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Regular Article

Morphology of block copolymer micelles formed via electrospray enabled interfacial instability

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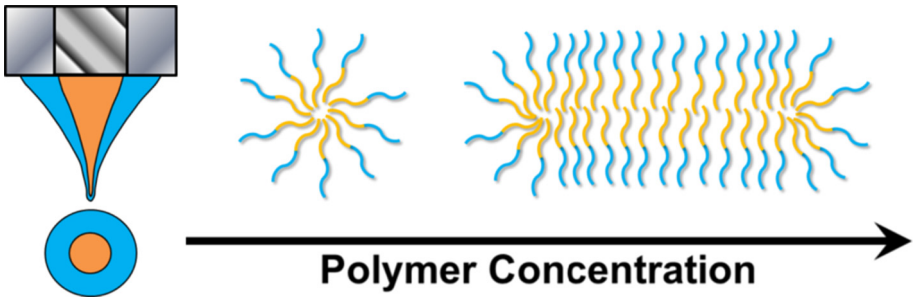
GRAPHICAL ABSTRACT

Electrospray-Enabled Interfacial Instability processes can lead to spherical and worm-like micelles with increasing polymer concentration.*Hypothesis:*



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ABSTRACT

Hypothesis: Elongated micelles may be preferred over spherical because of their increased loading capacity, differential mass transport and biodistribution. Although morphological transitions of block co-polymer (BCP) micelles have been extensively investigated in batch systems, research on continuous or semi-continuous scalable approaches such as flash nanoprecipitation and coaxial electrospray-enabled interfacial instability (Aero-IS) have primarily focused on producing spherical micelles. This paper investigates whether process changes intended to increase micelle production via Aero-IS also induce morphological transitions.

Experiments: BCP micelles were synthesized from carboxylated polystyrene-block-poly(ethylene oxide) (PS-b-PEO) (PS 9.5 kDa:PEO 18.0 kDa) using Aero-IS. Volumetric flowrates, polymer concentrations, and emulsion temperature were varied to investigate their effect on the micelle production rate and resulting micelle structure, including transitions to worm-like micelles.

Findings: These findings report the first worm-like micelles formed via a scalable, interfacial instability approach. The morphological transitions obtained by increasing polymer concentration occurred at lower nominal values than in corresponding batch processes. Optimizing operating conditions also led to a 12-fold increase in micelle production rates over prior electrospray reports (Duong, 2014). Thus, the Aero-IS approach holds promise for scalable nanomanufacturing of worm-like micelles, potentially enabling applications in drug delivery, imaging, diagnostics, and separations.

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1. Introduction

Micelles formed from amphiphilic block copolymers (BCPs) have broad application in the biomedical [1–8] and material [9–12] sciences, with uses ranging from chemotherapeutic delivery [13] to new methods of lithography [14]. This results in part from their narrow size distribution, controllable surface chemistry, and the ability to synthesize them via self-assembly. BCP micelles typically consist of a hydrophobic core with a hydrophilic corona and can adopt a variety of morphologies, including spheres, ellipses, and worm-like micelles. For BCPs with long hydrophobic blocks, forming micelles can be challenging, but the resulting micelles are more stable in an aqueous environment than those formed from BCPs with short hydrophobic blocks [15].

One common batch method of micelle synthesis is based on the gradual addition of water to a BCP-water miscible organic solution (i.e., water addition) [16]. The continuous version of this approach is flash nanoprecipitation (FNP), developed by Prud'homme and colleagues [15,17]. Here, large increases in throughput are achieved by turbulently mixing an organic stream containing the BCP with an aqueous stream. The rapid increase in supersaturation of the hydrophobic components leads to micelle formation via aggregation. The success of this method depends on short mixing times [18], and, therefore, high flow rates. Thus, this process is ideal for forming large quantities of nanocomposites, on the order of kilograms per day, as demonstrated by Lim et al. [19] Limitations of FNP include the time required to remove the remaining organic solvent and the high flow rates required to ensure adequate mixing. To the best of our knowledge, FNP has not been used to generate high aspect ratio micelles [15,20,21], although this may be possible under specific operating conditions.

Recently, Hayward and colleagues developed the 'interfacial instability' (IS) synthesis approach that relies on transient instabilities at the organic droplet-water interface to form micelles [22]. In this approach, amphiphilic BCPs are dissolved in a water immiscible organic solvent that is then emulsified in an aqueous solution containing a surfactant. As the organic solvent evaporates from the droplets, the polymer concentration increases. In addition, polymers and surfactant segregate to the organic-water interface, decreasing the interfacial tension. This leads to wave-like instabilities and transiently negative surface tension, resulting in droplet fission. The subsequent daughter droplets undergo similar fission events with continued evaporation of the organic solvent. Eventually, BCP micelles form when the BCP concentration reaches the critical micelle concentration (CMC) [23,24]. This technique is particularly effective with larger BCPs, but, because it is typically performed as a batch process, production rate and mass throughput are generally quite low (e.g., 0.01 mg polymer/h [25]).

