Mechanism for Rapid Self-Assembly of Block Copolymer Nanoparticles

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Amphiphilic block copolymers in solution spontaneously self-assemble when the solvent quality for one block is selectively decreased. We demonstrate that, for supersaturation ratio changes $[d(S)/dt]$ over 10^5 per second from equilibrium, nanoparticles are obtained with a formation mechanism and size dependent on the jumping rate and magnitude. The threshold rate for homogeneous precipitation is determined by the induction time of a particle, equivalent to the diffusion limited fusion of copolymer chains to form a corona of overlapping soluble brushes. Via determination of the induction time with a novel confined impinging jets mixer and use of a scaling relation, the interfacial free energy of a block copolymer nanoparticle was measured for the first time.

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The thermodynamics and kinetics of block copolymer self-assembly to micelles (in dynamic equilibrium) or nanoparticles (kinetically frozen) present challenging problems compared to micellization of surfactant molecules. The relatively large amphiphilic blocks lead to significantly different mechanisms and time scales for assembly and subsequent rearrangement. Nonetheless, recent theoretical [1,2] and experimental [3–5] studies are converging on the basic mechanisms involved in micellization, primarily solvent mediated unimer exchange and micelle fusion or fission. The relevant time scale for initial structure formation can be under 100 ms for molecules of 100 000 g/mole [3] and many complex structures depend on the kinetics of formation [6,7]. Two specific areas require additional research (1) the determination of the mechanism and absolute time scales for rapid self-assembly to nanoparticles and (2) the estimation or measurement of interfacial properties of nanoparticles.

Several distinguishing features characterize the rapid block copolymer self-assembly to produce kinetically frozen nanoparticles not in facile dynamic equilibrium: (a) The critical attribute, such as solvent content or temperature, that drives micellization should be rapidly passed to yield an initial supersaturation ratio that is high, $S_0 = C_p/C_{\text{cmc}} > 10^2$. C_p is the initial unimer concentration and C_{cmc} is the critical micelle concentration after the solvent quality jump. Mixing two solvents is the most common and flexible way to achieve a large and rapid change in solvent quality. In order to achieve homogeneous kinetics, the mixing time of the solvents, τ_{mix}, must be less than the time scale for block copolymer nanoparticle aggregation, τ_{agg}. (b) The block copolymers used must be soluble at the starting conditions, but have a low C_{cmc}, $\leq 10^{-3}$ wt %, at the final conditions. In turn, the free energy penalty required to expel a chain from the nanoparticle core at the final conditions should also be high, $\Delta > 5$ kT [6,8]. The high exchange energy and low C_{cmc} limits solvent mediated unimer exchange between micelles that normally leads to dynamic equilibrium [7]. (c) To impart colloidal stability and avoid fusion, the copolymers should contain a soluble block of sufficient length for steric or electrostatic repulsion. For example, the steric barrier of Triton X-100 micelles, 9.5 ethylene oxide monomer units, reduces the rate of fusion 5000-fold compared to Brownian collisions with instantaneous fusion [9]. Additional protection is required beyond this level.

Two processes control particle formation and stabilization: unimer addition and aggregate fusion. For a flat surface, Ligoure and Leibler have employed a self-consistent field theory to describe the deposition rate and the equilibrium surface coverage of diblock copolymers by unimer addition [8]. Starting with a bare surface and below the C_{cmc}, there are two sequential regimes with different mechanisms for deposition: the diffusion limited regime and brush dominated regime. The diffusion limited regime is the deposition of the individual polymer chain ends on the surface from the bulk solution via diffusion until the soluble brushes begin to overlap, with a characteristic time on the order of tens of milliseconds.

$$\tau_1 \approx \frac{a^2}{D\phi_0^2}. \tag{1}$$

Here a is the Kuhn statistical length, D is the chain diffusion coefficient, and ϕ_0 is the bulk solution volume fraction away from the surface.

Subsequently, a transition to deposition limited by the penetration time of the copolymer through the brush layer occurs. In this brush-dominated regime, the polymers move through the soluble brush layer to the surface via reptation in a potential field due to the stretching of the diffusing chain. Under these conditions, the transfer of copolymer from the bulk solution to the exterior brush interface is not limiting and the time to completely construct the film on the surface, τ_c, to the equilibrium concentration is long, over 3 orders of magnitude beyond the time to an overlapping brush. We can summarize these findings as

$$\text{unimer} \xrightarrow{\text{fast}} \text{overlapped brush} \xrightarrow{\text{slow}} \text{equilibrium}.$$

Recent theoretical work on spherical micelle formation implies similar results. Starting above the C_{cmc}, subcritical species aggregate to a critical size where fusion of the micelles becomes slow and unimer exchange dominates further micellar growth to an equilibrium size [1,2].

