Nonsolvent-Induced Phase Separation Inside Liquid Droplets

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(Dated: 2 June 2023)

Nonsolvent-induced phase separation (NIPS) is a popular method for creating polymeric particles with internal microstructure, but many fundamental questions remain surrounding the kinetics of the complex coupled mass-transfer and phase separation processes. In this work, we use simulations of a phase-field model to examine how (i) finite domain boundaries of a polymer droplet and (ii) solvent/nonsolvent miscibility affect the NIPS process. To isolate the effects of phase separation kinetics and solvent/nonsolvent mass transfer on the NIPS process, we study two different cases. First, we investigate droplet concentrations that originate inside the two-phase region, where phase separation kinetics alone governs the microstructure. Second, we investigate the effects of solvent/nonsolvent mass transfer by studying droplet concentrations that begin outside the two-phase region, where both phase separation kinetics and mass transfer play a role. In both cases we find that qualitative NIPS behavior is a strong function of the relative location of the initial droplet composition with respect to the phase diagram. We also find that polymer/nonsolvent miscibility competes with solvent/nonsolvent miscibility in driving NIPS kinetic behavior. Finally, we examine polymer droplets undergoing solvent/nonsolvent exchange and find that the model predicts droplets that shrink with nearly Fickian diffusion kinetics. We conclude with a brief perspective on the state of simulations of NIPS processes and some recommendations for future work.

I. INTRODUCTION

Nonsolvent-induced phase separation (NIPS) is widely known as a method for generating a porous microstructure, e.g., in the industrial production of polymer membranes. In the NIPS process a polymer solution is brought into contact with a nonsolvent bath, initiating a process of mass exchange where the good solvent from the polymer solution is exchanged for the nonsolvent. The increasing concentration of the poor solvent in the polymer solution drives the precipitation of a polymer-rich phase, which solidifies to form the porous microstructure.^{1–4} This microstructure can be controlled by varying process conditions such as the composition of the polymer in the initial solution, the bath composition, and the temperature, leading to materials with a variety of practical uses.^{5,6}

In addition to membranes, NIPS-like processes are also useful for making microscale or nanoscale polymer particles. NIPS has been used for the synthesis of porous polymer particles since at least the late 1980s.^{7,8} Recently, several researchers have become interested in using NIPS-like processes to produce industrial-scale quantities of complex particles that are porous, patchy, anisotropic, and/or compartmentalized.^{9,10} For example, Cabral et al. have used a microfluidic approach to generate a variety of porous particle morphologies with useful time-release properties for drug delivery.^{11–15} Considerable effort has also been expended to create polymer particles by first emulsifying a polymer solution and then performing a NIPS-like solvent exchange with a partially miscible nonsolvent or by evaporatively stripping the good solvent.^{10,16–18}



FIG. 1. (Left) Nonsolvent-induced phase separation (NIPS) in a semi-infinite film involves a diffusive exchange (represented by the wavy orange arrows) of a good solvent for a poor one, resulting in the precipitation of a porous solid. (Right) NIPS in a bounded domain adds additional complexity to the kinetics due to the finite and deformable droplet boundaries.

In spite of the recent interest, there are still many unanswered questions about the connections between NIPS kinetics and the formation of nano/microstructure in polymer particles. Indeed, NIPS processes have been studied for nearly half a century,¹⁹ yet a complete understanding of the formation mechanisms of various microstructures remains illusive. For example, in membranes a definitive mechanism for the generation of asymmetric porous structures has only recently been elucidated,^{2–4,20} and the origin of large-scale "macrovoids" remains controversial.^{21–24}

Even less is known about the NIPS process that takes place inside a droplet of polymer solution while forming a porous polymeric colloid. As illustrated in Figure 1, bounded domains, such as droplets, introduce boundary conditions that affect the mass transfer kinetics, hydrodynamics, and phase transition dynamics of the NIPS process. The confinement

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dictated by the droplet domain can be complex, because the boundaries are deformable when subject to forces and flows from both the phase-separating polymer solution and the non-solvent bath. In addition, miscibility between solvent and nonsolvent is an important consideration for NIPS inside droplets, because a variety of techniques rely on first emulsifying a droplet in a partially miscible solvent before undergoing solvent/nonsolvent exchange.^{10,12,15–18}

One reason for the lack of progress in understanding NIPS kinetics is the challenging task of modeling the full compliment of phenomena that are present, including moving boundaries, mass transfer, phase separation, hydrodynamic flows, and structural arrest. There are two generic approaches that can be used to accomplish this task. The first relies on particle-based models such as coarse-grained molecular dynamics. There has been some recent progress modeling the formation of polymer particles using such models. Panagiotopoulos et al. has successfully simulated Flash Nanoprecipitation of block copolymer nanoparticles using coarse-grained molecular dynamics,^{25–28} and Kim et al. used dissipative particle dynamics to model the formation of block copolymer nanoparticles in an emulsion/solvent-stripping processes.^{10,17,29,30} Such approaches are especially useful for capturing local chain dynamics, but struggle to reach larger length and time-scales. Notably, Panagiotopoulos et al. has made progress by parameterizing a larger-scale kinetic Monte Carlo model using data from coarse-grained molecular simulations.²⁷

