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Simulating copolymeric nanoparticle assembly in the co-solvent method: How mixing rates control final particle sizes and morphologies

Simon Keßler [a, b, *], Klaus Drese [a, 1], Friederike Schmid [b, **]

[a] Fraunhofer ICT-IMM, Carl-Zeiss-Str. 18-20, 55129 Mainz, Germany
[b] Institut für Physik, Johannes Gutenberg-Universität Mainz, D 55099 Mainz, Germany

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ABSTRACT

The self-assembly of copolymeric vesicles and micelles in micromixers is studied by External Potential Dynamics (EPD) simulations – a dynamic density functional approach that explicitly accounts for the polymer architecture both at the level of thermodynamics and dynamics. Specifically, we focus on the co-solvent method, where nanoparticle precipitation is triggered by mixing a poor co-solvent into a homogeneous copolymer solution in a micromixer. Experimentally, it has been reported that the flow rate in the micromixers influences the size of the resulting particles as well as their morphology: At small flow rates, vesicles dominate; with increasing flow rate, more and more micelles form, and the size of the particles decreases. Our simulation model is based on the assumption that the flow rate mainly sets the rate of mixing of solvent and co-solvent. The simulations reproduce the experimental observations at an almost quantitative level and provide insight into the underlying physical mechanisms: First, they confirm an earlier conjecture according to which the size control takes place in the earliest stage of the particle self-assembly, during the spinodal decomposition of polymers and solvent. Second, they reveal a crossover between different morphological regimes as a function of mixing rate. Hence they demonstrate that varying the mixing rate in a co-solvent setup is an effective way to control two key properties of drug delivery systems, their mean size and their morphology.

1. Introduction

Nanoparticles are molecule aggregates with spatial extensions on scales of ~ 10–100 nm. They have attracted growing interest during the last decades due to improved technologies for visualization and manipulation of nanoscale structures that have revealed their great potential for a wide range of applications. Depending on the chemical composition of the nanoparticles, these applications include mesoscopic models for atomic systems [1,2], optoelectronic devices [3], nanoreactors, models for biological cells [4,5], and most prominently, transport vehicles for medication, i.e. drug delivery systems [6–8].

Most commercially available drug delivery systems are liposomes [9,10], which are vesicular particles made of amphiphilic lipids. Biocompatible amphiphilic (diblock) copolymers represent promising alternatives to the lipids, since they are more stable and can be synthesized and modified more easily [11–13]. In analogy to their lipid counterparts, vesicles built from amphiphilic diblock-copolymers are often called polymersomes [11]. In the context of drug delivery systems one key property of nanoparticles is their size, since it not only determines their loading capacity, but also the composition of their protein corona in blood [14], which in turn affects retention times in the circulatory system. In addition, the nanoparticle size plays a critical role in passive targeting of tumors based on the Enhanced Permeability and Retention effect [15].

A method to manufacture nanoparticle populations with a specific mean size is the co-solvent method, also known as flash nanoprecipitation [16]. In this method, an initial solution containing the molecular constituents of the nanoparticles (e.g., the copolymers) in good solvent is mixed with a selective or bad solvent.

* Corresponding author. Institut für Physik, Johannes Gutenberg-Universität Mainz, D 55099 Mainz, Germany.
** Corresponding author.
E-mail addresses: simon_klr@gmx.net (S. Keßler), klaus.drese@hs-coburg.de (K. Drese), friederike.schmid@uni-mainz.de (F. Schmid).
[1] Current address: Fakultät für Angewandte Naturwissenschaften, Hochschule Coburg, 96450 Coburg.

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The mixing eventually triggers the precipitation of the constituents and the aggregation to particles. One way to tune the sizes of the particles is to vary the rate of solvent mixing [12,13,17,18]. In experiments, solvent mixing is often implemented by continuous flow mixing devices, called passive micromixers [12,13,17,18]. Mixing rates in passive micromixers increase with increasing flow rates v [19–21], and in turn, particle sizes are found to decrease with increasing v. Thiermann et al. [12,13] have recently carried out an extensive study on the relation between flow rates and particle size in such a micromixer setup. The constituents of their nanoparticles were amphiphilic diblock-copolymers with a hydrophobic polybutadiene block and a hydrophilic polyethylene-oxide block, and they used tetrahydrofuran as good solvent and water as selective co-solvent. They found that variations of v for symmetric flow conditions in passive micromixers enable a reproducible control over the mean size R of a particle population with relatively low polydispersity. The experimental data for R could be described reasonably well by scaling laws $R \propto v^{\alpha}$, where the exponent α differs from measurement to measurement, but scatters around a mean value of $\alpha = -0.158$ with a standard deviation $\sigma_{\alpha} = 0.058$ [22].

