Supporting Information: Solvent Controls
Nanoparticle Size during Nanoprecipitation by Limiting Block Copolymer Assembly

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Section S1: Characterization of nanoparticles by electron microscopy and light scattering

Nanoparticle size measured by dynamic light scattering and electron microscopy

For all solvents utilized in this study, the nanoparticles (NPs) formed were spherical (Figure S1a) with low dispersity (Figure S1b-f). The raw data of NP size for tests performed in this study is provided in Section S8.

Figure S1. a) TEM picture of PEG-\textit{b}-PLA NPs (10 mg mL\(^{-1}\) in acetonitrile). Scale bar, 100 nm. b) Size distribution of NPs synthesized from 10 mg mL\(^{-1}\) PEG-\textit{b}-PLA solutions in DMSO (\(R = 0.005\)), c) THF, d) acetonitrile, e) acetone, and f) DMF. Error bars represent mean ± standard deviation (SD) for three independent experiments.

Solvent partition and fraction in the obtained NPs

Block copolymer nanoprecipitation using water-miscible organic solvents could lead to the inclusion of solvent in the NP core leading to a change in NP size. In the literature, small
angle neutron scattering (SANS) has demonstrated that the residual solvent fraction inside similar block copolymer particles correlates with the total fraction of solvent of the particle suspension. Low solvent fraction in the suspension <0.10 is usually associated with low solvent fraction inside particles. In our work, the final NP suspension had a solvent fraction that was lower than 0.005 (R = 0.005) suggesting that the residual solvent in the NP core was negligible.

To ensure that the potential inclusion of solvent had limited or no effect on NP size and NP stability, we nanoprecipitated NPs with several of the polymer–solvent combinations tested in this work. To favor solvent diffusion from the NP core, the formed NP suspensions were dialyzed against water and NP size was monitored over 2 days (Figure S2). The results suggested that NP size was stable over time. Based on the reported literature studies, the low solvent fraction used for all conditions in this work, and the experimental data, we assumed that solvent inclusion in the NP core did not contribute to the size effects observed in this work.

Figure S2. NP size during dialysis against pure water. Particles were batch nanoprecipitated from 10 mg mL\(^{-1}\) precursor solutions in different water-miscible solvents (R = 0.005). Subsequently, the suspensions were dialyzed against water for up to 2 days.
Section S2: Hansen Solubility Parameter distance and pure solvent viscosity

Hansen Solubility Parameter (HSP) distances, $Ra$, were estimated based on the handbook *Hansen Solubility Parameters* by Charles M. Hansen. The distance between the HSP of water and the organic solvent, $Ra$, was calculated based on reported values for dispersion ($\delta_D$), permanent dipole–permanent dipole ($\delta_P$) interactions, and for hydrogen bonding ($\delta_H$) (Table S1). Lower $Ra$ values imply that two solvents are similar with respect to their intermolecular contributions and their mixing is more favorable compared to solvents with higher $Ra$.

$$Ra^2 = 4 \cdot (\delta_{D1} - \delta_{D2})^2 + (\delta_{P1} - \delta_{P2})^2 + (\delta_{H1} - \delta_{H2})^2 \quad (1)$$

$Ra$ was lowest for DMF followed by DMSO, acetone, THF, and acetonitrile.

The viscosity of pure solvents was compared: $\mu_{acetone} < \mu_{acetonitrile} < \mu_{THF} < \mu_{DMF} < \mu_{DMSO}$. 

Table S1: Solvent viscosity and HSPs

| Solvent    | $\delta_D$ | $\delta_P$ | $\delta_H$ | $Ra$  | $\mu$   |
|------------|------------|------------|------------|-------|---------|
|            | MPa$^{-\frac{1}{2}}$ | MPa$^{-\frac{1}{2}}$ | MPa$^{-\frac{1}{2}}$ | MPa$^{-\frac{1}{2}}$ | mPa s   |
| Water      | 15.5       | 16         | 42.3       | 0.00  | 0.82    |
| DMF        | 17.4       | 13.7       | 11.3       | 31.3  | 0.82    |
| DMSO       | 18.4       | 16.4       | 10.2       | 32.6  | 2.00    |
| Acetone    | 15.5       | 10.4       | 7          | 35.7  | 0.33    |
| THF        | 16.8       | 5.7        | 8          | 35.9  | 0.55    |
| Acetonitrile| 15.3      | 18         | 6.1        | 36.3  | 0.38    |

We further estimated HSP distances for all water–solvent solutions and core-forming copolymer blocks because nanoprecipitation is mainly governed by interactions between the hydrophobic polymer block and its surrounding environment. To achieve this, HSP distances were estimated for water–solvent solutions as a function of the water volume fraction, $\phi$, by
using the following equation:

$$\delta_{\text{mix}} = \delta_{\text{water}} \cdot \phi + \delta_{\text{solvent}} \cdot (1 - \phi)$$

(2)

HSP parameters for PLA, PLGA, and PCL were retrieved from literature and are reported in Table S2. The HSP distances shown in Figure S3 were estimated using the polymer HSP reported in Table S2. In total, no correlation between the resulting NP size and Ra was found.

Table S2: HSP for core-forming polymer blocks retrieved from ref. 5

| Polymer | $\delta_D$ | $\delta_P$ | $\delta_H$ |
|---------|-----------|-----------|-----------|
| PLA     | 16.1      | 10.3      | 6.4       |
| PLGA    | 17.4      | 14.3      | 6.7       |
| PCL     | 16.9      | 3.2       | 4.4       |

Figure S3. HSP distance, Ra, between core-forming polymer blocks and water–solvent solutions. Estimated data is shown for a) PLA, b) PLGA, and c) PCL.
Section S3: Comparison between turbidity and DLS data

To estimate if suspension turbidity was dependent on the $\phi$ step size, turbidity trends were performed with $\Delta\phi$ steps of 0.01, 0.02, and 0.03 (Figure S4a). There was no noticeable difference between the different turbidity curves, indicating that the $\phi$ step size had a negligible effect on the overall turbidity evolution.