A second approach to modeling NIPS processes employs phase-field models. In these models, continuum transport equations are coupled to a description of polymer thermodynamics described by a free energy functional derived from a statistical field theory.³¹ Importantly, these models have larger intrinsic length and time scales than particle-based models, but the polymer kinetics are not as straightforward.^{32,33} Another feature of phase-field models is that they possess a continuous interface between phases, making it considerably simpler to capture multiphase mass transport and fluid flow than in traditional continuum transport models that require interface-tracking. Phase-field models have already been used to investigate phase transition dynamics in related problems with finite-sized domains including two-component vesicles³⁴ and Janus fluid droplets.³⁵ Our group and other groups have also made progress using phase-field models to simulate the NIPS process in non-droplet domains while investigat-ing polymer membranes.^{2,20,36,37} Our recent work with these models has focused on semi-infinite films, characterizing the mass transport kinetics,3 examining the role of Marangoni flow as a mechanism for macrovoid formation,²⁴ and exploring the mechanisms of asymmetric pore formation.⁴

In this work, we use a phase-field model to address two outstanding questions related to the formation of porous polymeric colloids via NIPS. First, we address the question: "What role does a finite domain boundary have in dictating the microstructure generated during NIPS?" In answering this question, the droplet size is an especially important parameter to consider, as smaller droplets may experience faster solvent/nonsolvent exchange or phase separation due to their larger surface-to-volume ratio. Second, we ask "How does solvent exchange with a partially miscible solvent affect NIPS kinetics?" If the solvent and nonsolvent are not fully miscible, mass transfer will be retarded, leading to longer times before phase separation and microstructure formation. The droplet composition is relevant for both questions; therefore, we will also study mass transfer and phase separation kinetics as a function of the concentration of polymer and solvents within the droplet.

With these questions in mind, the manuscript below is organized as follows: In Section II, we introduce the phase field model, and we provide details related to obtaining phase diagrams when there is finite miscibility between solvent and nonsolvent. Next, we discuss the results in Section III where we split our work into two major parts: (a) Section III A presents our simulations and analysis of phase separation dynamics of droplet compositions that initially reside inside the two-phase gap, and (b) Section III B covers droplet compositions outside the two-phase gap. This division of parts allows us to separately analyze the effects of phase separation kinetics (in Section III A), and then study the combined effects of the coupled mass-transfer and phase separation kinetics (in Section III B). Finally, Section IV gives a brief summary and conclusion.

II. METHODS

A. Phase-Field Model

Our phase-field model of the NIPS process describes the diffusion, convection, and phase separation of a ternary mixture of a polymer (p), a nonsolvent (n), and a good solvent (s). The labels nonsolvent and good solvent are quantified more precisely using Flory interaction parameters in Table I below. Originally derived using the two-fluid formalism of Doi, Onuki, and de Gennes,^{2,36,38} our model consists of coupled diffusion and momentum equations,

$$\frac{\partial \phi_i}{\partial t} + \boldsymbol{v} \cdot \nabla \phi_i = \nabla \cdot \left[\sum_{j=1}^{p,n} M_{ij} \nabla \mu_j \right]$$
(1)

$$0 = -\nabla p + \nabla \cdot \left[\boldsymbol{\eta} \left(\nabla \boldsymbol{v} + \nabla \boldsymbol{v}^T \right) \right] - \nabla \cdot \boldsymbol{\Pi}$$
(2)

and the continuity equation guaranteeing incompressibility,

$$\nabla \cdot \boldsymbol{v} = \boldsymbol{0}.\tag{3}$$

In the above expressions, ϕ_i is the volume fraction of component *i* where *i* is in the set $\{p, n, s\}$, *t* is time, *v* is the (volume-averaged) velocity, M_{ij} is the volume-fraction-dependent mobility matrix, μ_j is the exchange chemical potential of component *j*, *p* is the pressure, η is a volume-fraction-dependent viscosity, and Π is the osmotic stress. The osmotic stress couples the diffusion equation to the momentum equation providing a source of concentration-driven convection, and thermodynamic consistency is maintained by a generalized Gibbs-

Duhem relation,³⁹

$$\nabla \cdot \mathbf{\Pi} = \frac{1}{\mathbf{v}_0} \sum_{i}^{p,n} \phi_i \nabla \mu_i. \tag{4}$$

where v_0 is the monomer volume. Note also that due to incompressibility, only two of the volume fractions and two of the diffusion equations in Eq. 1 are independent. Unless otherwise discussed, we assume that ϕ_p and ϕ_n are the independent variables.

The free energy functional of the system is composed of a homogeneous term and a summation of gradient terms,

$$F[\{\phi_i\}] = \frac{k_B T}{v_0} \int d\mathbf{r} \left[f_0(\{\phi_i\}) + \sum_{i}^{p,n,s} \frac{\kappa_i}{2} |\nabla\phi_i|^2 \right]$$
(5)

where k_B is Boltzmann's constant, *T* is the temperature, *r* is the spatial coordinate, and κ_i is a coefficient penalizing concentration gradients. The gradient terms in Eq. 5 provide surface interactions that allow for finite interface widths and an emergent surface tension. The homogeneous free energy density, f_0 , contributes mixing entropy and enthalpy terms, and provides the driving force for phase separation. In our model, we use a Flory–Huggins free energy,

$$f_0(\{\phi_i\}) = \sum_{i}^{p,n,s} \frac{\phi_i}{N_i} \ln \phi_i + \frac{1}{2} \sum_{i \neq j}^{p,n,s} \chi_{ij} \phi_i \phi_j$$
(6)

where N_i is the degree of polymerization for component *i*, and χ_{ij} is the binary Flory interaction parameter between components *i* and *j*. For simplicity, we fix κ_i to be a constant for all components, i.e., $\kappa_p = \kappa_n = \kappa_s = \kappa$ and we set the degree of polymerization of small molecule components $N_n = N_s = 1$.