In a recent publication we proposed an explanation for the experimentally observed nanoparticle size dependence on flow rates or equivalently, mixing times [23]. We combined a simple Cahn-Hilliard equation with a Flory-Huggins-de Gennes free energy functional for *homo*polymers and implemented solvent mixing by a time dependent interaction parameter. The simulation results for the size of *homopolymer* aggregates at the (relatively well-defined) crossover between spinodal decomposition and subsequent coarsening were in good semiquantitative agreement with the experimentally determined sizes for stabilized *copolymer* particles from Thiermann et al. [12,13] (apart from a factor of two). This lead us to hypothesize that particle sizes in the co-solvent method are determined during the very early stages of phase separation. The description also provided an explanation for the typical scaling laws observed in experiments and predicted an analytical expression, $R \sim v^{-\alpha}$ with the exponent $\alpha = 1/6$, which is in good agreement with the experimentally observed exponents. According to this theory, the particle sizes at different v result from a competition of the repulsion between solvent molecules and monomers of the solvent-phobic block with the interfacial tension of diffuse interfaces in the very early stages of phase separation, during spinodal decomposition. With respect to the entire particle growth process the description in terms of the Cahn-Hilliard model is, however, incomplete. The Flory-Huggins-de Gennes free energy functional for homopolymers can only be applied in the early segregation regime, it does not describe the internal reorganization of copolymers inside the particles at later stages. In particular, it does not include a mechanism that physically stabilizes particles of finite size, and cannot be used to describe particles with more complex morphologies as can be observed in copolymeric systems.

Amphiphilic molecules may form particles of different morphologies in solution, including spherical micelles or vesicles [5]. Apart from the size, particle morphology is another key property of drug delivery systems because it affects the loading possibilities. Spherical micelles consist of a hydrophobic core surrounded by a shell of hydrophilic blocks and they can only be loaded with hydrophobic substances. Vesicles allow both hydrophilic and hydrophobic loading, which makes them appealing candidates for multifunctional drug delivery systems: Hydrophilic substances can be enclosed in their solvent containing core, while the hydrophobic part of the bilayer shell can be loaded with hydrophobic substances. These loading possibilities are important because some therapeutic substances are hydrophilic and others hydrophobic. An example for a hydrophilic substance is the toxic anti-cancer drug camptothecin [24]. Hydrophilic materials are, for instance, the anti-cancer drug doxorubicin [25] or the dye pholoxine B, which can be used to trace particles in *in vitro* cell binding studies or studies on (hydrophilic) loading efficiencies [26]. Although vesicles are more versatile when it comes to loading possibilities, micelles have the advantage that, due to their smaller size compared to vesicles, they may enable ways of cellular uptake that bypass the drug efflux mechanism of cancer cells in order to treat multiresistant cancer [10,27].

The experiments by Thiermann et al. [12,13] clearly show that the flow rates in micromixers also affect the morphologies of the resulting particles. At small flow rates, vesicles dominate, while at larger flow rates, micelles become more frequent. Motivated by these observations, we here present a numerical study of copolymer aggregation in a co-solvent setup for different mixing rates, using a dynamic density functional approach that explicitly accounts for the molecular architecture of copolymers. To this end, we implement time dependent interaction parameters into the established 'External Potential Dynamics" (EPD) model [28], which has been successfully used to study spontaneous self-assembly of amphiphilic diblock-copolymers to nanoparticles [29,30]. We focus specifically on the effect of mixing rates on particle morphologies, and how the existence of different particle morphologies affects the typical scaling behavior $R \propto v^{\alpha}$.

The article is organized as follows. In section 2 we present the theoretical model. In section 3 we specify the input parameters used in the current article. The results and the discussion is presented in section 4, and the summary is given in 5. In the Appendix A, we discuss technical issues and describe a novel integration scheme which was used to perform the simulations.

2. Theoretical model

We consider a solution of an amphiphilic AB-diblock copolymer P and a single solvent S in a volume V at temperature T. To describe the phase separation dynamics we apply the EPD model [28,29,31], which is based on the free energy functional of the popular Self Consistent Field (SCF) Theory for polymers [32,33]:

$$\begin{aligned}\frac{\beta F}{n} &= -f_S \ln\left(\frac{Q_S}{V f_S}\right) - \frac{f_P}{N}\ln\left(\frac{Q_P N}{V f_P}\right) + \frac{1}{V}\int_V \big[-\omega_A\phi_A \\ &\quad -\omega_B\phi_B - \omega_S\phi_S + \chi_{AB}\phi_A\phi_B + \chi_{AS}\phi_A\phi_S \\ &\quad +\chi_{BS}\phi_B\phi_S + \frac{\kappa_H}{2}(\phi_A+\phi_B+\phi_S-1)^2\big]\, d\vec{r}.\end{aligned} \tag{1}$$

Here f_P and f_S are the mean polymer and solvent volume fractions, N is the number of monomers per polymer chain, κ_H a mean compressive modulus of the solution [33,34], χ_{ij} the Flory-Huggins interaction parameter between species i and j, and $\beta = 1/k_BT$ the Boltzmann factor. The fields ω_i for $i = A, B, S$ are potentials in units of $\beta^{-1} = k_BT$ that act on the respective monomer species i, and $\phi_i = \frac{\rho_i}{\rho_0}$ with $\rho_0 = \frac{n}{V}$ are normalized number densities, where $n = n_S + Nn_P$ is the total number of monomers and solvent molecules in the system. n_S is the number of solvent molecules and n_P the number of polymer chains. Q_P is the partition function of a polymer chain subject to ω_A and ω_B, while Q_S is the partition function of a single solvent molecule exposed to ω_S. These single chain partition functions are given by

$$Q_P = \int_V g(\vec{r}, 1)\, d\vec{r} \text{ and } Q_S = \int_V e^{-\omega_S(\vec{r})}\, d\vec{r}. \tag{2}$$

$g(\vec{r}, s)$ is the end-segment distribution function and describes the probability that one end of a polymer chain segment of length s is located at position $\vec{r}$. It obeys the inhomogeneous diffusion