In preliminary experiments, DLS measurements were performed on nanostructure suspensions during the turbidity measurements to further analyze polymer assemblies. For $\phi < \phi_c$ the formed assemblies were large and non-uniform (Figure S4b). Each replicate of the DLS measurement was different, indicative of the dispersity of the polymer assemblies or an unstable and dynamic population. Under these conditions, it was not possible to reliably fit the correlogram; therefore, DLS was not suitable for characterizing assemblies with $\phi < \phi_c$. The same polymer assemblies collapsed to small and stable particles beyond $\phi_c$. In this regime ($\phi \geq \phi_c$), the particles could be analyzed via DLS and were stable over time with $D \approx 0.1$. In total, the DLS results corroborated the turbidity data. A similar trend was found for increasing and decreasing $\phi$ showing that the relative positioning of $\phi$ and $\phi_c$ were critical for determining the properties of the polymer assemblies (Figure S4c, d).
**Figure S4.** Turbidity and DLS measurements were performed on 10 mg mL\(^{-1}\) PEG-b-PLA in acetonitrile–water mixtures. a) Turbidity trends for \(\Delta \phi\) 0.01, 0.02, and 0.03 steps were similar for all nanostructure suspensions. b) DLS results of PEG-b-PLA in acetonitrile as a function of \(\phi\) suggested polymer assembly stabilization if \(\phi \geq \phi_c\). Correlogram fitting for \(\phi < \phi_c\) was not reliable. The population was hypothesized to be too disperse or dynamic to be characterized. The same suspensions at \(\phi \geq \phi_c\) gave reliable DLS results with \(D \approx 0.1\). c) NP size and d) \(D\) of a 10 mg mL\(^{-1}\) PEG-b-PLA nanostructure population for increasing and decreasing \(\phi\). DLS corroborated that the relative positioning of \(\phi\) and \(\phi_c\) determined the properties of the suspensions. In total, higher turbidity (a) corresponded to larger and more disperse polymer assemblies in DLS measurements (b, c, and d). Lower turbidity was associated with smaller and colloidally stable assemblies.
Section S4: Supporting turbidity data

Turbidity measurements were extended to pure solvent solutions (without polymers; Figure S5a). The absolute turbidity data of Figure 2b is shown in Figure S5b. Solutions with other block copolymers such as PEG-b-PLGA and PEG-b-PCL (Figure S6).

Figure S5. Supplementary turbidity data. a) Turbidity of pure DMF, acetone, acetonitrile, THF, and DMSO as a function of $\phi$. The orange and blue regions highlight the dynamic and frozen regions respectively. b) Absolute absorbance related to 10 mg mL$^{-1}$ PEG-b-PLA solutions used in this study. This dataset is related to Figure 2b.

Figure S6. Turbidity of 10 mg mL$^{-1}$ PEG-b-PLGA (triangles) and PEG-b-PCL (squares) in various solvents. $\phi_c$ were found to be a) 0.18 ± 0.02, b) 0.24 ± 0.02, c) 0.22 ± 0.02, d) 0.14 ± 0.02, and e) 0.12 ± 0.02.
Section S5: Time-resolved turbidity showed aggregate dynamics

Rearrangement dynamics of nanostructures were described by monitoring the turbidity time evolution following a $\phi$ step change (Figure S7). For $\phi < \phi_c$ the polymer assemblies exhibited dynamics of rearrangement on the order of seconds or longer. For $\phi \geq \phi_c$ no turbidity evolution was measured, suggesting a stable system.

Figure S7. A nanostructure suspension of 4 mg mL$^{-1}$ PEG-$b$-PLA in acetonitrile was monitored upon 0.02 water fraction step changes. a) In the dynamic region ($\phi < \phi_c$), a $\phi$ increase b) or decrease showed nanostructure evolution dynamics on the order of seconds. The polymer assemblies seemed to become stable when the turbidity stopped evolving at $\phi \geq \phi_c$.

Eisenberg et al. reported that the timescale of block copolymer dynamics, $\tau_{\text{dyn}}$, during assembly can be estimated with the following exponential function:

$$T = a + b \cdot \left(1 - e^{-t/\tau_{\text{dyn}}}\right),$$

where $T$ represents turbidity, $t$ the time, and $a$ and $b$ are fitting constants. After fitting the equation to the experimental turbidity data, the results showed that for all $\phi$ step-changes in the dynamic region ($\phi < \phi_c$) $\tau_{\text{dyn}}$ was on the order of seconds (Figure S8 and Table S3 and S4).
Table S3: Regressed parameters of the exponential function (3) for the determination of τ_{dyn} upon increasing \( \phi \) steps. Data reported as mean ± SD for three independent experiments.

| \( \phi \)   | \( a \)          | \( b \)          | \( \tau_{dyn} \) | \( R^2 \) | Fig. S8 |
|-------------|------------------|------------------|------------------|----------|---------|
| 0.20 to 0.22 | 0.710 ± 0.114   | 0.176 ± 0.082   | 78 ± 36          | 0.962    | a       |
| 0.22 to 0.24 | 1.121 ± 0.070   | -0.014 ± 0.038  | 212 ± 295        | 0.425    | b       |
| 0.24 to 0.26 | 0.868 ± 0.111   | -0.154 ± 0.068  | 34 ± 14          | 0.909    | c       |
| 0.26 to 0.28 | 0.237 ± 0.104   | -0.038 ± 0.017  | 51 ± 25          | 0.960    | d       |