The exchange chemical potential that appears in Eq. 1 is given by the variational derivative of Eq. 5,

$$\mu_{i} = \frac{\delta F}{\delta \phi_{i}}$$

$$= \frac{k_{B}T}{v_{0}} \left(\frac{\partial f_{0}}{\partial \phi_{i}} - \sum_{j}^{p,n} K_{ij} \nabla^{2} \phi_{j} \right)$$
(7)

where

$$K_{ij} = \begin{bmatrix} 2\kappa & \kappa \\ \kappa & 2\kappa \end{bmatrix}$$
(8)

is a matrix containing the diagonal and off-diagonal gradient coefficients. There is a subtle difference between the free energy functional and chemical potential in Eq. 5 and Eq. 7 and their counterparts used in prior publications.^{2,3,24} This difference leads to the presence of off-diagonal terms in Eq. 8, which are necessary to properly account for the surface tension. As such, Eq. 7 and Eq. 8 are preferred to those used by Tree et al. in Refs. 2, 3, and 24. Additional details showing the origin of these terms are given in the Supplementary Information.

Table I gives the range of model parameters used in the present study. Notably, these parameters give quantitative

meaning to the qualitative terms "good solvent" and "nonsolvent" used above. The good solvent/polymer binary interaction parameter χ_{ps} is zero, and the nonsolvent/binary interaction parameter χ_{pn} is greater than

$$\chi_c = \frac{1}{2} \left(1 + \frac{1}{\sqrt{N_p}} \right)^2 \tag{9}$$

the critical interaction parameter for a binary mixture.² In addition, we often use a "base case" with $\kappa = 1$, the Flory– Huggins binary interaction parameter between the polymer and nonsolvent $\chi_{pn} = 1.048$ and between the solvent and nonsolvent $\chi_{ns} = 1.6$. This base case is used unless otherwise noted later in the results. The choice of the base case parameters and those in Table I represents a trade-off between the desire to match experimental reality and numerical convenience and tractability. For example the choice of the relatively small value of N_p reflects a numerical difficulty in resolving very small concentrations. Large values of χ_{ij} present similar numerical difficulties.

| TABLE I. Model Parameters | |
|---------------------------|------------------------|
| Parameter Value | |
| N _p | 20 |
| N_n | 1 |
| N_s | 1 |
| χ_{pn} | {1.048, 1.25, 1.5} |
| χ_{ps} | 0. |
| Xns | $\{0, 1.6, 2.0, 2.1\}$ |
| κ | 1 |
| Nr | 20 |
| b | 1 nm |
| η_r | 1 cP |
| Т | 293 K |

We numerically solve Eqs. 1–3 with a custom-written GPUaccelerated C++ code using psuedo-spectral methods with a semi-implicit time-stepping scheme. The pseudo-spectral derivatives provide excellent accuracy properties for handling the narrow interfaces between phase separated domains, and they give a simulation box with periodic boundary conditions, which is sufficient for the questions investigated here. Additional details regarding the numerical methods can be found in Ref. 2 by Tree and coworkers.

For ease of analysis, Eqs. 1–3 are non-dimensionalized using a characteristic length scale R_0 , time scale τ , and pressure scale p^* , and simulations are performed in these units. R_0 is the RMS end-to-end distance $bN_r^{1/2}$ of a reference polymer with Kuhn length *b* and degree of polymerization N_r , τ is the Rouse time $N_r^2 \eta_r v_0 / k_B T$ of the reference polymer in a fluid with a viscosity η_r and monomer volume $v_0 = b^3$, and $p^* = \eta_r / \tau$ is the viscous pressure.² Using the parameters specified in Table I gives simulation scales of $R_0 = 4.47$ nm, $\tau = 98.9$ ns, and $p^* = 10.1$ kPa. All of the results presented in Sec. III are given in these units.

Finally, the simulations presented here are primarily twodimensional (2D). 2D simulations are commonly used in phase field simulations of polymer solutions because they include most of the relevant physics, but are considerably less expensive than three-dimensional (3D) simulations. For simulations of phase separating droplets, 2D simulations capture key qualitative features of the NIPS process including mass transfer, phase separation, the formation and motion of interfaces, capillary-driven fluid flow, and coarsening dynamics. However, 2D simulations miss some quantitative features of mass transfer kinetics and microstructure evolution that are beyond the scope of the present study.⁴

B. Phase Diagrams with Finite Miscibility

We make extensive use of ternary phase diagrams to make sense of the phase separation behavior of the model described in Section II A. It is not trivial to calculate these phase diagrams when there is finite miscibility between both (i) the polymer and the nonsolvent and (ii) the solvent and the nonsolvent. Phase diagrams were obtained using the classical Flory–Huggins Helmholtz free energy⁴⁰

$$A = k_B T f_0 n_{\text{tot}} \tag{10}$$

where f_0 is the same homogeneous free energy appearing in Eq. 5, $n_{\text{tot}} = N_p n_p + N_n n_n + N_s n_s$ is the total number of monomers (Flory-Huggins "sites"), and n_p , n_n , and n_s are the number of polymer, nonsolvent, and solvent molecules respectively.

Binodals are determined by equating chemical potentials of each species

$$\tilde{\mu}_p^{\alpha} = \tilde{\mu}_p^{\beta} \tag{11}$$

$$\tilde{\mu}_n^{\alpha} = \tilde{\mu}_n^{\beta} \tag{12}$$

$$\tilde{\mu}_{s}^{\alpha} = \tilde{\mu}_{s}^{\beta} \tag{13}$$

for the α and β phases that compose the two branches of the binodal. Note that

$$\tilde{\mu}_i = \frac{\partial A}{\partial n_i} \tag{14}$$

is the traditional chemical potential, not the exchange chemical potential used in the phase field model in Eq. 7. The two are related through the expression³⁹

$$\mu_i = \frac{\tilde{\mu}_i}{N_i} - \frac{\tilde{\mu}_s}{N_s}.$$
(15)

