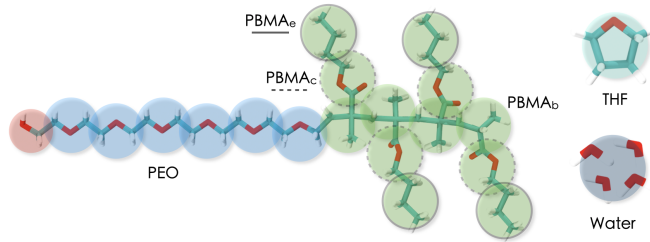


Figure 1: Coarse-grained and underlying atomistic representations of $\text{PEO}_6\text{-}b\text{-PBMA}_4$, water and THF. At the CG level, a PEO segment of n monomers consist of $n + 1$ sites due to the terminal $\text{HO-CH}_2\text{-}$ group. The PBMA_e , PBMA_c and PBMA_b sites denote terminal, bridging, and backbone beads of the PBMA repeating unit, respectively. THF is represented by a single bead and the standard MARTINI 4-to-1 water model is employed. Red, white and light blue solid segments in the atomistic model represent oxygen, hydrogen and carbon atoms, respectively. The interested reader is referred to Ref. [44] for additional details on the model.

PEO monomer and THF are modelled by a single site, as reported in Fig. 1 for
 120 $\text{PEO}_6\text{-}b\text{-PBMA}_4$.

Pairs of non-bonded CG beads interact with each other via a truncated and shifted Lennard-Jones (LJ) potential:

$$U^{\text{LJ}}(r) = 4\epsilon \left[\left(\frac{\sigma}{\epsilon} \right)^{12} - \left(\frac{\sigma}{\epsilon} \right)^6 \right] - U(r_c), \quad (1)$$

where σ and ϵ are, respectively, the length- and energy-scale parameters of the pair interaction, r is the separation distance between pairs of spherically-
 125 symmetric CG sites, and $U(r_c)$ is the value of the LJ potential at the cut-off radius, r_c . Within the BCP chains, intramolecular interactions acting on the centres of bonded sites are described using a harmonic bond-stretching potential:

$$U^{\text{bond}}(l) = \frac{1}{2} K_l (l - l_0)^2 \quad (2)$$

with K_l the bond force constant, and l and l_0 the instantaneous and equilibrium bond distances, respectively. Similarly, the angle-bending between triplets of

130 connected beads is modelled via a harmonic potential:

$$U^{\text{angle}}(\theta) = \frac{1}{2}K_{\theta}(\cos\theta - \cos\theta_0)^2 \quad (3)$$

where K_{θ} is the angle force constant, and θ and θ_0 the instantaneous and equilibrium angle-bending values, respectively. The list of all the parameters employed in this work is available to the interested reader in the Supporting Information.

2.2. Molecular Simulations

135 We have investigated the aggregation behavior of PEO₆-*b*-PBMA₄ and PEO₁₂-*b*-PBMA₁₀ BCPs in mixtures of water and THF of varying composition. The PEO content of these BCPs, defined as the ratio of the mass of the PEO block and the whole BCP chain, $M_{\text{PEO}}/M_{\text{BCP}}$, are 0.31 and 0.27, respectively. These BCPs have been selected to study mainly the effect of chain
140 length, and to a lesser extent the hydrophobic/hydrophilic ratio on the equilibrium morphologies. In order to accurately map the phase diagrams of such ternary systems, we performed simulations at $0.05 \leq \omega_{\text{BCP}} \leq 0.50$, where ω_{BCP} is the copolymer mass fraction. At each value of ω_{BCP} , different solvent ratios, $f_{\text{w}} \equiv \omega_{\text{w}}/(\omega_{\text{w}} + \omega_{\text{THF}})$, with ω_{w} and ω_{THF} the water and THF mass fractions,
145 respectively, have been analyzed. It follows from the above definitions that $\omega_{\text{w}} + \omega_{\text{THF}} + \omega_{\text{BCP}} = 1$. Each state, characterized by fixed values of ω_{BCP} and f_{w} , was simulated independently without altering the compositions from the original (initial) configuration. Experimentally, the composition of the system changes by stepwise addition of water [8]. Therefore, our simulations do not
150 mimic the full synthesis process, but they are expected to be consistent with intermediate steps in a solvent-switch experiment being performed at slow rates of water addition, where the systems at each intermediate composition are allowed to reach equilibrium.

