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A competitive aggregation model for *Flash NanoPrecipitation*

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ABSTRACT

Flash NanoPrecipitation (FNP) is a novel approach for producing functional nanoparticles stabilized by amphiphilic block copolymers. FNP involves the rapid mixing of a hydrophobic active (organic) and an amphiphilic di-block copolymer with a non-solvent (water) and subsequent co-precipitation of nanoparticles composed of both the organic and copolymer. During this process, the particle size distribution (PSD) is frozen and stabilized by the hydrophilic portion of the amphiphilic di-block copolymer residing on the particle surface. That is, the particle growth is kinetically arrested and thus a narrow PSD can be attained. To model the co-precipitation process, a bivariate population balance equation (PBE) has been formulated to account for the competitive aggregation of the organic and copolymer versus pure organic–organic or copolymer–copolymer aggregation. Aggregation rate kernels have been derived to account for the major aggregation events: free coupling, unimer insertion, and aggregate fusion. The resulting PBE is solved both by direct integration and by using the conditional quadrature method of moments (CQMOM). By solving the competitive aggregation model under well-mixed conditions, it is demonstrated that the PSD is controlled primarily by the copolymer–copolymer aggregation process and that the energy barrier to aggregate fusion plays a key role in determining the PSD. It is also shown that the characteristic aggregation times are smaller than the turbulent mixing time so that the FNP process is always mixing limited.

1. Introduction

One method for producing nanoparticles is precipitation of an active (organic) compound using a non-solvent (water) [1]; however, the obtainable particle size distribution (PSD) is usually not optimal [2–12]. A promising alternative is *Flash NanoPrecipitation* (FNP) [13–15], wherein the PSD is controlled by co-precipitating an amphiphilic di-block copolymer. The FNP process has been used to produce nanoparticles from a wide range of organic compounds [16–23]. In the FNP process, the organic compound and the block copolymer are initially dissolved in a good solvent in either a pre-mixed or in separate feed streams [13]. This solution is then rapidly mixed in a few milliseconds with the non-solvent in a microreactor to induce precipitation of the organic compound and micellization of the block copolymer. As with precipitation [3,5–7,9,10], the FNP process is known to be sensitive to the rate of turbulent mixing between the solvent and non-solvent [15].

Using Brownian dynamics simulations [24,25], it has been shown that during the FNP process organic particles aggregate with each other or onto the hydrophobic block (A-block) of the copolymer, while the hydrophilic block (B-block) of the copolymer stretches in the non-solvent to stabilize the resulting nanoparticles. As the resulting copolymer–organic particle aggregates form micelles, organic protected nanoparticles are formed in the interior of the micelles and further growth is arrested. Micellization kinetics in block copolymer solutions have been observed by using the stopped-flow method [26], temperature-jump experiments (T-jump), time-resolved light scattering [27–30], non-radiative energy transfer and fluorescence-quenching techniques [31–33], transmission electron microscopy [34,35], and sedimentation velocity methods for co-micellization experiments [36,37]. Theoretical models describing micellization kinetics have also been proposed [38–40]. In these studies, two distinct mechanisms have been identified. The first is unimer exchange, during which the micelles grow by consecutive incorporation of one block copolymer molecule at a time: $C_{p-1} + C_1 \leftrightarrow C_p$, where C_p denotes micelles with aggregation number p (i.e., the number of block copolymer molecules in a micelle). The second is micelle fusion/fission, which involves association between two micelles: $C_p + C_i \leftrightarrow C_{p+i}$.

It is important to note that the initial precipitation process, which we model as Brownian aggregation, occurs on much faster time scales than the mixing process. Hence, the initial organic nanoparticle formation kinetics will be mixing limited. However, as the nanoparticles grow in mass and are diluted by mixing, their number concentration decreases rapidly and the kinetics of the aggregation process, which is second order in the number concentration, becomes substantially slower. Furthermore, the presence of the hydrophilic block in the co-precipitated nanoparticles creates a steric hindrance to aggregation that further slows the aggregation

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kinetics. Eventually, the combined effects of dilution and steric hindrance effectively stop the aggregation process, and thus the properties of the protected nanoparticles will be determined by the kinetics of the mixing-limited competitive aggregation process.

In previous work, we have developed flow models for mixing-limited chemical reactions and validated them in the flow devices used for the FNP process [41,20,42]. Thus, the primary objective of this work is to develop a competitive aggregation model for the co-precipitation of organic and block copolymer that can be combined with turbulent flow models to describe the FNP process. By making use of the Brownian motion assumption and known micellization kinetics, an aggregation kernel for protected nanoparticles is formulated. In order to develop an appropriate reactor-scale model of this system, we employ a mean-field aggregation population balance equation (PBE). Because the competitive aggregation mechanism depends upon whether or not a pair of aggregating particles consists of two free organic particles (unattached to any copolymer), two copolymer molecules/clusters without any organic particles attached, or particle–copolymer mixtures, the first step in developing the competitive aggregation model is to construct aggregation rate kernels that depend upon the particle composition (the number of organic particles and copolymer molecules).

