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Microparticles

Hierarchically Structured Microparticles Formed by Interfacial Instabilities of Emulsion Droplets Containing Amphiphilic Block Copolymers**

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The extraction of organic solvent from oil-in-water emulsions is a simple and widely-used technique to prepare polymeric microparticles and microcapsules for drug delivery applications.[1,2] Typically, a hydrophobic polymer is first dissolved in an organic solvent that is immiscible or slightly miscible with water; this solution is then emulsified with water and suitable stabilizers to form a single or double emulsion. The solvent is subsequently removed by evaporation or extraction into an excess of the continuous phase, converting the solvent droplets into solid particles or capsules with shapes that are generally spherical as dictated by the interfacial tension between water and the organic phase.

Herein we show that when this process is conducted using primarily amphiphilic block copolymers dissolved in the organic phase, solvent removal gives rise to instabilities of the solvent/water interface, generating microparticles with novel hierarchical structures. We studied the behavior of polystyrene–poly(ethylene oxide) (PS-PEO) diblock copolymers, which are known to assemble into a variety of micellar and vesicular morphologies when water is added to solutions of polymer in water-miscible organic solvents.[3–6] We show that, upon removal of organic solvent from emulsion droplets containing PS-PEO, microparticles with foam-like, budding vesicle, and dendritic structures can be prepared. Although a variety of techniques for creating nonspherical particles exist (see Glotzer and Solomon's work[7] for a recent compilation of examples), the current approach offers a simple route for self-assembly of polymers into multicompartment and high-surface-area particle morphologies that may present new opportunities for applications in drug delivery,[8,9] coatings, and catalysis.[10]

To facilitate study of the structural evolution of droplets and to produce microparticles of well-defined sizes, flow-focusing[11,12] was used in a microcapillary device (Figure 1) to generate solvent droplets with uniform, tunable sizes of 30–50 μm dispersed in water. (For details see the Supporting Information.) Chloroform, a good solvent for both PS and PEO and only slightly miscible with water, is used as the dispersed phase, in which 10 mg mL^{-1} of copolymer is dissolved, and poly(vinyl alcohol) is added to the aqueous phase to prevent droplet coalescence. After collecting the emulsion, chloroform diffuses through the aqueous phase and evaporates, causing the droplets to shrink and the concentration of PS-PEO within each droplet to increase.

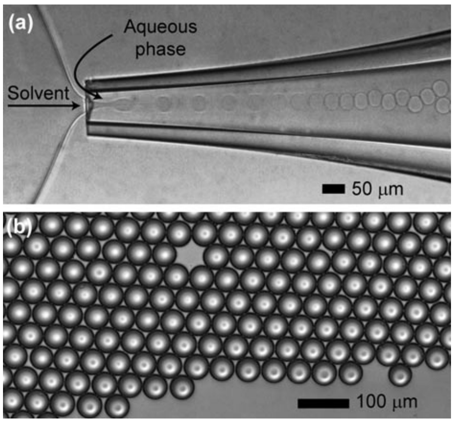

Figure 1. a) Formation of solvent-in-water droplets using a microcapillary device. The organic solvent phase consists of a dilute concentration of PS-PEO copolymer in chloroform, and the aqueous phase consists of a water–glycerol mixture (50 vol%) including 5 mg mL^{-1} poly(vinyl alcohol). b) Uniformly-sized emulsion droplets of chloroform containing PS-PEO after collection on a glass slide.

When the concentration of PS-PEO reaches about 30 wt%, the droplets no longer remain spherical, but instead undergo an instability in which their interfacial areas spontaneously increase. As shown in Figure 2a and b, as solvent is removed from droplets containing PS_{19k}-$PEO_{6.4k}$, the interfaces become corrugated and micrometer-sized fluid tendrils grow out from each droplet. It appears that, at this concentration of PS-PEO, the macrophase-separated emulsion is no longer thermodynamically stable, and the system seeks to evolve towards a new equilibrium state of solvated PS-PEO assemblies dispersed in water. Cates and co-workers have modeled such a situation in terms of a transiently negative interfacial tension that drives growth of the interfacial area.[13] Similar processes of interfacial roughening and droplet ejection, often called "spontaneous emulsification", have been reported for oil–water–amphiphile systems[14] and polymer blends,[15–17] in which roughening occurs at an interfacial excess of copolymer at which the interfacial