Initial configurations were obtained by random spatial distribution and ori-
155 entation of chain and solvent molecules in cubic simulation boxes with periodic boundaries using PACKMOL [48]. The number of BCP chains was set to $N_{\text{BCP}} = 750$ and the amount of solvent was estimated so as to obtain the

desired mixture composition. The packing of molecules in the initial state was performed at relatively low density ($\sim 800 \text{ kg m}^{-3}$) in order to avoid molecular overlaps. Energy minimization was applied prior to equilibration and production runs to eliminate unrealistic high-energy structures using the steepest-descent method. MD simulations were carried out in the isothermal-isobaric (NPT) ensemble using the GROMACS 5.0.4 package [49]. The temperature, $T = 300 \text{ K}$, was controlled by means of the stochastic velocity-rescale algorithm by Bussi *et al.* [50] with a coupling constant of 1.0 ps. The Berendsen barostat [51] was employed to restrict pressure fluctuations about the equilibrium value of $P = 1 \text{ bar}$ with a relaxation constant of 3.0 ps and a standard compressibility of $5 \times 10^{-5} \text{ bar}^{-1}$. With this algorithm, the initial configurations with densities around 800 kg m^{-3} were rapidly compressed to their equilibrium values during the first hundreds of picoseconds. Integration of the classical equations of motion was accomplished by means of the leapfrog algorithm with a timestep of 20 fs. Dispersion interactions were truncated at $r_c = 1.2 \text{ nm}$ as in the standard MARTINI force-field. Long-range corrections, compensating the potential truncation, were added to the total energy and pressure. In order to guarantee equilibration and discard the occurrence of artificial non-ergodic structures, all simulations were run for $7 \mu\text{s}$ and for each state we performed two independent simulations starting from different velocity distributions and molecular coordinates. When necessary, reversibility along the BCP iso-concentration lines (direct transition) was tested by extra MD runs using the final configuration of a state point as the initial one for a neighbouring state and manually modifying the solvent composition. All the morphologies reported in the remaining of this article were stable for at least $3 \mu\text{s}$.

3. Results

In this section, we present the morphologies resulting from the self-assembly of PEO₆-*b*-PBMA₄ in THF and water, and include the analysis of the mesophases containing PEO₁₂-*b*-PBMA₁₀ in the Supplementary Informa-

tion. The morphological ternary diagram, unveiling the aggregation behavior of PEO₆-*b*-PBMA₄ as function of the common/selective solvent composition, is reported in Fig. 2, while some pictorial representations of the corresponding nanostructures are reported in Fig. 3. In total, we have identified 6 different assembled structures: (i) *clusters*, in which the chains are in close contact to each other, but the hydrophobic and hydrophilic cores are not clearly segregated; (ii) *rod-like vesicles*, being anisotropic hollow structures with a hydrophobic wall, hydrophilic internal and external coronas, and some solvent in the inner core; (iii) *vesicles*, being characterized by a hollow structure with a spherical symmetry; (iv) *sheets or disk-like aggregates*, which are dissolved flat bilayers; (v) *kinetically-trapped spheres*, resembling large crew-cut micelles with fully segregated hydrophobic cores; and (vi) *lamellae*, being ordered arrays of bilayers adjacent to each other and presenting solvent in the interstices. The conditions at which these aggregates are formed are discussed in the remaining of this article.

Following any of the horizontal lines in the ternary diagram of Fig. 2, between $\omega_W = 0$ and $\omega_{\text{THF}} = 0$, one can appreciate the effect of the solvent quality on the formation of the equilibrium morphologies. In particular, at a given BCP concentration, between $\omega_{\text{BCP}} = 0.05$ and 0.50, we find at least one transition involving ordered and disordered mesophases. At low BCP concentrations, the morphological transitions are dominated by changes in the solvent conditions, whereas at relatively high BCP concentrations this effect becomes less evident. At $\omega_{\text{BCP}} = 0.50$, the copolymer's chains are unable to form long-range order structures at $f_w \leq 0.20$. However, at $f_w = 0.30$, lamellar phases, which remain substantially unchanged upon further addition of water, are observed. A more intriguing behavior is detected at slightly lower BCP concentrations, precisely at $\omega_{\text{BCP}} = 0.40$, where dispersed finite-size sheets or disk-like aggregates, forming at $f_w = 0.50$, are found in between disordered phases and lamellae. Both disk-like aggregates and lamellae are reported in Fig. 3(d) and (f), respectively.