The spinodals are calculated by setting the determinant of the Hessian matrix of A to zero,

$$Z \equiv \begin{vmatrix} A_{pp} & A_{pn} \\ A_{np} & A_{nn} \end{vmatrix}$$

$$= A_{pp}A_{nn} - A_{pn}A_{np} = 0$$
(16)

and the critical point can be found when Eq. 16 and

$$Y \equiv \begin{vmatrix} \frac{\partial Z}{\partial \phi_p} & A_{pn} \\ \frac{\partial Z}{\partial \phi_n} & A_{nn} \end{vmatrix}$$

$$= A_{ppp} A_{nn}^2 - 3A_{ppn} A_{pn} A_{nn} + 3A_{pnn} A_{pn}^2 - A_{pp} A_{pn} A_{nnn} = 0$$
(17)

are both satisfied.^{2,41–43} Eqs. 16 and 17 both use

$$A_{ij} = \frac{\partial^2 A}{\partial \phi_i \partial \phi_j} \tag{18}$$

$$A_{ijk} = \frac{\partial^3 A}{\partial \phi_i \partial \phi_j \partial \phi_k} \tag{19}$$

as a shorthand for derivatives of the Flory–Huggins free energy with respect to volume fraction. Additional expressions that show the explicit dependence on volume fraction and model parameters for the chemical potentials in Eq. 11–13, the stability criteria in Eq. 16, and the critical criteria in Eq. 17 are given in the Supplementary Information. Phase diagrams were calculated using Eqs. 11–17 via a numerical procedure outlined in the Supplementary Information.

III. RESULTS AND DISCUSSION

The NIPS process consists of two coupled kinetic processes: (i) solvent/nonsolvent mass transfer and (ii) phase separation of a polymer-rich phase from a solvent/nonsolvent rich phase.³ Mass transfer is initiated when the polymer solution sometimes also referred to as the polymer "dope"—is exposed to a nonsolvent bath, and solvent and nonsolvent are exchanged between the bath and the dope phase via diffusion.³ If all or part of the dope concentration lies inside a two-phase region (see e.g., Fig. 3), the dope will begin to phase separate into a polymer-rich and a polymer-lean phase.

A key element to the mass transfer process is the diffusion time scale

$$\tau \sim L^2 / \mathscr{D} \tag{20}$$

where *L* is the characteristic size of the dope geometry and \mathscr{D} is the characteristic diffusion coefficient. At times much less than τ , solvent and nonsolvent do not have significant time to exchange; therefore, the phase separation behavior of the dope is governed by the initial concentration and its location on the phase diagram. As expected, dope compositions that are within the two-phase region begin to phase separate instantaneously. Interestingly, an instantaneous phase separation is also possible for a dope with a concentration that is close to, but not strictly within, the two-phase region.³ At times much greater than τ , solvent/nonsolvent exchange can drive the concentration of the dope within the two-phase region, leading to a so-called "delayed phase separation." Even though diffusion is important for the latter case, the delay time

before phase separation also depends strongly on the initial dope concentration.³

The kinetics of the phase separation process and the resulting phase separated morphology are also governed by location of the dope concentration relative to the two-phase window. If the concentration is located inside the binodal envelope but outside the spinodal envelope, phase separation proceeds via nucleation and growth kinetics.⁴⁴ If the concentration is inside the spinodal region, the mixture becomes thermodynamically unstable and spontaneously phase separates via spinodal decomposition. Note that the model we employ does not include fluctuations; therefore, all of the phase separations presented here proceed via spinodal decomposition. Shortly after phase separation, the morphology is dominated by droplets of the size of the critical nucleus (for nucleation kinetics) or by domains with the fastest growing rate (for spinodal decomposition kinetics).² Regardless of the initial mechanism, as time proceeds, domains coarsen and aggregate causing growth of the characteristic size. The kinetics of these coarsening processes depends on the dominant transport mechanism: bulk diffusion (i.e. Ostwald ripening) produces domains which grow at a rate proportional to $t^{1/3}$, surface diffusion coarsens domains at a rate proportional to $t^{1/4}$, and viscous hydrodynamics rapidly grows domains with a rate proportional to t^{2}

In the discussion that follows, we separate our results into two categories. First, we describe the phase separation kinetics of droplets whose initial compositions put them *within* the two-phase window. Second, we describe the combined mass-transfer and phase separation kinetics of droplets whose compositions are initially *outside* the two-phase window. This division allows us to study phenomena driven by phase separation kinetics alone (Section III A) separately from those that are coupled with mass-transfer kinetics (Section III B).

A. Separation Dynamics from Unstable Conditions

1. Microstructural Evolution

In this section, we investigate the NIPS process occurring within a droplet with a composition that initially resides inside the two-phase gap. Such a droplet will immediately undergo spinodal decomposition. Two different patterns of spinodal decomposition are possible in the presence of the droplet surface. Isotropic, bulk spinodal decomposition (IBSD) is the classical mode of phase separation that occurs away from interfaces. Additionally, due to the broken symmetry provided by the boundary between the dope and the bath, surface-directed spinodal decomposition (SDSD) can also initiate a wave of phase separation that propagates from the boundary into the bulk of the film.⁴⁵ The relative importance of SDSD compared to IBSD, and the distance the front propagates into the droplet depends on the quench depth and the strength of the thermal fluctuations.⁴⁵

Figure 2 shows a prototypical example of circular droplets undergoing NIPS via IBSD in panel (a) and SDSD in panel (b). The simulations were performed using the base



FIG. 2. (a) Phase separation of a droplet via isotropic, bulk spinodal decomposition (IBSD). (b) Phase separation of a droplet via surfacedirected spinodal decomposition (SDSD).