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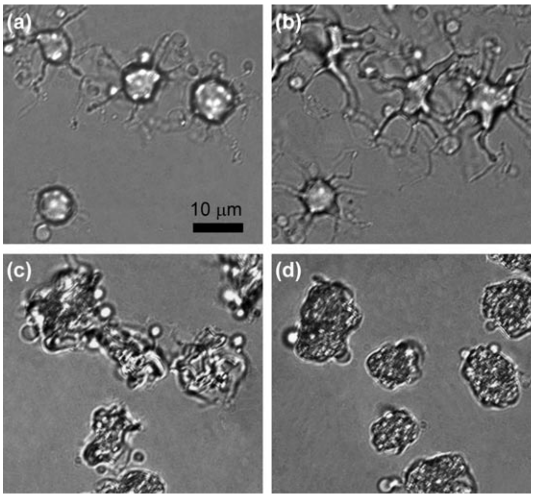

Figure 2. Optical micrographs showing the interfacial instability of emulsion drops containing PS_{19k}-$PEO_{6.4k}$ as chloroform is removed. The same four droplets seen in (a) remain in the center of images (b–d), which are taken b) 72 s, c) 192 s, and d) 262 s after (a). The scale bar applies to all images.

tension is predicted to vanish.[18] An instability of this type has also recently been harnessed to create titania–silica particles with spiny surfaces.[19]

Remarkably, for PS_{19k}-$PEO_{6.4k}$, the fluid tendrils reach a length of up to 20–50 μm, then retract to yield a compact structure, as shown in Figure 2 c and d (see Supporting Information for a movie). The timescale for growth and retraction is dictated by the rate of solvent removal, typically requiring tens of seconds to minutes. The mechanism giving rise to this particular behavior remains under investigation, but it likely reflects a complex interplay between polymer transport to the interface, hydrodynamic deformation of the droplet surface, and interfacial characteristics of the adsorbed polymer.[13] Typically, the interfacial instabilities discussed above are transient phenomena leading to dispersion of the amphiphile as micelles, vesicles, or a microemulsion.[14–18] In the present case, the system becomes kinetically trapped in a complex microparticulate structure owing to the glassy nature of the unsolvated PS blocks. Particles formed by PS_{19k}-$PEO_{6.4k}$ are found by scanning electron microscopy (SEM) and transmission electron microscopy (TEM) to have cellular foam-like morphologies (Figure 3 a). TEM imaging of thin particle cross-sections (ca. 60 nm thick) reveals that the internal structure consists of water-filled cavities with sizes of tens of nanometers to several micrometers (Figure 3 b.)

Owing to the non-equilibrium nature of this phenomenon, the details of the final structure depend on the processing conditions; however this sort of interfacial instability is quite general over wide ranges of droplet size, solvent removal rate, and initial polymer concentration. The morphologies described herein are prepared reproducibly using different samples of the stated compositions and droplet sizes. Within a given sample, local variations in solvent removal rate exist; however, more than 90 % of particles adopt the reported structures. The nature of the solvent is also important, presumably reflecting differences in the quality of the solvent for PEO: in dichloromethane, similar phenomena are observed, whereas toluene or benzene lead to almost complete suppression of the instability.