By gradually decreasing the BCP's concentration, the complexity and richness of the aggregation behavior significantly increase with more morphologies

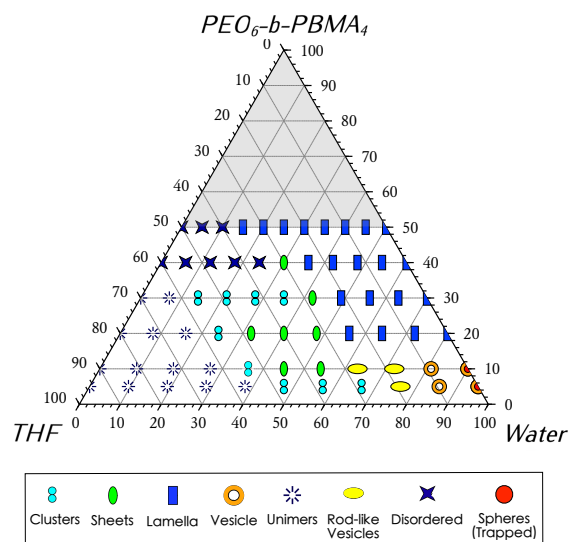


Figure 2: Morphological diagram of PEO_6 - b - $PBMA_4$ in water and THF at $T = 300$ K. The compositions are given in wt%. The symbols refer to different self-assembled structures as indicated in the legend panel. The shaded area has not been studied.

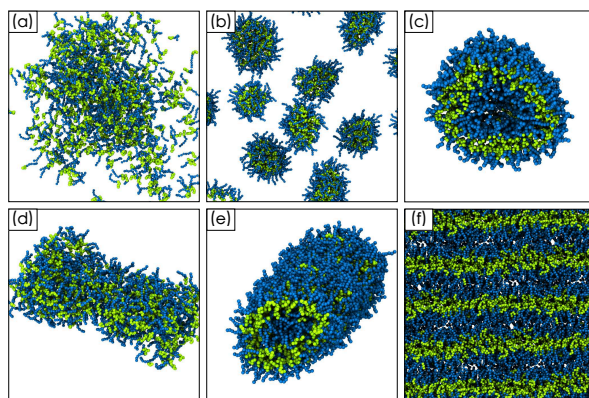


Figure 3: Representative snapshots of the morphologies obtained from the self-assembly of PEO_6 - b - $PBMA_4$ in water and THF: (a) clusters, (b) kinetically-trapped spheres (see text for details), (c) spherical vesicles, (d) dispersed sheets or disk-like aggregates, (e) rod-like vesicles and (f) lamellae. Green and blue beads correspond to PBMA and PEO blocks, respectively. THF and water are not shown for clarity.