case parameters described in Sec II A, with $\{\bar{\phi}_p, \bar{\phi}_n, \bar{\phi}_s\} = \{0.1, 0.7, 0.2\}$ for panel (a) and $\{\bar{\phi}_p, \bar{\phi}_n, \bar{\phi}_s\} = \{0.2, 0.5, 0.3\}$ for panel (b). The droplet size in both panels is D = 128, which was chosen to enable inspection of the internal changes in droplet morphology. As expected for IBSD, Figure 2a shows phase separated domains that are isotropically oriented and phase separation that proceeds simultaneously throughout the droplet. By contrast, the droplet in Figure 2b phase separates initially at the boundary between the dope and the bath with a front that proceeds towards the center of the droplet. Comparison of the volume fractions to the phase diagrams presented below in Sec. III A 2 shows that IBSD dominates at compositions that are deep inside the spinodal, whereas SDSD occurs for relatively shallow quenches.

Just as the initial concentration of the droplet dictates the dominance of IBSD or SDSD, the location of the initial composition within the spinodal envelop also determines the phase-separated morphology². Figure 3 shows a schematic phase diagram illustrating the expected behavior. Near the center of the spinodal region, there is a line of concentrations known as the "static symmetry line" (SSL) where spinodal decomposition in a dynamically symmetric mixture gives a bicontinuous morphology.⁴⁶ To the right of this line, the average polymer concentration of the dope is relatively lean, and the phase separation results in "isolated" droplets of a polymer-

rich phase in a matrix of a nonsolvent-rich phase. This pattern of isolated polymer droplets should also extend into the nucleation and growth region further to the right, though we do not explore this region in the present work. To the left of the SSL, the pattern is "inverted", and the relatively polymer-rich dope forms droplets of a nonsolvent-rich phase within a network of a polymer-rich phase. Again, this pattern should also extend into the metastable region of the phase diagram to the left of the spinodal curve. This pattern is qualitatively consistent with the familiar "lever rule", where the volume fraction of a phase is given by the relative distance along the tie line betwen the average composition and the binodal of the opposite phase. However, the lever rule is not quantitative in this case because of the existence of interfaces and (at short times) the dynamic asymmetry between the phases.



FIG. 3. A schematic of the phase diagram for the "base case" parameters labelling the important curves on the phase diagram and the regions where qualitatively different morphologies are observed.

Figure 4 shows examples of these three morphologies as manifested during the spinodal decomposition of a droplet, again using the base case parameters. Figure 4a shows a case of "isolated" polymer-rich droplets resulting from an initial dope composition of $\{\bar{\phi}_p, \bar{\phi}_n, \bar{\phi}_s\} = \{0.15, 0.8, 0.05\}$ (on the right of the SSL). Figure 4b shows a phase separation near the SSL that results in a nearly bicontinuous morphology (i.e., the droplets are highly elongated) when $\{\bar{\phi}_p, \bar{\phi}_n, \bar{\phi}_s\} =$ $\{0.25, 0.7, 0.05\}$ (near the SSL). Note that asymmetries in the polymer and solvent/nonsolvent diffusivities and slight deviations from the exact SSL composition make it impossible for the system to remain exactly on the SSL, causing the bicontinuous morphology to become either the isolated or inverted morphology as time proceeds. Finally, Figure 4c gives a case of the "inverted" morphology at an initial dope concentration of $\{\bar{\phi}_p, \bar{\phi}_n, \bar{\phi}_s\} = \{0.35, 0.6, 0.05\}$ (on the left of the SSL). A more quantitative analysis of where these morphologies occur in relation to the phase diagram is given in Section III A 2.

The above results illustrate that for compositions within the two-phase gap, NIPS in droplets shares the same qualitative morphological trends as the NIPS process in films. The final morphology for both geometries is highly dependent on



FIG. 4. Three morphologies observed during spinodal decomposition at different initial dope concentrations inside the spinodal envelope featuring: (a) "isolated" polymer droplets, (b) nearly bicontinuous "elongated" domains, and (c) "inverted" droplets of nonsolvent in a polymer-rich matrix.

the initial composition of the polymeric dope, i.e., the location inside the two-phase gap. However, there remain some important differences between droplets and films. As indicated previously, finite miscibility between solvent and nonsolvent is highly relevant for applications with droplets, so we examine the effects of solvent/nonsolvent immiscibility on morphology in the next section. In addition, because SDSD can influence morphology, the size and shape of the droplet determines the interface location, which can also affect phase separation morphology. Consequently, the following section discusses the effects of droplet size and shape on spinodal decomposition dynamics and morphology. Having established the qualitative features of NIPS kinetics, in this section we take a more detailed look at the effect of solvent/nonsolvent miscibility. Specifically, we examine three systems with decreasing compatibility between solvent and nonsolvent: (a) complete miscibility ($\chi_{ns} = 1.6$, the base case), (b) the cusp between miscibility and finite miscibility ($\chi_{ns} = 2.0$), and (c) finite miscibility ($\chi_{ns} = 2.1$).

Figure 5 shows phase diagrams for each of these three cases using the ternary Flory–Huggins model described in Section II B. Corresponding phase diagrams with tie lines are available in the Supplementary Information. As χ_{ns} increases from less than two to the critical value of $\chi_{ns} = 2$, the size of the spinodal and binodal regions increase and the plait point approaches the $\phi_p = 0$ boundary. When $\chi_{ns} > 2$, the system has a tie line at the terminus of the spinodal at $\phi_p = 0$ (the plait point disappears), and there is a clear separation or "finite miscibility" between a solvent-rich phase and a nonsolvent-rich one.^{47,48} In addition, the spinodal and binodal regions, and the tie-lines increases (towards the high-solvent region), and the tie-lines increasingly skew from being aligned close to parallel with the $\phi_s = 0$ axis to aligning more parallel with the $\phi_p = 0$ axis.