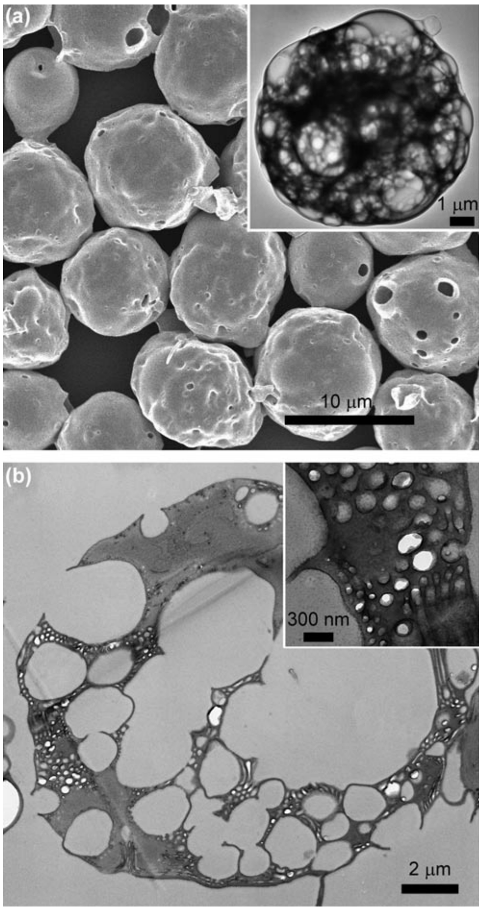

Figure 3. a) SEM and TEM (inset) images of PS_{19k}-$PEO_{6.4k}$ foam-like microparticles formed by removal of chloroform from emulsion droplets. b) TEM images of a thin particle cross-section stained by RuO_4. The stained regions that are devoid of nanoscale features are interpreted as being walls of foam cells oriented nearly parallel to the image plane.

To test the generality of this phenomenon, we study another copolymer, PS_{38k}-PEO_{11k}, with slightly lower PEO content (22 wt %), and almost twice the molecular weight. Upon removal of chloroform, an interfacial instability takes place; however, the structures formed are too small to be resolved by optical microscopy. The result is PS-PEO microparticles with surfaces coated with about 1 μm sized “budding” vesicles, as seen by SEM and TEM images in Figure 4 a. Imaging of a particle cross-section with TEM (Figure 4 b) shows the vesicular nature of the buds, which occasionally have onion-like structures (Figure 4 b, inset). The interior of the central particle consists of disordered hydrated lamellar bilayers with thicknesses of about 30 nm. The process by which these particles form may be related to the well-known budding mechanisms of lipid[20–22] and block copolymer[23] vesicles; however in the present case, the process is kinetically arrested, leading to microparticles with highly corrugated surfaces.

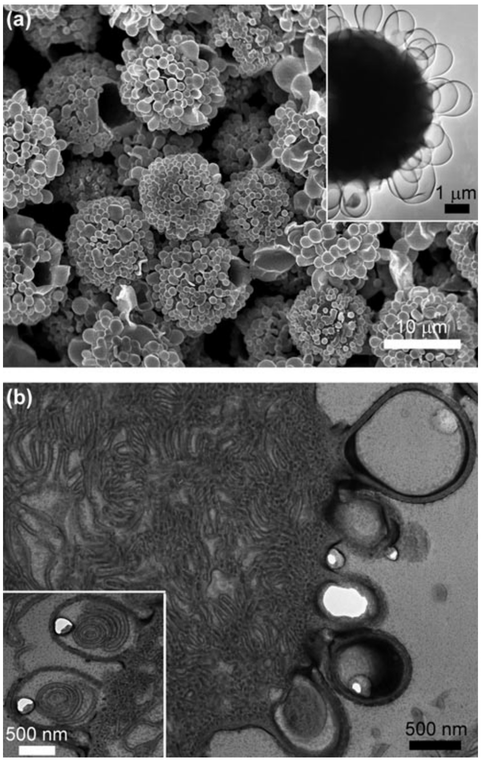

Figure 4. a) SEM and TEM (inset) images of PS_{38k}-PEO_{11k} budding vesicle microparticles formed by removal of chloroform from emulsion droplets. b) TEM images of thin particle cross-sections stained by RuO_4.

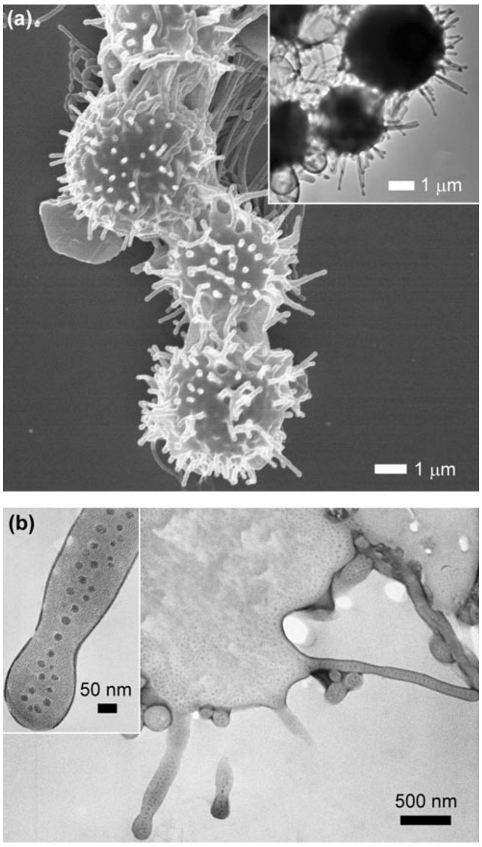

Figure 5. a) SEM and TEM (inset) images of dendritic particles formed from a blend of PS_{38k}-PEO_{11k} with $PS_{13.7k}$ homopolymer (1:1 weight ratio) by removal of chloroform from emulsion droplets. b) TEM images of a thin particle cross-section stained by RuO_4.