forming. The iso-concentration line $\omega_{\text{BCP}} = 0.30$ displays dissolved chains or unimers at $f_w \leq 0.10$, small quasi-spherical clusters at $0.20 \leq f_w \leq 0.50$, dispersed sheets or disk-like aggregates at $f_w = 0.60$, and lamellae at $f_w \geq 0.70$. The difference between the unimer and disordered state is based solely on the composition: while in the unimer state chains can be considered as being dissolved in a continuous liquid phase of solvents, the disordered state is characterized by a dense phase where the BCP can be regarded as the continuous phase. The clusters of Fig. 3(a), forming at weak segregation conditions for $0.20 \leq f_w \leq 0.50$, do not present fully-separated hydrophobic and hydrophilic domains, and thus cannot be classified as micelles. A similar set of morphologies are also obtained at $\omega_{\text{BCP}} = 0.20$, where the stability region of dispersed sheets or disk-like aggregates is significantly larger as compared to $\omega_{\text{BCP}} = 0.30$. The impact of the solvent composition on the self-assembly of the BCP chains was found to be more pronounced at very low copolymer concentrations. In particular, at $\omega_{\text{BCP}} = 0.05$, chains are completely dispersed in the solvent for $f_w \leq 0.40$. Under these conditions, the dissolving effect of THF, which is a good solvent for both PEO and PBMA blocks, dominates over the block-selective interactions that are established by water. However, for $f_w > 0.40$, the amount of water is sufficient to promote segregation between the hydrophilic and hydrophobic blocks as a consequence of its repulsive interactions with the bulky PBMA segments. It is very remarkable to notice that the water content at $f_w = 0.50$, corresponding to 0.48 wt%, lies within the range of the typical experimental values of the so-called *critical water concentration (CWC)*, defined as the minimum water concentration that produces micellization in the presence of a common solvent [8]. The CWC is analogue to the CMC for aqueous solutions of small surfactants and depends on the properties of both BCP and common solvent [52]. At $0.50 \leq f_w \leq 0.70$, we observe a dispersion of quasi-spherical clusters that, by further addition of water, transform into rod-like vesicles at $f_w = 0.80$. These vesicles, reported in Fig. 3(e), undergo a transition to spherical vesicles at $f_w = 0.90$ and eventually evolve into spheres upon further increasing of the water/THF ratio and up to $f_w = 1$. The aforementioned

morphologies have been experimentally observed on a family of PEO-*b*-PBMA
 250 copolymers, whose aggregation behavior in water/THF mixtures was shown to
 be determined by the proportion of the PEO and PBMA blocks in the chains
 and the non-selective (common) cosolvent [45].

To gain a clearer understanding on how the relative content of co-solvents
 influences our system's polymorphism, we now focus on the iso-concentration
 255 line $\omega_{\text{BCP}} = 0.10$. It is well-known that the self-assembly of BCPs is mainly
 governed by the balance of three free-energy contributions determined by (i) the
 chains' conformation within the aggregate, (ii) the interface tension between the
 hydrophobic core and selective solvent, and (iii) the repulsive interactions be-
 tween the hydrophilic groups in the aggregate's corona [8]. All these properties
 260 can be altered by modifying the ratio between the selective and non-selective
 solvent. It is therefore crucial to understand how the local environment of both
 PEO and PBMA blocks changes with f_w . To this end, we analyzed the spa-
 tial correlations established between these two blocks and the co-solvents. More
 specifically, given a bead of type A, the average number of beads of type B, z_{AB} ,
 265 that can be found within a spherical shell of radius $r_c = 1.2$ nm (corresponding
 to the cut-off distance of the pair interactions) centred on particle A, is obtained
 from the spatial integration of the pair-correlation function $g_{\text{AB}}(r)$ and reads

$$z_{\text{AB}} = \langle \rho_{\text{B}} \rangle \int_0^{r_c} 4\pi r^2 g_{\text{AB}}(r) dr, \quad (4)$$

where $\langle \rho_{\text{B}} \rangle$ is the number density of beads of type B averaged over all spheres
 around particles A. In Fig. 4, we report z_{AB} for the PEO and PBMA_b beads
 270 as obtained at $\omega_{\text{BCP}} = 0.10$ and for a range of common/selective solvent ratios
 producing aggregates, that is $0.30 \leq f_w \leq 1.0$.

By gradually increasing f_w , the local distribution of the co-solvents around
 the two BCP's blocks changes. On the one hand, $z_{\text{PEO-THF}}$ and $z_{\text{PBMA}_b\text{-THF}}$
 decrease by approximately 60% and 70%, respectively, upon an increase of f_w
 275 from 0.3 to 0.9. Such a comparable decrease is due to the similar affinity of
 THF with both BCP blocks. On the other hand, $z_{\text{PEO-Water}}$ and $z_{\text{PBMA}_b\text{-Water}}$

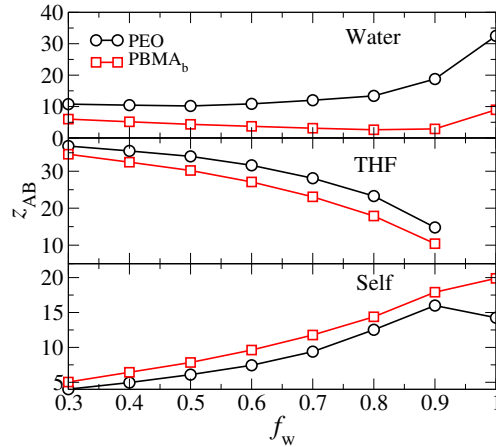


Figure 4: Average number of water (top frame), THF (middle frame), and PEO and PBMA_b (bottom frame) beads in a sphere of radius $r_c = 1.2$ nm centred on a PEO (black circles) or PBMA_b (red squares) site as a function of f_w at $\omega_{BCP} = 0.10$. The solid lines are guides for the eye.