Our view of the rapid self-assembly of diblock copolymer nanoparticles from a homogeneous solution of unimers after rapid micromixing under conditions of a high supersaturation follows Fig. 1. This view can be summarized as "fusion dominated" or diffusion limited fusion to a critical size corresponding to an overlapping brush, at which point the particles are kinetically frozen. Additional interparticle fusion and unimer exchange are precluded by the steric brush layer and essentially zero monomer solubility. Simulations by Dormidontova [1] suggest the aggregation number at this critical size is a small fraction of equilibrium, $Q_c < Q_{\text{eq}}^{5/9}$.

Based on the fusion-only mechanism, several features of a homogeneous precipitation can be deduced. (i) Since the time scale for brush penetration by a unimer, > 1000 ms, is sufficiently long compared to the time scale for diffusion to nucleate a new particle, ≅ 10 ms, one expects the starting concentration of block copolymer should have little effect on the final critical size of the particles corresponding to an overlapping brush. (ii) A higher starting concentration decreases the length scale between molecules, the diffusion time [Eq. (1)], and the characteristic aggregation time. (iii) The final solvent quality will affect the size of the particles by changing the brush repulsion characteristics (critical Q and brush height) plus any core swelling due to solvent partitioning. (iv) Since the fusion of two critical particles is energetically unfavorable and the mechanism of unimer exchange is not active, any subsequent rearrangement with a nanoparticle is at a constant aggregation number. These four predictions have not, heretofore, been experimentally demonstrated for block copolymer micelle assembly. The final result, micelles of uniform size independent of starting concentration is similar in result to small molecule surfactant assembly but comes from fundamentally opposite mechanisms. Surfactant micelles reach a uniform aggregation number as monomers equilibrate through the solvent phase, and steric "packing parameter" constraints dictate the equilibrium aggregation number [10]. In contrast, the uniform size for these block copolymers is a nonequilibrium quenching of the unimers which depends on the unperturbed dimension of the solvated amphiphilic block. It is also fundamentally different from traditional nucleation and crystal growth where particle size depends on initial concentration.

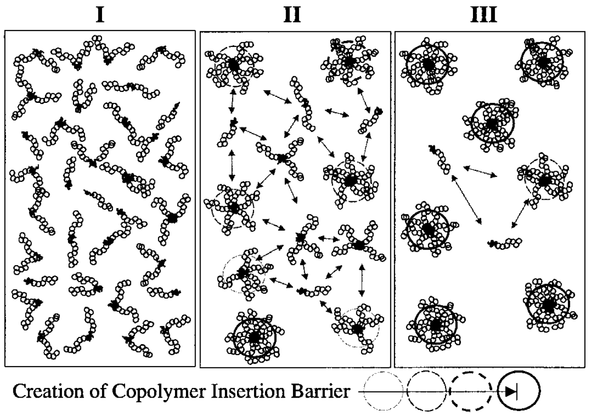

FIG. 1. Rapid self-assembly of diblock copolymer nanoparticles via a diffusion limited fusion dominated process from starting conditions of high supersaturation and homogeneous solution. (I) Particle nucleation occurs rapidly and simultaneously with intramolecular and intermolecular insoluble blocks. (II) The nascent particles proceed to fuse with each other depending on the magnitude of the steric and electrostatic insertion barriers until a critical size, that corresponding to an overlapping brush corona. (III) Remaining copolymer must fuse to create nascent particles or find particles with a low insertion barrier. The resulting particles are kinetically frozen, not reaching the equilibrium size due to a slow solvent mediated unimer exchange rate.

To study the mechanism and kinetics of the block copolymer nano precipitation, we used a novel analytical confined impinging jets (CIJ) mixer. It consists of two opposed 0.5 mm jets of fluid fed to a 2.4 mm diameter chamber at a constant rate with their momentum matched. The characteristic micromixing time for the two solvents, which is less than a residence time, has been characterized using competitive reactions to below 10 ms and scales as the inverse of the jet velocity to the three halves power [11]. The characteristic mixing time has been found to be

$$\tau_{\text{mix}} = 171\,[\text{m}^{1/2}] \frac{\nu_3^{1/2}}{u_1^{3/2}(\frac{\rho_1}{\rho_3})^{1/2}(1 + \frac{m_1}{m_2})^{1/2}}. \tag{2}$$

The times measured for this Letter fall within the range where this expression has been shown to be valid for low viscosity systems, Re = 100 to 3000 [11]. The jet velocity of stream 1 is u_1 and the jet diameter is d. The momentum diffusivity, density, and mass flow rate of stream i are ν_i, ρ_i, and m_i, respectively. Stream 3 is the effluent of the mixer.