In our earlier work, we showed [25] that combining interfacial instability with electrohydrodynamic spraying, in a process we call Aero-IS, led to an increase in the micelle production rate of at least 30-fold over batch methods. In 'electrospray' (also called electrohydrodynamic atomization), an electric field is applied to a charged fluid flowing through a capillary. Increasing voltage deforms the fluid into a conical shape that expels a jet of liquid from the tip [26]. Eventually, the jet breaks into droplets [27] creating a fine mist that may further fission if the charge on the droplet reaches the Rayleigh limit. In the micelle formation process, electrospray forms the emulsion in which interfacial instability takes place. Efficiency gains are achieved by reducing the energy input required to form the emulsion, as droplets are generated directly from the organic phase rather than by applying power to the entire organic-aqueous mixture. Furthermore, recent work by Sun et al. demonstrated that the size of the emulsion droplet can affect the quality of the product made via interfacial instability. In particular, the fine emulsions produced in the electrospray approach yielded micelle-encapsulated quantum dots with more stable fluorescence than micelles formed from coarse emulsions [28]. To date, electrospray has primarily been used to generate spherical structures at the nanoscale [29,30], particularly in combination with the interfacial instability approach [25].

In some applications, non-spherical micelles are preferred [5]. For example, wormlike micelles may provide greater drug loading efficiency than spherical structures without altering drug release rates [13]. In addition, the cylindrical shape of worm-like micelles enhances cellular uptake versus spherical assemblies with equivalent cargo loading [31]. The development of a versatile, scalable synthesis technique that provides access to multiple BCP assembly morphologies could help advance these applications.

Here, we further develop the work of Duong et al. [25] by exploring the potential of the Aero-IS approach to produce spherical micelles and higher-order BCP assemblies at increased throughput. We first examine the effect of electrospray operating parameters, including flow rates and voltage, on electrospray stability, and evaluate micelle morphology at two operating extremes. These studies significantly expand on the single fixed electrospray condition used by Duong et al. [25], and provide evidence for the robustness of the electrospray process. We also systematically vary key micelle processing conditions, including the emulsion processing temperature and BCP concentration, to determine their effect on BCP morphology as well as the overall micelle production rate. To our knowledge, the effect polymer concentration may have on morphology has not been systematically studied in the interfacial instability process [22,24] as it has been in the co-solvent approach. Morphological transitions in micelles made via Aero-IS are compared to transition points observed when micelles are produced the corresponding batch process. Collectively, these studies evaluate the robustness of scalable processes and their potential to induce morphological transitions to higher order structures.

2. Materials and methods

2.1. Materials

Carboxylated polystyrene-block-poly(ethylene oxide) (PS-b-PEO) (PS 9.5 kDa:PEO 18.0 kDa) was purchased from Polymer Source (Montreal, Canada). Poly(vinyl alcohol) (PVA) (13–23 kDa, 87–89% hydrolyzed) was purchased from Sigma-Aldrich. Chloroform (ACS grade) was purchased from Mallinckrodt. Distilled deionized water (dd-H_2O) was produced from a Millipore Milli-Q ultrapure filtration system. All materials were used as received.

2.2. Coaxial electrospray (Aero-IS)

Aero-IS experiments were performed following the approach of Duong et al. [25] (Fig. 1). Briefly, a 27 gauge (410 μm o.d.; 201 μm i.d.) stainless steel capillary was used as the inner needle and a 20 gauge (910 μm o.d.; 600 μm i.d.) stainless steel three-way connector was used as the outer needle. The nozzle tip was positioned 0.5 cm above a grounded copper ring and 10 cm above a grounded aluminum collection dish containing distilled, deionized (dd)-H_2O. The collection dish was placed on a Scilogix MS-H280 digital control hotplate for temperature control. Temperatures between 20 °C and 60 °C were investigated. The organic phase passing through the inner needle consisted of PS-b-PEO BCP dissolved in chloroform at concentrations ranging from 2 mg/ml to 50 mg/ml, whereas the outer needle contained an aqueous phase consisting of 50 mg/ml (5 wt%) PVA dissolved in dd-H_2O. The outer and inner flow rates (Q_{outer}, Q_{inner}) were controlled using syringe pumps. Values of the