present a rather slight variation with f_w . In particular, the number of water molecules around the PEO beads slowly increases as a consequence of the removal of THF. Significant changes are detected at $f_w > 0.8$ where $z_{\text{PEO-Water}}$ increases from 15 up to 32 at $f_w = 1.0$. In contrast, $z_{\text{PBMA}_b\text{-Water}}$ remains effectively unchanged and exhibits a very small decrease up to $f_w = 0.9$. This indicates the tendency of the PBMA blocks to avoid the unfavourable contacts with water. Therefore in order to keep $z_{\text{PBMA}_b\text{-Water}}$ at a minimum value upon the additon of water, the BCP chains start to aggregate into the increasingly packed structures as suggested by the increase in the local number of like sites (bottom frame in Fig. 4). This mechanism results in the morphological transitions reported in Fig. 2, which follow a cluster→sheet→rod-like vesicle→spherical vesicle sequence. From previous studies, it has been demonstrated that the aggregate-solvent interfacial area always decreases when BCP assemblies change from spherical clusters to rods to vesicles [53, 41], suggesting that the morphological transformations arise in part as a thermodynamic response of the system to reduce the interfacial energy component of the total

free energy.

It should also be mentioned that while water and THF are macroscopically
295 miscible in the whole range of compositions at $T = 300$ K [54], the presence of
the BCP's aggregates seems to promote a small-scale segregation resulting in
the redistribution of THF around the assemblies. This can be appreciated in
Fig. 5, where we report the density profiles of water, THF, PEO and PBMA_b
beads as a function of the radial distance from the center of mass of a vesicle
300 formed at $\omega_{\text{BCP}} = 0.10$ and $f_w = 0.90$. From these profiles one can observe
that the aggregate is a hollow sphere with a well-defined hydrophobic wall and
hydrophilic internal and external coronas, and entrapping water and THF in
the interior (see Fig. 3(c)). The THF density distribution follows very closely
that of the PEO block, suggesting a strong spatial correlation between these two
305 type of beads. Consequently, the relative water-to-THF content decreases from
9, in the center of the vesicle, to 0.4 at $r \approx 40$ Å, where the inner hydrophilic
wall surrounding the internal solvents and indicated by the first peak of ρ_{PEO} is
located. The slightly asymmetric profile of ρ_{PEO} is most likely due to the shape
fluctuations of the vesicle's cross sectional area, here assumed circular to esti-
310 mate the density distribution profiles, but actually ellipsoidal over a significant
simulation time window (additional details in the Supporting Information).

Special attention deserve the systems at $f_w = 1.0$ and $\omega_{\text{BCP}} \leq 0.10$. These
systems, which are binary mixtures of water and BCP, do not form the spherical
vesicles observed at $\omega_{\text{THF}} = 0.10$, but rather a nearly mono-dispersed popula-
315 tion of spherical aggregates, resembling large micelles. According to Johnson
and Prud'homme, *micelles* are dynamic systems characterized by fast unimer
exchange rates, while *nanoparticles* are kinetically trapped systems, where the
unimer exchange rate is extremely slow [55]. Although no inter-aggregate chain
exchange has been detected over a significant simulation time, spanning several
320 microseconds, we are aware that in selective solvents the unimer exchange rate
can vary between milliseconds and minutes [56]. Consequently, we are not in
the position to unambiguously affirm whether the spherical aggregates formed
at $f_w = 1.0$ are frozen or dynamic objects. Because very slow exchange rates