Table S4: Regressed parameters of the exponential function (3) for the determination of τ_{dyn} upon decreasing \( \phi \) steps. Data reported as mean ± SD for three independent experiments.

| \( \phi \)   | \( a \)          | \( b \)          | \( \tau_{dyn} \) | \( R^2 \) | Fig S8 |
|-------------|------------------|------------------|------------------|----------|--------|
| 0.30 to 0.28 | 0.170 ± 0.011   | 0.034 ± 0.074   | 328 ± 444        | 0.959    | e      |
| 0.28 to 0.26 | 0.288 ± 0.054   | 0.812 ± 0.055   | 919 ± 111        | 0.997    | f      |
| 0.26 to 0.24 | 0.902 ± 0.024   | 0.210 ± 0.022   | 147 ± 31         | 0.990    | g      |
| 0.24 to 0.22 | 0.586 ± 0.095   | 0.137 ± 0.036   | 96 ± 36          | 0.981    | h      |

Figure S8. Experimental turbidity evolution and fitted exponential model of 4 mg mL\(^{-1}\) PEG-\(b\)-PLA in acetonitrile for a-d) increasing 0.02 water fraction steps and e-h) decreasing 0.02 water fraction steps. Experimental data (circles) and regressed model (line) shown for one independent experiment.
Section S6: Short- and long-term stability of NPs

The short-term NP stability is dictated by the extent of polymer dynamics

NP stability measurements were performed by measuring the turbidity of the nanostructure suspension over hours. Absorbance was measured each second at $\lambda \approx 500$ nm. A decrease in suspension turbidity showed that dynamic nanostructures ($\phi < \phi_c$) were prone to sedimentation (Figure S9). Sedimentation could be caused by aggregation as unimer exchange and growth can still take place in the dynamic region. The same population in an environment associated with limited polymer dynamics ($\phi > \phi_c$), showed stable turbidity over hours indicating short-term stability.

![Figure S9](image)

Figure S9. Sedimentation of 10 mg mL$^{-1}$ PEG-b-PLA solutions. a) NPs in 0.24 $\phi$ ($\phi < \phi_c$; orange line) showed a decrease in turbidity over time. The same sample population at 0.50 $\phi$ ($\phi > \phi_c$; blue line) demonstrated a constant turbidity over the same time course. b) Magnification of data shown in a). The data suggested that polymer assemblies in a dynamic environment ($\phi < \phi_c$) were more prone to aggregation and sedimentation. The same population in a kinetically trapped environment ($\phi > \phi_c$) formed colloidally stable NPs.
The long-term NP stability is governed by the properties of the polyester core

When the $\phi$ is greater than $\phi_c$ the nanostructures are colloidally stable. NP stability is governed by the properties of the PEG surface chains present on each particle corona. In a particle suspension, when two particles come into proximity, the two particle coronas start overlapping and the PEG chain mobility decreases. This PEG confinement is associated with a state of unfavorable entropy. Therefore, a repulsive force pushes the particles apart to restore the more favorable entropic state with higher PEG chain mobility. This stabilization mechanism is preserved as long as the chemical block copolymer structure is intact. The NP cores tested in this study were made of polyesters, which can be hydrolytically cleaved over time depending on the monomer structure, chain molecular weight, hydrophilicity, crystallinity, phase separation, and material processing. This degradation process is beneficial for the application of these polymers as NPs and biodegradable medical devices.
Section S7: Full derivation of the scaling law based on spinodal decomposition and growth kinetics

To explain the NP sizes observed with different solvents and block copolymers, we developed a physical model of nanoprecipitation based on spinodal decomposition. We assumed that the size of the formed NPs was controlled during the first phase of unimer assembly, where mixing between solvent and water triggers aggregate growth up to a point of growth arrest: the critical water fraction of growth arrest, $\phi_c$. In our proposed model, the main mechanism of block copolymer (unimer) assembly is via unimer insertion (Section S7.1: Model based on spinodal decomposition).\(^{13,14}\) The driving forces of this process are the Free Energy of the system and unimer diffusion, which are both described by the Cahn–Hilliard equation.\(^{15}\)

During nanoprecipitation, mixing between the organic solvent and water is modelled as a single solvent with varying $\chi$, thus tuning the interfacial energy between the hydrophobic aggregate core and the surrounding medium, $\gamma_e$ (Section S7.2: Effects of the mixing kinetics).\(^{16}\) Finally, we consider that, at a specific solvent–water composition, $\phi_c$, the growth of the formed aggregates is arrested and the NPs become kinetically trapped (Section S7.3: Arrest of NP growth and termination of unimer exchange).

Section S7.1: Model based on spinodal decomposition

Section S7.1.1: The initial phase of unimer assembly is governed by diffusion.