With these phase diagrams, it is possible to examine the phase-separated morphology of these three systems as a function of initial concentration. Consequently, we performed 2D simulations of a circular droplet undergoing the NIPS process for each system, sweeping the initial composition inside the spinodal envelope. Figure 5 summarizes the results of dozens of these simulations. Note that because the present model does not include kinetic arrest. Figure 5 characterizes the early-time morphology immediately after phase separation. As the name suggests, we anticipate that kinetic arrest will stop the evolution of the morphology at late times, but a detailed study is needed to determine if there is a more complex late-time behavior. We observe three classes of early-time morphologies: (i) isolated polymer-rich droplets in a nonsolvent matrix ("isolated" droplets), (ii) nearly bicontinuous regions of polymer-rich and nonsolvent-rich phases ("elongated droplets"), and (iii) isolated nonsolvent-rich regions in a polymer-rich matrix ("inverted" droplets). These morphologies are qualitatively similar to those shown in Fig. 4 and to those observed in planar films².

The locations of these different morphological features in concentration space, as seen Figure 5, are in good agreement with the schematic phase diagram in Figure 3. As expected, isolated droplets appear on the right side when the overall concentration of the droplet is polymer-lean. Inverted droplets appear on the left (polymer-rich) side, and elongated droplets appear near the center of the spinodal region, which again means that the morphology is almost completely determined by the volume fraction inside the dope. Note that there are occasional differences between the observed morphologies at concentrations that are shared between the three cases, especially near the boundaries between morphologies, but the overall trend remains consistent. This pattern of three distinct structures holds regardless of the value of χ_{ns} , but grows upwards (in



FIG. 5. Morphology as a function of initial droplet concentration for three different values of χ_{ns} : (a) A case of complete miscibility between solvent and nonsolvent ($\chi_{ns} = 1.6$), (b) The critical case where a binary solution of solvent and nonsolvent is immiscible ($\chi_{ns} = 2.0$), and (c) A case where solvent and nonsolvent have a defined region of immiscibility ($\chi_{ns} = 2.1$). Each point on the ternary diagram represents a different initial composition of the droplet.

the higher solvent direction) as the spinodal envelope enlarges with increasing χ_{ns} .

Figure 6 shows examples of each morphology for each of the three cases. Proceeding from the fully miscible case to an immiscible one has minimal effect on the emerging morphology of the droplet. However, we do observe that the phase separation kinetics are slightly faster as χ_{ns} increases, consistent with the idea that the effective "quench depth" increases as the spinodal envelope increases in size.

It is interesting to note that the relative size of the twophase region increases when both the solvent/nonsolvent compatibility decreases (e.g., Figure 5) and when the polymer/nonsolvent compatibility decreases (e.g., Figure S5 of the Supplementary Information). However, the orientation of the tie-lines, the SSL, and the relative location of different phaseseparated morphologies are not the same in both of these cases. Consequently, it may be difficult to know from a simple experimental observation of the phase envelope what phase-



FIG. 6. Color density plot of the polymer volume fraction ϕ_p showing the isolated, elongated, and inverted morphologies for three different values of the Flory–Huggins binary interaction parameter between the solvent and the nonsolvent (χ_{ns}). Images are taken from all nine simulations at t = 7 in simulation units.

separated morphologies would be anticipated. Additionally, these different types of incompatibilities certainly lead to differences in the mass transfer kinetics. We address this latter point in more detail in Section III B 1.

We conclude that a decrease in miscibility between the solvent and the nonsolvent has a significant influence on the shape and the size of the two-phase region, but that within this region, the qualitative sequence of morphologies remains the same. This result is congruent with the recent conclusion by Garcia et al.⁴ that more complex morphologies¹⁴ require the inclusion of thermal fluctuations, a mechanism for kinetic arrest, and 3D simulations.

3. Droplet Size

The distinctive aspect of a droplet is the finite size of its domain. Accordingly, we turn our attention to the effect of droplet size on morphology and the kinetics of the NIPS process. The effect of droplet size can be examined by performing simulations with the base case parameters using three different droplet diameters: D = 32, 64, and 128. Additionally, we examine the effect of droplet size on each class of morphology (isolated, elongated, and inverted) by varying initial composition. Accordingly, the three upcoming figures follow a similar pattern. Each figure represents one average composition (giving either isolated, elongated, or an inverted morphology) with rows that represent different droplet sizes. The dynamic evolution of the morphology is shown across the columns with time proceeding from left to right.

Figure 7 shows simulations that result in isolated droplets.

In this case, the droplet phase separation closely mirrors IBSD. With the exception of a small region near the interface, the droplet quickly phase separates into isotropically distributed regions of polymer-rich phase. The early-time domain size and rate of coarsening appear to be independent of the size of the droplet despite the presence of nearby interfaces. The main effect of increasing droplet size is a greater number of isolated droplets, which can been seen by visual inspection across rows at a fixed time.



FIG. 7. Phase separated morphologies of three droplets of different diameters (D = 32, D = 64, D = 128) with an average concentration $\bar{\phi}_p = 0.15$, $\bar{\phi}_n = 0.8$ and $\bar{\phi}_s = 0.05$ as a function of time. This average concentration is inside the two-phase gap to the right of the SSL and results in isolated droplets.