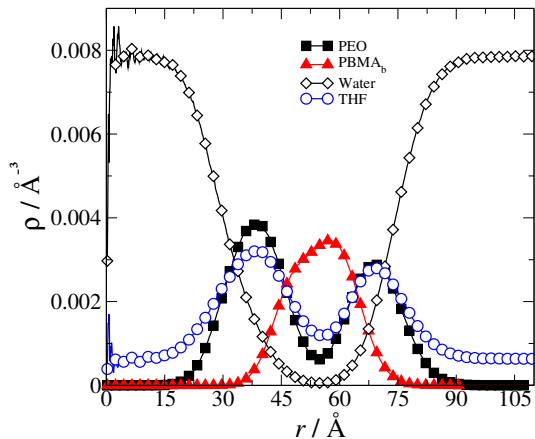


Figure 5: Local number density profile of PEO, PBMA_b, THF and water beads as a function of the radial distance, r , from the center of mass of a vesicle at $\omega_{\text{BCP}} = 0.10$ and $f_w = 0.90$.

can still spark morphological transitions at very long time scales [57], the relative stability of the spherical aggregates found at $f_w = 1.0$ with respect to the
325 (expected) vesicular structures was also assessed by using as starting configuration the vesicular system obtained at $f_w = 0.9$. To this end, all the THF beads in this configuration were replaced by water beads and an extra $5 \mu\text{s}$ MD trajectory produced. Over this simulation time, no vesicle-to-sphere transition
330 occurred, confirming the key role played by the common solvent in determining the aggregation kinetics. Similarly, by simulating the spheres obtained at $f_w = 1.0$ and adding the amount of THF to get $f_w = 0.9$, we observed the direct transition to the vesicular structure after the first microsecond. We conclude that the dispersed spheres at $f_w = 1.0$, although being highly stable (for about
335 $6 \mu\text{s}$) and monodisperse (with a mean aggregation number $N_{\text{agg}} = 143 \pm 11$) might be kinetically-frozen morphologies as we indicate in the ternary diagram of Fig. 2.

To better understand the effect of the non-selective solvent on the self-assembly process, we now focus our attention on the aggregation kinetics by tracking the number of clusters, N_{cluster} , as a function of time at varying f_w .
340 In this work, two chains are considered to be part of the same cluster, if the

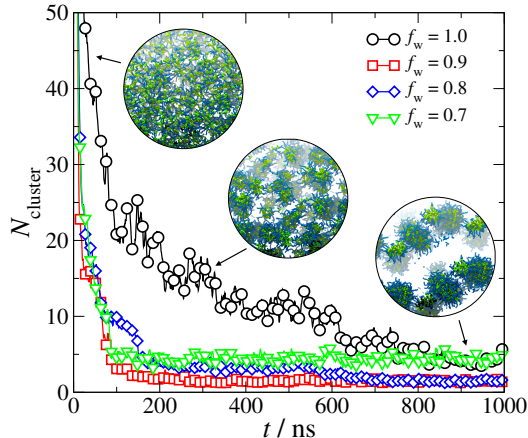


Figure 6: Time dependence of the number of clusters forming in water/THF/BCP mixtures at $\omega_{\text{BCP}} = 0.10$ and $0.70 \leq f_w \leq 1.0$. Chains are dissolved at time $t = 0$ ns. The three insets are intermediate configurations of the system with $f_w = 1.0$.

distance between any of their beads is lower than 1.2 nm. In Fig. 6, we present the time dependence of N_{cluster} in systems with solvent ratio $0.70 \leq f_w \leq 1.0$. The initial configuration of these systems consists of randomly dissolved unimers
345 that start assembling into small spherical clusters during the first hundreds of nanoseconds. Over larger time scales, such small aggregates merge into larger-sized assemblies and then stabilize into the final morphologies. It is interesting to note that the evolution from the initially dissolved unimers to the equilibrium segregated state occurs at different rates depending on the solvent quality. It is
350 during the first 500 ns that the effect of the presence of THF is more evident. The fast decay of N_{cluster} for $f_w = [0.7, 0.9]$ suggests that the BCP chains can more easily diffuse in solution and relax into the self-assembled aggregates as compared to the system without THF. When only water is present, the strong segregation conditions and poor solvent quality for the PBMA blocks impose a
355 kinetic frustration of the components into spherical assemblies and the formation of vesicular nanostructures is suppressed, at least in the time-scale of our simulations.