In nanoprecipitation, the mixing process between block copolymer solvent and antisolvent is convective owing to the high shears exerted by the mixing unit or potential turbulence generated in flow devices. To understand whether convection or diffusion controlled unimer aggregation, we compared the characteristic length scales of the two processes. Given the high velocity and presence of vortcities in the CJM, we assumed that the convective length scale can be described by the Kolmogorov length scale. The Kolmogorov length scale, $L_K$, represents the characteristic size of the smallest fluid element in a turbulent flow at which
the kinetic energy is dissipated. Below $L_K$ viscosity dominates and mixing processes are dominated by diffusion, whereas above $L_K$ mixing processes are dominated by convection. $L_K$ was estimated as follows:

$$L_K = \left( \frac{\nu^3}{\bar{\epsilon}} \right)^{\frac{1}{4}} \quad (4)$$

where $\nu$ is the kinematic viscosity of a fluid and $\bar{\epsilon}$ is the average rate of dissipation of turbulence kinetic energy per unit mass and was calculated as

$$\bar{\epsilon} = 0.0668 \left( \frac{\bar{u}^3}{Re^{0.25} L_{CJM}} \right) \quad (5)$$

where $\bar{u}$ is the average flow velocity, $Re$ is the Reynolds number, and $L_{CJM}$ is the inner diameter of the flow channel. During nanoprecipitation in our CJM, we estimated the Kolmogorov length scale to be $L_K \sim 0.1–1 \mu m$. The average distance between two unimers in solution was calculated by assuming a homogeneous spatial distribution of 10 mg mL$^{-1}$ of unimers in an organic solvent. This yielded a characteristic distance between polymer chains of $\sim 16$ nm. As the distance between polymer chains is orders of magnitude smaller than the Kolmogorov length scale, we concluded that the beginning of unimer aggregation into NPs was mainly driven by diffusion.

**Section S7.1.2: The formed aggregates are kinetically trapped.**

Lim et al. have proposed the following expression to calculate $\tau_{mix}$ in CJMs:

$$\tau_{mix} \approx 12.7 \left( \frac{\nu^3}{\bar{\epsilon}} \right)^{\frac{1}{2}} \quad (6)$$

This expression leads to values of $\tau_{mix}$ in the order of ms, which are similar to estimations of Lim et al. who found $\tau_{mix} \approx 10–100$ ms in a similar system. If stream viscosities and CJM dimensions are kept constant, eq. [5] and eq. [6] can be combined to express a scaling
between $\tau_{\text{mix}}$ and $Re$

$$\tau_{\text{mix}} \propto Re^{-\frac{11}{8}}$$

(7)

The assembly of block copolymers reach equilibrium on timescales of seconds, and, in nanoprecipitation processes, mixing between solvent and water is completed before the assembly process is terminated. In these conditions, the final aggregates are kinetically trapped, meaning that no unimer exchange or particle rearrangement occurs on experimental timescales. In other words, rapid mixing stops polymer aggregation into a "frozen" or kinetically trapped state, which does not coincide with the the minimum of the Free Energy.

**Section S7.1.3: Cahn–Hilliard approach to model spinodal decomposition**

Under intermediate solvent quality conditions, there is evidence that block copolymer self-assembly is preceded by an initial event of liquid–liquid phase separation. Schmid and coworkers studied the dynamics of vesicle formation from a dilute solution of amphiphilic diblock copolymers using the external potential dynamics method and found that a polymer-rich phase separation could precede block copolymer self-assembly into vesicles. Sato and Takahashi formulated the mixing Gibbs energy density of an amphiphilic block copolymer solution and investigated the competition between micellization and liquid–liquid phase separation. Theoretically, liquid–liquid phase separation preceding self-assembly can occur for moderately amphiphilic block copolymers and this was recently observed using a combination of liquid-phase TEM and self-consistent mean field theory. The initial size of the polymer-rich liquid droplets affected the final block copolymer aggregate size. The initial phase of nanoprecipitation is governed by the diffusion of polymer chains and a thermodynamic driving force driving unimer assembly. These processes can be described with spinodal decomposition models (Figure S10). Similarly to the approach of Drese and colleagues, we applied the Cahn–Hilliard equation to provide a generalized diffusion equation in
a system with two components, polymer unimers (P) and solvent (S; Figure S10a): \[ J_P = M \cdot \text{grad}(\mu_P - \mu_S) \] (8)

where \( J_P \) is the flux of species P, \( \mu_P \) is the chemical potential of species P, \( \mu_S \) is the chemical potential of species S, and \( M \) is the degenerate mobility. Following the Cahn–Hilliard approach, we found an expression for the difference in the chemical potentials of the two species

\[ \mu_P - \mu_S = \frac{\partial f}{\partial c} - \lambda \Delta c \] (9)

where \( f \) is the Free Energy per unit volume and \( c \) is the composition of the system. The composition is usually taken as the volume fraction of the species of interest, in this case, unimers, but any conserved dimensionless scalar field can be also considered. To introduce the constraint of conservation of the scalar field (in this case mass conservation), the conservation equation, \( \frac{\partial c}{\partial t} = -\text{div} J \), was rewritten by substituting the flux, \( J \), from eq. 8 and the difference in chemical potentials, \( \mu_P - \mu_S \), from eq. 9. Therefore, the change in composition with time, \( \frac{\partial c}{\partial t} \), was written as

\[ \frac{\partial c}{\partial t} = \text{div} \left( M(c) \cdot \text{grad} \left( \frac{\partial f}{\partial c} - \lambda \Delta c \right) \right). \] (10)

**Section S7.1.4: Definition of the Free Energy of unimer assemblies**

To describe the evolution of the Free Energy per unit volume, \( f \), we derived an expression based on the physics of unimer aggregation. Similarly to work of Drese and colleagues, we modeled our experiments with a two component system composed of unimers in a single solvent with time-dependent quality, \( \chi \). The solvent–water mixing process was described by increasing \( \chi \).
Figure S10. Spinodal decomposition processes are governed by diffusion and thermodynamics. We applied this general approach, following the work of Drese and colleagues, to model block copolymer nanoprecipitation.\textsuperscript{10} a) We assumed that unimer diffusion formed aggregates. b) The difference in Free Energy between free and aggregated unimers controlled the assembly. In our case, the interfacial Free Energy between the aggregate core and the solvent was controlling the assembly process (see Section S7.1.4). c) In our modified Cahn–Hilliard approach, we considered both diffusion- and thermodynamic-driven processes.