The precipitation of a polybutylacrylate-*b*-polyacrylic acid, 7.5-*b*–7.5 kg/mole or PBA(59)-*b*-PAA(104) in monomer units, was conducted as shown in Fig. 2. The copolymer was molecularly dissolved [as verified via dynamic light scattering (DLS)] in methanol and mixed at 35 ± 1 °C with a stream of water to selectively precipitate the polybutylacrylate block. The critical water

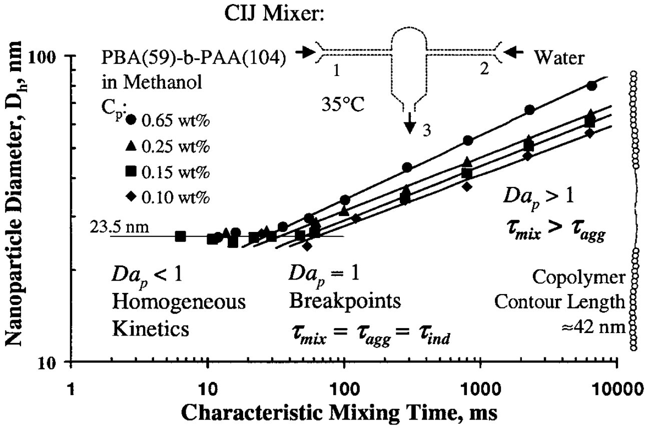

FIG. 2. Rapid self-assembly of diblock copolymer nanoparticles in a CIJ mixer induced by selective nonsolvent addition to a stream of soluble copolymer. Jet velocities of 8.5 to 0.1 m/s are shown. The resulting particle hydrodynamic diameter via dynamic light scattering (3) is shown to be a strong function of the characteristic time for mixing [Eq. (2)] of the two solvent streams (1,2) until homogeneous kinetics are obtained, $Da_p < 1$. The mixing time and aggregation time are equivalent at the break point, $Da_p = 1$.

content, cwc, for micellization is very low, <5%, and $S_0 > 10^4$. The effluent was measured via DLS (Brookhaven, ALV 5000 correlation, second cumulant fit) for particle size as the hydrodynamic diameter, D_h. As the jet velocity increased, the particle size decreased until a break point, beyond which the particle size was independent of mixing intensity. This break point has been shown to correspond to a Damköhler number of 1 [12].

$$Da_p \equiv \frac{\tau_{\rm mix}}{\tau_{\rm agg}}. \tag{3}$$

The concentration has been increased 6.5-fold, yet the critical particle size formed under homogeneous conditions ($Da_p < 1$) did not change. On the other hand, the characteristic aggregation time ($Da_p = 1$) decreased from 60 to 26 ms. We have monitored both large and small particles via DLS and found the particles to have the same size (± 15%) for at least three months. We did not measure the aggregation number as a function of time, but frozen nanoparticles of polystyrene-*b*-polyacrylic acid have been shown to be stable and maintain the same aggregation number upon any slow morphology transition [6]. In a separate data set at 0.25 wt % copolymer, the magnitude of the solvent quality jump was changed by mixing with 36/64 water/MeOH to yield a final solvent content of 83 vol % MeOH versus 53 vol % MeOH. The hydrodynamic radius increased 5–10 nm at all mixing times (not shown), but again a critical size was reached. Once formed, the particle size did not change upon adding more water or dilution. Thus, the critical aggregation number was a function of solvent ratio, but was stable to subsequent perturbations. Although not shown, we mixed a solution of polystyrene(10)-*b*-polyethylene oxide(68) in tetrahydrofuran at comparable concentrations with a stream of water. The cwc of this polymer is near 20% and $S_0 > 100$. Again, the same trends were seen with the particle size decreasing until a break point and remaining stable over time. We conclude that all of the above observations are consistent with a fusion-only mechanism to frozen nanoparticles where the characteristic aggregation time is the diffusion limited construction of an overlapping brush.

The process of forming a block copolymer nanoparticle from a homogeneous solution ($Da_p < 1$) comprises a nucleation event and diffusion limited growth, similar in form to that for organic crystals. The primary difference is that the growth process is truncated at the critical size where the brush dominated regime begins. It might seem that small block copolymer self-assembly is in a different class than normal crystallization processes since the internal degrees of freedom of the polymer chain would lead to entropic contributions to self-assembly of polymers that are not significant for small molecules or proteins. It is true that in the final stages of equilibrium assembly chain stretching would be significant [8]; however, the rapid quenching and nonequilibrium structures that result from rapid micromixing and quenching stop self-assembly at the first overlap of the soluble chain blocks—before significant compression of the chain begins. Therefore, the framework of classical nucleation and crystallization theory, we believe, provides a useful model for analyzing this self-assembly process. The induction time, or a time to the overlapping brush regime, is being measured.

$$\tau_{\rm agg} = \tau_{\rm ind} = \tau_{\rm nucleation} + \tau_{\text{growth to a size}}. \tag{4}$$

It has been shown [13,14] that the induction time for the process of nucleation plus diffusion limited growth to a given particle size follows

$$\ln \tau_{\rm ind} = \alpha[\ln(C/C_{\rm eq})]^{-2} + \text{const}, \tag{5}$$

where $\alpha = \beta\gamma^3\omega^2/2.5k_b^2T^3$, γ is the interfacial free energy in mJ/m^2, ω is the solute molecular volume, k_b is Boltzmann's constant, T is the temperature in K, β is a shape factor equal to $16\pi/3$ for spheres, and C is the concentration of solute.