This kinetic frustration might strongly be related to the impact of the solvent quality on the BCP chains' conformation, which ultimately regulates their ability to diffuse from and to the aggregates. It is also known that the morphological transitions in BCP aggregates are influenced by the entropic penalty associated to the reduction in the available conformations due to confinement of the chains within the assemblies [8]. To determine how the chain conformation changes as a function of the common/selective solvent ratio, we estimated the BCP mean-square end-to-end distance, which reads

$$\langle R_{ee}^2 \rangle = \left\langle \left(\sum_i^n \vec{r}_i \right) \cdot \left(\sum_j^n \vec{r}_j \right) \right\rangle \quad (5)$$

where \vec{r}_i is the bond vector i in the chain of size $N_b = n + 1$ sites. We compute $\langle R_{ee}^2 \rangle$ for the whole chain by a summation of the bond vectors over the PEO and PBMA_b segments. The resulting dependence of $\langle R_{ee}^2 \rangle$ on f_w is reported in Fig. 7. As a general tendency, $\langle R_{ee}^2 \rangle$ increases up to $f_w = 0.9$, indicating that the individual chains gradually stretch when the BCP assemblies undergo morphological transitions in the cluster \rightarrow sheet \rightarrow rod-like vesicle \rightarrow spherical vesicle sequence. However, an inversion is observed at $f_w = 1.0$, where kinetically-trapped spheres are formed. These structural changes are in agreement with experimental observations [9] and simulation results [41].

By further analyzing the structure of the chains, we note that the ratio between $\langle R_{ee}^2 \rangle$ and the mean-square radius of gyration, $\langle R_g^2 \rangle = 1/N_b \sum_{i=1}^{N_b} \sum_{j=1}^{N_b} \left\langle \left(\vec{R}_i - \vec{R}_j \right)^2 \right\rangle$, with \vec{R}_i the position vector of site i , is in all the cases $\langle R_{ee}^2 \rangle / \langle R_g^2 \rangle \approx 6$ (see Supporting Information), which agrees with the Debye result of ideal linear chains [58]. The quasi-ideal conformations adopted by the chains are not specially surprising, because the interactions between BCP sites are highly screened in both the dissolved and aggregated states. Under these considerations, the change in the ideal conformational entropy per BCP chain within the assemblies with respect to the unimer state can be assumed to

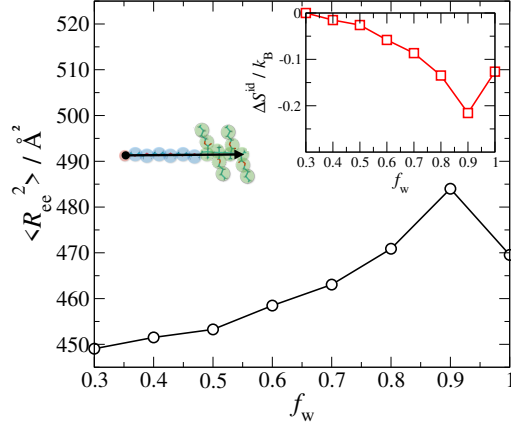


Figure 7: Mean-square end-to-end distance of BCP chains as a function of f_w at $\omega_{\text{BCP}} = 0.10$. The corresponding changes in the ideal chain entropy per chain, ΔS^{id} , with respect to the unimer state are reported in the inset. The solid lines are a guide for the eye.

depend only on $\langle R_{ee}^2 \rangle$ and roughly approximated to [58]:

$$\Delta S^{\text{id}} = 3k_B \left[\langle R_{ee}^2 \rangle_{f_w=0} - \langle R_{ee}^2 \rangle_{f_w} \right] / 2N_b \langle \sigma \rangle^2, \quad (6)$$

375 where $\langle \sigma \rangle = 4.66 \text{\AA}$ is the average bead size. The dependence of ΔS^{id} on f_w is reported in the inset of Fig. 7. The balance between this entropically unfavourable effect (increase in the conformational term of the free energy) and the energetic interactions leads to the observed morphological transitions.