We calculated $f$ considering the Free Energy of single micelles following the work of Nose and Iyama and Leibler.\textsuperscript{30,31} Three terms in the calculation of the Free Energy of single micelles were considered: the Free Energy associated with the interface between the core and the overall solvent $f_{\text{int}}$, the Free Energy associated with chain stretching in the corona $f_{\text{corona}}$, and chain compression in the core $f_{\text{core}}$. To describe the composition, $c$, we considered the local aggregation number, $p$, which was related to the evolution of the aggregate size. The local aggregation number is a conserved, dimensionless scalar quantity, satisfying the assumptions of eq. 10. Based on refs.\textsuperscript{30} and \textsuperscript{31} mathematical expressions for $f$ are

$$f = f_{\text{int}} + f_{\text{corona}} + f_{\text{core}}$$

(11)
\[ f_{\text{int}} = \gamma_e (N_1)^{\frac{5}{2}} p^{\frac{3}{2}} \]
\[ f_{\text{corona}} = p^{\frac{3}{2}} \ln \left( 1 + N_2^{\frac{3}{2}} N_1^{-\frac{1}{2}} p^{-\frac{1}{2}} \right) \]  \hspace{1cm} (12)
\[ f_{\text{core}} = \frac{3}{2} p \left( p^{\frac{3}{2}} N_1^{-\frac{1}{2}} + p^{-\frac{3}{2}} N_1^{\frac{1}{2}} - 2 \right) \]

where \( \gamma_e \) is the effective interfacial energy between the hydrophobic core and the surroundings, and \( N_1 \) and \( N_2 \) are the number of Kuhn monomers in the hydrophobic block and the hydrophilic block, respectively. As we modeled solvent–water mixing as a single effective solvent, \( \gamma_e \) varied with water fraction and, thus, with time. We estimated the Free Energy associated with the core–solvent interface, \( \Delta F_{\text{int}}(p) \), the Free Energy associated with the core, \( \Delta F_{\text{core}}(p) \), and the Free Energy associated with the corona, \( \Delta F_{\text{corona}}(p) \), as a function of the aggregation number based on the work of Nose and Iyama.\(^{30}\) From literature, the surface tension for PLA in water was taken as 36 mN m\(^{-1}\) and the Kuhn length of PLA was taken as one lactide monomer, 10 Å.\(^{32–34}\) For small aggregation numbers, \( p \leq 300 \), the energy associated to \( \Delta F_{\text{int}}(p) \gg \Delta F_{\text{corona}}(p) \sim \Delta F_{\text{core}}(p) \) (Figure S11a). This was also evident by computing the ratio \( \frac{\Delta F_{\text{int}}(p)}{\max(\Delta F_{\text{core}}(p), \Delta F_{\text{corona}}(p))} \) (Figure S11b). Therefore, as we considered the early phases of assembly (small \( p \)), the total Free Energy expression was reduced to the Free Energy associated with the interface between the core and the solvent (Figure S10b):
\[ f \simeq f_{\text{int}} = \gamma_e N_1^{\frac{5}{2}} p^{\frac{3}{2}} \]  \hspace{1cm} (13)

Section S7.1.5: Definition of the unimer mobility

The unimer mobility was chosen based on the work of Drese and colleagues, \( M(u) = u \cdot (1-u) \), where \( u \) is a globally conserved dimensionless composition, such as the volume fraction of polymer assemblies.\(^{16,35}\) This expression originates from the hypothesis that the fluxes of matter are locally balanced and was introduced by de Gennes to satisfy the conservation of matter.\(^{36}\) In the particular case of a two-component system, we have \( J_1 + J_2 = 0 \) locally. Thus, the motion of assemblies of component 1 requires locally the motion of assemblies of component 2 in the opposite direction. This creates additional friction, which is expressed
Figure S11. Comparison of the three contributions to the total Free Energy of a micelle. a) Free Energy associated with the core-solvent interface, $\Delta F_{\text{int}}(p)$, the Free Energy associated with the core, $\Delta F_{\text{core}}(p)$, and the Free Energy associated with the corona, $\Delta F_{\text{corona}}(p)$, as a function of the aggregation number. b) The ratio $\frac{\Delta F_{\text{int}}(p)}{\max(\Delta F_{\text{core}}(p), \Delta F_{\text{corona}}(p))}$ is depicted. In total, for small aggregation numbers, $p \leq 300$, it results that the contribution of $\Delta F_{\text{int}}(p)$ is dominant.

by the factors $u \cdot (1 - u)$. In the early phases of polymer assembly, with small aggregation numbers and thus volume fractions, $u \ll 1$ and $M(u) \propto u$, hence the assumption taken here was

$$M(p) \propto p$$  \hspace{1cm} (14)

Replacing $f$ and $M$ in eq. [10] with their expressions in eq. [13] and eq. [14] (Figure S10c), we find

$$\frac{\partial p}{\partial t} \propto \text{div} \left( p \text{ grad} \left( \frac{\partial}{\partial p} \left( \gamma_e N_1^2 p^2 \right) - \lambda \Delta p \right) \right)$$  \hspace{1cm} (15)