The remainder of this work is organized as follows: In Section 2 we introduce the competitive aggregation model and derive expressions for the aggregation kernels by extending the micellization kinetics proposed by Dormidontova [40]. In Section 3 we introduce and validate a novel numerical method, conditional quadrature method of moments (CQMOM), for solving the bivariate PBE that results from the competitive aggregation model. In comparison to direct quadrature method of moments (DQMOM) [43], which was formulated to solve multivariate problems by tracking the primitive variables weights and abscissas, CQMOM has the advantage of tracking the conserved variables, the moments, to always yield realizable abscissas. In Section 4 we use solutions to the PBE for well-mixed systems to investigate the effect of physical parameters appearing in the competitive aggregation model and of operating condition on the PSD. Conclusions are drawn in Section 5. Details on the diffusion-limited aggregation model are given in Appendix A.

2. The competitive aggregation model

Nanoparticle aggregation occurs when the solubility limits of the organic and polymer compounds are crossed due to dilution by the non-solvent. A typical solubility diagram for the FNP process is shown in Fig. 1. In order to quantify the solubility, we introduce the mixture fraction ξ [44], which has value $\xi = 0$ in the solvent and $\xi = 1$ in the non-solvent. Intermediate values of ξ correspond to the mole fraction of non-solvent in the mixture, and ξ_{mix} is the value of the mixture fraction in the final mixture. Let ξ_{o} and ξ_{p} be the solubility limits of the organic and block copolymer, respectively. In the FNP process, ξ_{o} and ξ_{p} are chosen to be less than ξ_{mix}, and hence the organic and block copolymer precipitate together from the final mixture. In this work, we assume that once the solubility limit is crossed, diffusion-limited aggregation of the organic and polymer will occur spontaneously due to the extremely poor solubility of these compounds in the non-solvent. The final PSD will depend on the relative rates of organic–organic, polymer–polymer, and organic–polymer aggregation, which we refer to as *competitive* aggregation. In general, the aggregation kernels will depend on the value of ξ (i.e., whether the compounds are soluble or insoluble). However, under well-mixed conditions $\xi = \xi_{\text{mix}}$ so that both compounds are insoluble.

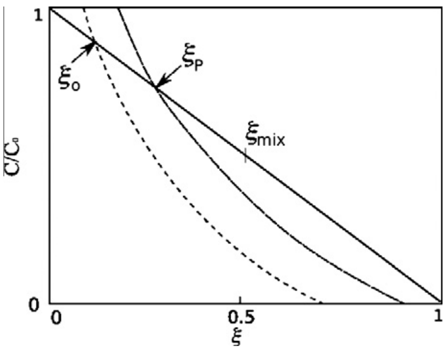

Fig. 1. A typical solubility diagram for the *Flash NanoPrecipitation* process. The straight solid line connecting the solvent (0,1) and the non-solvent (1,0) is the mixing line. The solubility curves for organic and block copolymer are shown by dashed curves, to the right of which the compounds are insoluble. The value of the mixture fraction after complete mixing is ξ_{mix}. During the mixing process, the organic becomes insoluble first at ξ_{o}, followed by the copolymer at ξ_{p}.

2.1. Population balance equation

In the FNP process, nanoparticle aggregation is arrested by the presence of block copolymer. The di-block unimer has a chain shape composed of a hydrophobic block (A-block) and a hydrophilic block (B-block). When a unimer aggregates with an organic nanoparticle, the A-block attaches to the nanoparticle and the B-block 'deactivates' the attached area so that no other organic nanoparticles can attach. When the number of unimers attached to organic nanoparticles increases sufficiently, the nanoparticles are stabilized since it is impossible for other organic nanoparticles or unimers to pass the energy barrier needed to aggregate. The composite organic nanoparticles are then stabilized, encapsuled in star-like micelles. To obtain a description of the nanoparticle size distribution, which is crucial for applications, the system can be modeled by a bivariate PBE. In the FNP process, different aggregation mechanisms are determined by the way the aggregates are coupled, which is highly dependent on the aggregate types.

In this work, a nanoparticle aggregate is denoted as $C_{p,q}$ and consists of p unimers and q organic molecules as illustrated in Fig. 2. Letting $n(p,q)$ denote the number concentration of such aggregates, a bivariate PBE can be formulated to describe the time evolution of $n(p,q)$ due to aggregation:

$$\frac{dn(p,q)}{dt} = \frac{1}{2}\sum_{i=0}^{p}\sum_{j=0}^{q}\beta(i,j;p-i,q-j)n(i,j)n(p-i,q-j) - n(p,q)\sum_{i=0}^{\infty}\sum_{j=0}^{\infty}\beta(p,q;i,j)n(i,j) \tag{1}$$

where $\beta(p,q;\, i,j)$ is the kernel describing aggregation between $C_{p,q}$ and $C_{i,j}$:

$$C_{p,q} + C_{i,j} \overset{\beta(p,q;i,j)}{\longrightarrow} C_{p+i,q+j} \tag{2}$$

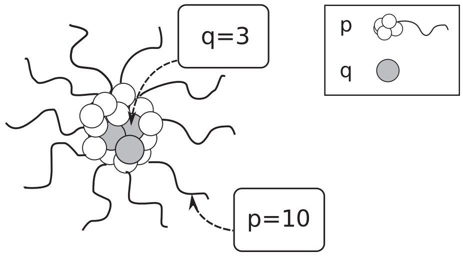

Fig. 2. Illustration of a composite nanoparticle. The unimer is comprised of the A-block (white beads) and B-block (black tails). An organic molecule is represented by a gray bead.