Finally, the distinct BCP size of $\text{PEO}_{12}\text{-}b\text{-PBMA}_{10}$ leads to the formation
 380 of significantly different self-assembled structures as observed in the morphological phase diagram reported in the Supplementary Information. This ternary system produced just few common morphologies observed in the THF/water solutions of $\text{PEO}_6\text{-}b\text{-PBMA}_4$. These include lamellar phases, which were observed at $\omega_{\text{BCP}} = 0.40$ and solvent ratios $0.10 \leq f_w \leq 0.30$, and kinetically-stabilized
 385 spheres, found at the BCP concentrations of $\omega_{\text{BCP}} = 0.10$ and $\omega_{\text{BCP}} = 0.20$, only in the presence of water. The curve of the CWC, which defines the boundary between the disordered and aggregated states, closely follows that of the $\text{PEO}_6\text{-}b\text{-PBMA}_4$ diagram. Other interesting meshophases such as rod-like micelles

and distorted lamellae appear at intermediate values of f_w and BCP contents.
390 More importantly, we detected a large region where bicontinuous structures
are formed. In a bicontinuous phase, a twisted network of the hydrophobic
blocks intertwines with that of the hydrated hydrophilic segments. Sommerdijk
and coworkers recently reported the formation of bicontinuous structures from
the spontaneous self-assembly of a family of PEO-*b*-PBMA diblock copolymers
395 in water/THF mixtures [45]. They found that the PEO content was critical
in the stabilization of such morphology as BCPs with PEO contents of
 $M_{\text{PEO}}/M_{\text{BCP}} = 0.14$ and 0.17 allowed for its formation. In contrast, BCPs with
PEO contents of 0.40 did not exhibit this mesophase. In our case, PEO₁₂-*b*-
PBMA₁₀, with a PEO content of 0.27 , produces bicontinuous structures whereas
400 PEO₆-*b*-PBMA₄, with a relatively larger PEO content (0.31) does not present
such a phase. Thus our simulation results also point to the importance of the
molecular weight and hydrophilic/hydrophobic balance on the self-assembling
behavior.

4. Conclusions

405 In summary, we have performed extensive MD simulations to investigate
the self-assembly of PEO₆-*b*-PBMA₄ and PEO₁₂-*b*-PBMA₁₀ copolymers in bi-
nary mixtures of water (selective solvent) and THF (common solvent). The
dependence of the aggregate morphology on the molecular weight and hy-
drophilic/hydrophobic ratio of the copolymer chains has been evidenced, with
410 the general observation that finite-size aggregates including spherical clusters,
dispersed sheets or disk-like aggregates, anisotropic rod-like vesicles and spher-
ical vesicles are predominantly formed from PEO₆-*b*-PBMA₄, which is char-
acterized by a lower hydrophilic content of $M_{\text{PEO}}/M_{\text{BCP}} = 0.27$ with respect
to the 0.31 of PEO₁₂-*b*-PBMA₁₀. The latter exhibits mainly distorted lamel-
415 lae, rod-like micelles, spheres and more importantly, a large portion of the
non-conventional and technologically attractive bicontinuous structures. The
majority of these mesophases have been experimentally obtained from the self-

assembly of PEO-*b*-PBMA BCPs in mixtures of water and THF [45]. Furthermore, we have demonstrated that the equilibrium morphology of the self-assembled aggregates is not solely determined by the BCP chain size and concentration. Our simulation results unambiguously indicate that for a fixed BCP content and size, tuning the solvent conditions, in particular the selective/common solvent ratio, is sufficient to induce reversible morphological transitions of the aggregates. This is a consequence of the changes in the spatial correlations between the solvent molecules and each of the copolymer blocks as the mixture composition is modified. Our results also confirm that the morphological transformations promoted by an increase in the amount of selective solvent (water) are accompanied by an entropically unfavourable effect associated to the systematic stretching of the individual chains. Finally, we have seen that the presence of the common solvent strongly influences the self-assembly mechanism by facilitating the aggregation of the chains and thus minimizing the possible formation of kinetically-frozen assemblies.

Acknowledgements

The authors acknowledge useful discussions on the experimental methods with Dr Joe Patterson (University of California, Irvine) and Paula Vena (Eindhoven University of Technology). The project leading to these results has received funding from the European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 676045 (MULTIMAT).

Appendix A. Supporting Information

Detailed information on the employed force-field parameters, simulation systems, pair-correlation functions, vesicle shape fluctuations and PEO₁₂-*b*-PBMA₁₀/water/THF phase diagram can be found in the online version, at <http://>

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