Section S7.1.6: Scaling law approximation

We then estimated the gradient and divergence of $c$ and $\frac{\partial f}{\partial c}$. We assumed that the variation of these quantities were smooth on a characteristic length scale and that a linear approximation of the derivative would capture the main physics of the problem. Following this assumption, for each general quantity $g$ we defined a characteristic length $L_2$ such that most of the
variation of g occurs over $L_x$ and that this variation is smooth. As free unimers were brought into contact with formed aggregates by convective motion in the fluid stream of the CJM, an appropriate length scale for the variation of $c$, and all spatial derivatives ($\frac{\partial}{\partial x}$, $\frac{\partial}{\partial y}$, and $\frac{\partial}{\partial z}$) was chosen to be $L_x \propto L_{\text{aggregate}}$, where $L_{\text{aggregate}}$ represented the characteristic size of an aggregate. Following the work of Drese and colleagues, NP formation is influenced by the early phase of nanoprecipitation. Given that water is a bad solvent for the hydrophobic polymer chain, we assumed that the presence of water leads to a collapse of the hydrophobic block. As we considered the initial stages of nanoprecipitation, we approximated the aggregate size at low $p$ as a "hairy micelle" composed of a corona of hydrophilic PEG chains. Therefore, the length of tethered polymer layers was estimated by using the Alexander–de Gennes model.

As shown by Daoud and Cotton, for curved surfaces such as NPs, the radius of the NP corona scales as follows:

$$L_{\text{aggregate}} \propto R_{NP} \sim R_{\text{corona}} \sim N_2^{\frac{3}{5}} p^{\frac{4}{5}} b_{\text{PEG}}$$

(16)

where $R_{NP}$ is the NP radius, $R_{\text{corona}}$ is the radius of the PEG corona, and $b_{\text{PEG}}$ is the Kuhn length of PEG. Eq. [15] was then solved using these approximations for the spatial derivatives. The term $\lambda \Delta p$ resulted in $\lambda \cdot p^{\frac{3}{5}} N_2^{-\frac{6}{5}}$; for $N_2 \gg p^{\frac{1}{2}}$ this term approached 0 and was neglected.

From this, the following differential equation described the change in $p$, the local aggregation number, as a function of time

$$\frac{\partial p}{\partial t} = C \cdot \gamma_c \cdot p^{\frac{4}{5}}$$

(17)

where $C$ is a constant that depends on several factors including the number of monomers in the hydrophilic and hydrophobic blocks, the diffusion coefficient of unimers, the volume of the monomers, and geometric parameters.
Section S7.2: Effects of the mixing kinetics

Our main assumption is that $\gamma_e$ is the key parameter representing mixing kinetics in our model. Other studies have experimentally observed a direct relation between surface tension and water fraction with diblock copolymers. As a first approximation, we considered that the water fraction increased linearly with time during mixing in the CJM (Figure S12). Taking $\tau_{\text{mix}}$ as the total time of mixing and $\phi(\tau_{\text{mix}}) = \phi_{\text{mix}}$ as the final water fraction, we could write

$$\phi(t) = \phi_{\text{mix}} \frac{t}{\tau_{\text{mix}}},$$  

(18)

Thus,

$$\gamma_e(t) = \gamma_s \cdot \phi_{\text{mix}} \frac{t}{\tau_{\text{mix}}},$$  

(19)

where $\gamma_s$ incorporates the interaction energy per unit surface of a core monomer and a water molecule, and a factor for the conversion from molar to volume fractions. Combining eq. [19] with eq. [17] and including $\gamma_s \cdot \phi_{\text{mix}}$ in $C$, we found

$$\frac{\partial p}{\partial t} = C \cdot \frac{t}{\tau_{\text{mix}}} p^{4}. $$  

(20)

Eq. [20] formed the basis of our scaling model as it describe the evolution of the average aggregation number in the polymer assemblies as a function of time and mixing kinetics, $\tau_{\text{mix}}$.

Figure S12. The extent of mixing governs the effective interfacial energy between the hydrophobic core and the surroundings, $\gamma_e$. At $\phi = 0$, the single unimers are completely solvated, hence $\gamma_e = 0$. Over time, mixing with water increases $\phi$ and, thus, $\gamma_e$ up to $\approx \gamma_s$, where $\gamma_s$ corresponds to the interfacial energy per unit surface of a hydrophobic unimer and pure water.
Section S7.3: Arrest of NP growth and termination of unimer exchange

Our experimental evidence demonstrated that the system becomes kinetically trapped once the water fraction reaches a threshold value, which we referred to as the critical water fraction of exchange arrest, \( \phi_c \). At the point of growth arrest, no more unimers can be inserted into the particle and \( p \) does not evolve further. Therefore, we defined the characteristic time to growth arrest, \( \tau_c \), as when \( \phi \) reached \( \phi_c \) (\( \phi(\tau_c) = \phi_c \)). \textbf{Figure S13} which can be estimated with eq. 18

\[
\tau_c = \tau_{\text{mix}} \cdot \frac{\phi_c}{\phi_{\text{mix}}}
\]  

To estimate how \( p \) scaled with time and with \( \tau_{\text{mix}} \), the differential equation in eq. 20 was solved by considering a function of the form \( p = At^k \). For this problem, \( k = \frac{30}{11} \) and

\[
A = \left( \frac{11 C}{30 \tau_{\text{mix}}} \right)^{\frac{15}{11}}.
\]

\textbf{Figure S13.} The point of growth arrest, \( \phi_c \), terminates unimer exchange and aggregate growth. At the beginning of nanoprecipitation, \( t < \tau_c \) and \( \phi < \phi_c \), unimers can rearrange and aggregates grow. Unimer exchange and growth is terminated at \( t = \tau_c \) and \( \phi = \phi_c \) at which the formed aggregates are kinetically frozen. In our model, \( p \) does not change beyond \( \phi_c \).