Increasing the average polymer concentration gives droplets that result in an elongated morphology as shown in Figure 8. In this case, the phase separation kinetics are a mix of SDSD and IBSD with a few layers of surface directed phase separation propagating into the droplet, and a bulk phase separation following near the droplet center. Similar to the previous case, the phase separation kinetics (including the early-time domain sizes and coarsening rates) are largely independent of droplet size. Again, droplet size simply results in a greater number of phase-segregated domains inside the droplet. Interestingly, the droplet shape is highly unstable in this region of the composition space. This instability results from the drive for highly elongated droplets to minimize surface area, giving rise to significant surface-tension driven flows.²⁴ Ultimately, at this composition, the droplet cannot hold together and it decomposes into numerous smaller isolated droplets.

Finally, as seen in Figure 9, a further increase in the average polymer concentration results in droplets with an inverted morphology. Continuing the trend from isolated to elongated morphologies, the inverted morphology shows a yet larger region of SDSD near the droplet interface. IBSD appears to be slower at these larger polymer concentrations, which is especially evident in the delayed microstructure formation for



FIG. 8. Phase separated morphologies of three droplets of different diameters (D = 32, D = 64, D = 128) with an average concentration $\bar{\phi}_p = 0.25$, $\bar{\phi}_n = 0.7$ and $\bar{\phi}_s = 0.05$ as a function of time. This average concentration is inside the two-phase gap near the SSL and results in elongated domains.

larger droplets. The resulting inverted (porous) microstructure eventually begins to coarsen at longer times as expected. However, the lingering effects of the SDSD wave are evident in an elevated region of polymer concentration for the largest droplet even at t = 50.



FIG. 9. Phase separated morphologies of three droplets of different diameters (D = 32, D = 64, D = 128) with an average concentration $\bar{\phi}_p = 0.35$, $\bar{\phi}_n = 0.6$ and $\bar{\phi}_s = 0.05$ as a function of time. This average concentration is inside the two-phase gap to the left of the SSL and results in inverted phases (porous structures).

In summary, we find that in droplets with a lower average polymer concentration, the phase separated morphology is nearly independent of the size of the droplet. However, for droplets with the largest average polymer concentration, there is a weak effect due to a retardation of IBSD. Consequently, SDSD plays a more significant role in the latter case, and smaller droplets that have a relatively larger interfacial area appear to phase separate more quickly. In addition to size, the initial droplet shape also plays a role in determining the microstructure produced by the NIPS process. An investigation of the effect of non-circular droplet shapes is given in the Supplementary Information.

B. Separation Dynamics from Stable Conditions

In the previous section, we examined droplets with average concentrations located inside the two-phase gap where phase separation by spinodal decomposition proceeds immediately. However, a typical droplet usually contains no nonsolvent, a high solvent concentration, and a low polymer concentration, putting its composition outside the two-phase gap. For these droplets the NIPS process includes both phase segregation and solvent/nonsolvent mass transfer. Mass transfer has two important effects on the NIPS process for droplets. First, it leads to a change in the average dope concentration of the droplet, possibly leading to a phase separation of the droplet. Second, the droplet itself can change size or shape as solvent and nonsolvent move in and out of the droplet.^{12,15} In this section, we will examine these two effects, first focusing on the impact that solvent/nonsolvent exchange has on phase separation kinetics and then studying changes in droplet size induced by mass transfer. Additionally, we take a special interest in the case where the binary interaction parameter between the solvent and the nonsolvent (χ_{ns}) is nonzero. As previously discussed, solvent/nonsolvent miscibility is an important consideration in experimental work on NIPS in droplets.^{12-15,49}

1. Microstructural Evolution and Finite Miscibility

In this section, we examine the effects of solvent/nonsolvent immiscibility on phase separation and microstructure, focusing specifically on the effects of solvent/nonsolvent mass transfer. The work in this section builds on a recent study of the effects of mass transfer effects on the NIPS process in a film geometry in Ref. 3. In that work, Tree et al. showed that the diffusion time, τ , of the solvent/nonsolvent is a key variable separating two cases of dynamic behavior. At "early times" ($t \ll \tau$), solvent and nonsolvent exchange are initiated, but the average dope concentration does not have time to change significantly. By contrast at "late times" ($t \gg \tau$), the average dope concentration can change significantly.

In both cases, three different Regimes are possible and are shown in Figure 10. Figure 10a shows Regime I, where the dope and bath freely mix, causing the droplet to dissipate. Figure 10b shows Regime II with a dope and bath that remain two separate phases interchanging solvent and nonsolvent. Figure 10c shows Regime III, which is the "NIPS case" where



FIG. 10. Examples of droplets in (a) Regime I with no phase separation between the dope and bath, (b) Regime II where the dope remains phase separated from the bath as solvent and non-solvent are exchanged, and (c) Regime III where the dope undergoes spinodal decomposition. These results were obtained using the base case parameters with an initial droplet size D = 32 and are shown at t = 30. The initial compositions used were: (a) $\{\bar{\phi}_p, \bar{\phi}_n, \bar{\phi}_s\} = \{0.05, 0.05, 0.945\}$, (b) $\{\bar{\phi}_p, \bar{\phi}_n, \bar{\phi}_s\} = \{0.2, 0.05, 0.75\}$, and (c) $\{\bar{\phi}_p, \bar{\phi}_n, \bar{\phi}_s\} = \{0.05, 0.5, 0.45\}$.