When a diblock copolymer is the solute, the supersaturation becomes $C_p/C_{\rm cmc}$. As shown in Fig. 3, the block copolymer nanoparticle formation is a nucleation and diffusion limited growth process, as expected via the fusion-only mechanism. From the slope in Eq. (5), we can extract the interfacial free energy of the block copolymer nanoparticle, $\gamma = 1.9$ mJ/m^2. This value is similar to those obtained for other organic compounds

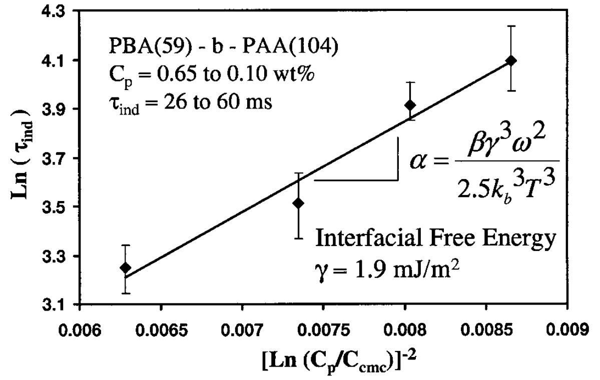

FIG. 3. Determination of the interfacial free energy of a diblock copolymer nanoparticle via use of a scaling relation [Eq. (5)] for induction time versus supersaturation. The induction time is nucleation followed by diffusion limited growth to critical size nanoparticle equivalent to an overlapping brush which is determined via the characteristic mixing time at a Damköhler number of 1 (Fig. 2). The C_{cmc} estimate $= 10^{-6}$ wt % and $\alpha = 369$.

0.2 to 6 mJ/m^2 [15] and far away from those for ionic compounds > 20 mJ/m^2 [13,14].

An assumption inherent in the classical nucleation theory to derive Eq. (5) is that a critical nucleus is at equilibrium and comprises a finite number of molecules. We find the critical size nucleus is small, $n^* \approx 3$ to 2 molecules for 0.10 to 0.65 wt %. This is a similar dilemma faced by the reactive precipitation of sparingly soluble salts at supersaturations over 10^3, such as barium sulfate, where the "mesoscopic" nucleation theory has been shown to explain kinetic behavior effectively although the calculated critical nuclei sizes are exceedingly small [13,14]. Although the C_{cmc} of our polymers is low, estimated $C_{\mathrm{cmc}} \approx 10^{-6}$ wt %, the presence of a C_{cmc} indicates that a thermodynamic equilibrium exists where a critical nucleus will dissolve. Note that the "critical size" associated with an overlapping brush, 23.5 nm, is not a function of concentration and is therefore *not* the critical size nucleus, n^*.

The rapid precipitation mechanism in Fig. 1 is for homogeneous kinetics, $Da_p < 1$ (e.g., $\tau_{\mathrm{mix}} < 30$ ms in Fig. 2). What happens under conditions of a slower (but still large) solvent quality jump, when $Da_p > 1$? As shown above, the time scale to form local structures is $\sim$40 ms but the time to homogenize the solvent and nonsolvent can be > 1000 ms at low jet velocities, as in Fig. 2. In this case the slow change in solvent quality permits fusion *and* unimer exchange to take place for a longer time. The result is structures with higher aggregation numbers, as witnessed when the final nonsolvent ratio was decreased and the mixing rate was not at issue. These larger structures have been observed by others in experiments involving solvent changes near the critical solvent concentration where even large hollow vesicles have been observed [6,7,16].

The rapid and nonequilibrium self-assembly of diblock copolymer micelles using high supersaturation and low C_{cmc} produce kinetically frozen nanoparticles, for which size or aggregation number is dependent on the *rate* and magnitude of solvent quality change. The fusion dominated mechanisms presented here captures each of the experimental trends we have observed for the rapidly micromixed homogeneous precipitation kinetics: a particle size independent of initial concentration, an induction time that decreases with increasing concentration, and kinetically frozen particles after formation. The CIJ mixer and the scaling relationship for induction time [Eq. (5)] enable the effective interfacial free energy of a block copolymer nanoparticle to be measured. With this knowledge, the initial conditions of a precipitation and the physical structure of the block copolymer can be designed to tune the characteristic induction time or aggregation number.

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