\[
p \propto \tau_{\text{mix}}^{-\frac{15}{11}} t^{\frac{30}{11}}
\]  

22
To relate the scaling relation to observable physical parameters of the system, we replaced $t$ in eq. 22 with its expression in eq. 21

$$p \propto \phi_c^{30/11} \tau_{mix}^{15/11}$$

(23)

Taking the relation between NP size, $R_{NP} \propto L_{aggregate}$, and aggregation number, $p$, we arrived at a scaling law for NP size based on $\phi_c$ and $\tau_{mix}$

$$R_{NP} \propto \phi_c^{6/11} \tau_{mix}^{3/11}$$

(24)

Finally, we related the characteristic time of mixing in the CJM, $\tau_{mix}$, to the Reynolds number by using eq. 7 to obtain the scaling for $R_{NP}$ with $\phi_c$ and $Re$.

$$R_{NP} \propto \phi_c^{6/11} Re^{-3/8}$$

(25)
Section S8: Supplementary NP size and estimated aggregation numbers

Raw NP size data

Table S5: Raw data of batch nanoprecipitation experiments with PEG-b-PLA, \( n = 3, R = 0.005 \)

| Solv     | Conc. [mgmL\(^{-1}\)] | Size ± S.D. [nm] dB ± S.D. [-] |
|----------|------------------------|---------------------------|
| DMSO     | 10                     | 96 ± 5 0.06 0.02          |
| THF      | 10                     | 105 ± 2 0.11 0.02          |
| Acetonitrile | 10               | 76 ± 1 0.07 0.01          |
| Acetone  | 10                     | 73 ± 1 0.08 0.01          |
| DMF      | 10                     | 70 ± 2 0.07 0.01          |
| DMSO     | 5                      | 101 ± 2 0.10 0.02         |
| THF      | 5                      | 87 ± 2 0.13 0.01          |
| Acetonitrile | 5               | 74 ± 2 0.09 0.02          |
| Acetone  | 5                      | 66 ± 2 0.13 0.05          |
| DMF      | 5                      | 65 ± 3 0.15 0.05          |
| DMSO     | 2.5                    | 93 ± 3 0.15 0.03          |
| THF      | 2.5                    | 79 ± 4 0.15 0.03          |
| Acetonitrile | 2.5            | 68 ± 3 0.11 0.03          |
| Acetone  | 2.5                    | 62 ± 3 0.19 0.02          |
| DMF      | 2.5                    | 59 ± 4 0.19 0.04          |

Table S6: Raw data of batch nanoprecipitation experiments with other block copolymers, \( n = 3, R = 0.005 \)

| Polymer    | Solvent     | Conc. [mgmL\(^{-1}\)] | \( D_b \) ± S.E.M. [nm] dB ± S.E.M. [-] |
|------------|-------------|------------------------|------------------------------------------|
| PEG-b-PCL  | Acetone     | 10                     | 56 ± 4 0.11 0.05                          |
| PEG-b-PCL  | Acetonitrile| 10                     | 55 ± 1 0.09 0.01                          |
| PEG-b-PLGA | DMF         | 10                     | 60 ± 4 0.09 0.02                          |
| PEG-b-PLGA | Acetone     | 10                     | 59 ± 2 0.12 0.05                          |
| PEG-b-PLGA | Acetonitrile| 10                     | 62 ± 1 0.09 0.02                          |
Table S7: Raw data of CJM experiments, $R = 0.005$; Part I

| Polymer     | Solvent     | $Re$ | $n$ | $D_h$ ± S.E.M. | $D$ ± S.E.M. |
|-------------|-------------|------|-----|----------------|--------------|
| PEG-$b$-PLA | DMF         | 428  | 3   | 58 ± 0.07      | 0.01         |
| PEG-$b$-PLA | DMF         | 482  | 3   | 53 ± 0.08      | 0.02         |
| PEG-$b$-PLA | DMF         | 535  | 3   | 51 ± 0.10      | 0.03         |
| PEG-$b$-PLA | DMF         | 589  | 4   | 50 ± 0.10      | 0.02         |
| PEG-$b$-PLA | DMF         | 642  | 4   | 48 ± 0.11      | 0.03         |
| PEG-$b$-PLA | DMF         | 696  | 4   | 47 ± 0.12      | 0.03         |
| PEG-$b$-PLA | DMF         | 749  | 4   | 48 ± 0.17      | 0.02         |
| PEG-$b$-PLA | DMF         | 803  | 4   | 46 ± 0.19      | 0.01         |
| PEG-$b$-PLA | DMF         | 856  | 3   | 44 ± 0.15      | 0.05         |
| PEG-$b$-PLA | DMF         | 937  | 3   | 46 ± 0.17      | 0.04         |
| PEG-$b$-PLA | Acetone     | 428  | 3   | 66 ± 0.04      | 0.01         |
| PEG-$b$-PLA | Acetone     | 482  | 3   | 61 ± 0.06      | 0.01         |
| PEG-$b$-PLA | Acetone     | 535  | 3   | 58 ± 0.07      | 0.02         |
| PEG-$b$-PLA | Acetone     | 589  | 3   | 55 ± 0.09      | 0.02         |
| PEG-$b$-PLA | Acetone     | 642  | 4   | 53 ± 0.08      | 0.00         |
| PEG-$b$-PLA | Acetone     | 696  | 4   | 53 ± 0.09      | 0.01         |
| PEG-$b$-PLA | Acetone     | 749  | 4   | 51 ± 0.07      | 0.01         |
| PEG-$b$-PLA | Acetone     | 803  | 4   | 50 ± 0.09      | 0.01         |
| PEG-$b$-PLA | Acetone     | 856  | 3   | 49 ± 0.06      | 0.01         |
| PEG-$b$-PLA | Acetone     | 937  | 3   | 49 ± 0.08      | 0.01         |
| PEG-$b$-PLA | Acetonitrile| 428  | 8   | 70 ± 0.06      | 0.01         |
| PEG-$b$-PLA | Acetonitrile| 482  | 3   | 70 ± 0.06      | 0.01         |
| PEG-$b$-PLA | Acetonitrile| 535  | 7   | 63 ± 0.06      | 0.01         |
| PEG-$b$-PLA | Acetonitrile| 589  | 3   | 62 ± 0.10      | 0.04         |
| PEG-$b$-PLA | Acetonitrile| 642  | 7   | 60 ± 0.06      | 0.01         |
| PEG-$b$-PLA | Acetonitrile| 696  | 3   | 58 ± 0.07      | 0.01         |
| PEG-$b$-PLA | Acetonitrile| 749  | 7   | 58 ± 0.07      | 0.01         |
| PEG-$b$-PLA | Acetonitrile| 803  | 3   | 55 ± 0.06      | 0.01         |
| PEG-$b$-PLA | Acetonitrile| 856  | 5   | 56 ± 0.07      | 0.01         |
| PEG-$b$-PLA | Acetonitrile| 937  | 3   | 54 ± 0.08      | 0.02         |
Table S8: Raw data of CJM experiments, $R = 0.005$; Part II