To establish the effect of the relative lengths of the PS and PEO blocks on particle morphology, we tested several PS-PEO copolymers with different compositions. Polymers with greater PEO content (≥ 35 wt%) show interfacial instabilities, with continued division of the droplet into spherical or cylindrical micelles, which will be the subject of a separate report. For a polymer with lower PEO content, PS_{37k}-$PEO_{6.5k}$ (15 wt% PEO), the instability is largely suppressed, resulting in nearly spherical microparticles with rough surfaces and internal organization into disordered hydrated lamellar bilayers or cylindrical channels (see the Supporting Information).

A powerful way to tune the morphology of these PS-PEO particles is by blending polymers of different compositions. By blending $PS_{13.7k}$ homopolymer with PS_{38k}-PEO_{11k} (1:1 weight ratio) and working with smaller droplet sizes (diameter < 20 μm), we observe the formation of “dendritic” particles where cylindrical protrusions of 1–2-μm length branch out of a central microparticle of about 3-μm diameter, as shown in Figure 5a. In the interior of both the branches and the central particle, the polymer organizes into spherical domains of PEO with an average diameter of circa 20 nm, as shown by cross-sectional TEM imaging (Figure 5b). The addition of PS homopolymer appears to trap the fluid tendrils encountered in the first stages of interfacial instability, preventing reorganization into bilayer structures. The addition of PS homopolymer may act in at least two ways: 1) by serving as a non-volatile, selective “solvent” for the PS block of the copolymer, altering its interfacial activity and preferred curvature, and 2) replacing solvent molecules by polymer chains, slowing the dynamics of the system and perhaps trapping the structure in an earlier stage of the instability.

The PS-PEO microparticles described herein are capable of encapsulating both hydrophilic and hydrophobic species. As a model hydrophobic compound, we use the fluorescent anticancer drug camptothecin, which is dissolved in chloroform along with PS-PEO. Fluorescence images of the resulting microparticles shown in Figure 6a and b show that the

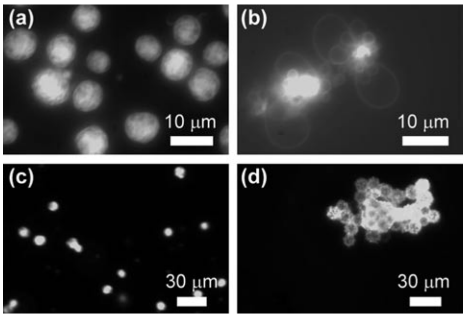

Figure 6. Fluorescence images of microparticles with camptothecin encapsulated in the hydrophobic regions: a) PS_{19k}-$PEO_{6.4k}$ foam-like particles, b) PS_{38k}-PEO_{11k} budding vesicle particles. Images of microparticles with carboxyfluorescein encapsulated in the hydrophilic regions: c) PS_{19k}-$PEO_{6.4k}$ particles, d) PS_{38k}-PEO_{11k} particles.

probe is distributed homogeneously throughout the hydrophobic portions of the microparticles. To demonstrate the encapsulation of hydrophilic species, carboxyfluorescein is dissolved in the aqueous phase surrounding the emulsion drops. As the interfacial instability takes place, the microparticles entrap the fluorescent probe, which is retained upon redispersion in deionized water (Figure 6c and d).

In summary, we have demonstrated the use of interfacial instabilities in shrinking emulsion droplets as a simple route to prepare hierarchically structured microparticles of amphiphilic diblock copolymers. Solvent droplets with well-defined sizes provide a model system allowing the structural evolution of droplets to be followed, and giving rise to relatively uniform particle sizes. The resulting particles, with foam-like, budding vesicle, and dendritic morphologies, can encapsulate both hydrophilic and hydrophobic species, and may offer new opportunities in areas, such as drug delivery and particulate coatings. Further work is required to understand the mechanisms that give rise to these structures, and to fully define the roles of polymer composition, molecular weight, and blending of different polymers in the process.

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