| Polymer | Solvent | $Re$ | $n$ | $D_h$ [nm] | $\pm$ S.E.M. [nm] | $D$ | $\pm$ S.E.M. |
|---------|---------|------|-----|-----------|-----------------|-----|---------------|
| PEG-$b$-PLA | THF | 428 | 3 | 92 | 7 | 0.10 | 0.01 |
| PEG-$b$-PLA | THF | 482 | 3 | 85 | 4 | 0.10 | 0.01 |
| PEG-$b$-PLA | THF | 535 | 3 | 78 | 3 | 0.10 | 0.01 |
| PEG-$b$-PLA | THF | 589 | 3 | 75 | 3 | 0.11 | 0.01 |
| PEG-$b$-PLA | THF | 642 | 3 | 70 | 4 | 0.09 | 0.01 |
| PEG-$b$-PLA | THF | 696 | 4 | 69 | 2 | 0.12 | 0.01 |
| PEG-$b$-PLA | THF | 749 | 4 | 67 | 2 | 0.09 | 0.01 |
| PEG-$b$-PLA | THF | 803 | 4 | 64 | 3 | 0.09 | 0.01 |
| PEG-$b$-PLA | THF | 856 | 3 | 65 | 4 | 0.10 | 0.01 |
| PEG-$b$-PLA | THF | 937 | 3 | 64 | 3 | 0.11 | 0.02 |
| PEG-$b$-PLA | DMSO | 428 | 3 | 99 | 3 | 0.08 | 0.01 |
| PEG-$b$-PLA | DMSO | 482 | 3 | 96 | 3 | 0.08 | 0.01 |
| PEG-$b$-PLA | DMSO | 535 | 3 | 91 | 3 | 0.09 | 0.01 |
| PEG-$b$-PLA | DMSO | 589 | 3 | 85 | 3 | 0.11 | 0.01 |
| PEG-$b$-PLA | DMSO | 642 | 3 | 84 | 1 | 0.10 | 0.01 |
| PEG-$b$-PLA | DMSO | 696 | 4 | 80 | 3 | 0.11 | 0.01 |
| PEG-$b$-PLA | DMSO | 749 | 4 | 79 | 3 | 0.11 | 0.01 |
| PEG-$b$-PLA | DMSO | 803 | 5 | 75 | 3 | 0.10 | 0.01 |
| PEG-$b$-PLA | DMSO | 856 | 3 | 77 | 5 | 0.11 | 0.01 |
| PEG-$b$-PLA | DMSO | 937 | 3 | 79 | 2 | 0.11 | 0.01 |
Figure S14. Dispersity index of PEG-\(b\)-PLA NPs formed in the CJM from 10 mg mL\(^{-1}\) precursor solutions in different water-miscible solvents (\(R = 0.005\)) as a function of Re. The area below \(D= 0.1\) is highlighted in grey.

**Estimated aggregation numbers of the formed NPs**

We estimated the final aggregation number based on the experimental data and the work of Daoud and Cotton.\(^{38}\) Due to the large fraction of water present in the system at the end of nanoprecipitation (>0.99), we assumed that the PLA core of the NPs was fully collapsed. Under these conditions, the NP size can be modeled with eq. 16 (Section S7.1.6) by taking only the PEG corona into account as water is a good PEG solvent. The same model has been applied in literature, including in recent studies on the synthesis of polymeric NPs by Prud’homme and coworkers.\(^{40-42}\) As \(R_{\text{corona}} \sim NP_{\text{size}}\), the aggregation number can be estimated by inverting eq. 16, therefore

\[
p \propto \left( \frac{R_{\text{NP}}}{b_{\text{PEG}}} \right)^5 N_2^{-3}
\]

\(^{26}\) where \(N_2 = 57\), \(b_{\text{PEG}} = 0.86\) nm.\(^{43,44}\) The measured NP size resulted in aggregation numbers shown in the Figure S15 and was consistent with values found in literature for similar NP systems.\(^{11}\)
Figure S15. Aggregation number of PEG-b-PLA NPs as a function of $Re$. Particles were formed in the CJM from 10 mg mL$^{-1}$ precursor solutions in different water-miscible solvents ($R = 0.005$).

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