microstructure forms as the dope separates into polymer-rich and polymer-lean phases. The appearance of these Regimes are highly dependent on the initial concentration of the polymer dope, as well as the interaction parameters between the polymer, solvent, and nonsolvent. Additionally, it is common for a system that exists in one state at early times (e.g., Regime II where the bath and dope are separate phases) to transition to a different state at late times (e.g., Regime III where dope phase separation occurs) due to ongoing solvent and nonsolvent diffusion. Consequently, at early times Regime III corresponds to observations of "instantaneous phase separation" in NIPS systems, and at late times Regime III corresponds to "delayed phase separation."³ We first investigate the early-time phase separation behavior ($t \ll \tau$) of a droplet as a function of solvent/nonsolvent miscibility (i.e., $\chi_{ns} \in \{1.6, 2.0, 2.1\}$) with $\chi_{pn} = 1.048$ and all of the other parameters as given in Table I. It is possible to determine the type of phase behavior (i.e., Regime I, Regime II, or Regime III) by only performing 1D simulations if the details of the microstucture are not needed.³ In these 1D simulations, a droplet of polymer dope with some average composition is placed within a nonsolvent bath, and solvent/nonsolvent mass transfer is allowed to proceed for a very

vent/nonsolvent mass transfer is allowed to proceed for a very short time. By using these short, efficient 1D simulations, we were able to perform dozens of simulations spanning the composition space outside the two-phase gap as shown in Figure 11. Additional details related to the differences between 1D and 2D simulations are given in the Supplementary Information.



FIG. 11. Early-time separation regimes as a function of initial droplet concentration for a fixed $\chi_{pn} = 1.048$, and three different values of χ_{ns} : (a) $\chi_{ns} = 1.6$, (b) $\chi_{ns} = 2.0$, and (c) $\chi_{ns} = 2.1$. Each point on the ternary diagram represents a different initial composition of the dope with Regime I in red, Regime II in green, and Regime III in blue.

In Figure 11, we observe all three Regimes described above. In Figure 11a, χ_{ns} is at its smallest value and the solvent and nonsolvent are still miscible. Here, Regime II is the most common behavior observed throughout composition space, but there is a small area of Regime I at low polymer

concentrations, and a small area of Regime III near the critical point. As solvent/nonsolvent miscibility is decreased (by increasing χ_{ns} to 2.0) in Figure 11b, Regime II covers even more of the composition space, leaving only a small sliver of the other regimes. Finally, Regime II is the only observed behavior in Figure 11c, when $\chi_{ns} = 2.1$ and the solvent and nonsolvent are immiscible as $\phi_p \rightarrow 0$.

The dominance of Regime II is somewhat counter-intuitive, as one might expect Regime III to dominate as the two-phase gap grows. This intuition is presumably caused by the assumption that the drive for dope phase separation increases as the two-phase gap area increases. Indeed, this intuition holds when the binary interaction parameter between the polymer and the nonsolvent χ_{pn} increases. As demonstrated in Figure S5 in the Supplementary Information, increasing χ_{pn} increases the size of the two-phase gap as well as the range of concentrations for which Regime III is observed. However, Figure 11 shows the opposite trend with Regime II replacing Regime III as χ_{ns} increases.

We hypothesize that the dominance of Regime II over Regime III in Figure 11 is due to a competition between solvent/nonsolvent compatibility (χ_{ns}) and polymer/nonsolvent incompatibility (χ_{pn}). When polymer/nonsolvent incompatibility dominates, solvent and nonsolvent are free to mix (and because the polymer mobility is low), the dope prefers to phase segregate. By contrast, when solvent/nonsolvent incompatibility dominates, solvent and nonsolvent have little or no drive to mix, and the droplet prefers to stay in a single phase.

At late times ($t \gg \tau$), the average concentration inside the droplet can change significantly, causing a transition from one regime of phase separation to another.³ Similar to the case at early times, the dynamics of the NIPS process remains highly dependent on initial droplet composition. We again use 1D simulations to investigate late-time phase separation, with the added benefit that larger domains can easily be used in 1D to capture long-time diffusion from the bath.

Figure 12 shows the qualitative results of these simulations as a function of solvent/nonsolvent miscibility, which are in effect the $t \rightarrow \infty$ results for the same conditions in Figure 11. Compared to the early-time behavior in Figure 11, we do not observe Regime I in any of the simulations, indicating that the dope will eventually undergo some form of separation at late times. In Figure 12a, where χ_{ns} is the smallest, Regime III dominates at low polymer concentration. However, in Figure 12b and Figure 12c where $\chi_{ns} \ge 2$, nearly all compositions result in Regime II.

We interpret these results again in context of a competition between polymer/nonsolvent compatibility and solvent/nonsolvent compatibility. When χ_{ns} is relatively small, droplet spinodal decomposition (Regime III) eventually occurs as solvent and nonsolvent are exchanged and the polymer has little mobility to escape this process. However, at high χ_{ns} the solvent and nonsolvent prefer to remain demixed and no polymer phase segregation takes place.



FIG. 12. Late-time separation regimes $(t \to \infty)$ as a function of initial droplet concentration for a fixed $\chi_{pn} = 1.048$, and three different values of χ_{ns} : (a) $\chi_{ns} = 1.6$, (b) $\chi_{ns} = 2.0$, and (c) $\chi_{ns} = 2.1$. Each point on the ternary diagram represents a different initial composition of the dope with Regime I in red, Regime II in green, and Regime III in blue.

2. Size

While size played only a minor role in determining the phase separated morphology in Section III A 3, droplets with compositions outside the two-phase region experience significant mass exchange with the bath leading to a potentially large change in droplet size.^{3,12} Indeed, droplet shrinkage during so-called "solvent extraction" or "polymer nanoprecipitation" has been widely reported in the experimental literature.^{11–15,49,50} In this section, we carefully track solvent/nonsolvent flows and the change in droplet size in 2D simulations of solvent/nonsolvent exchange to better understand this phenomenon.

Figure 13 shows a time series of a prototypical 2D simulation of a polymer droplet placed in a pure bath of a nonsolvent. The initial concentration of the droplet is set outside the two-phase gap (in Regime II at both early and late times) with $\{\bar{\phi}_p, \bar{\phi}_n, \bar{\phi}_s\} = \{0.2, 0.2, 0.6\}$ using the base case model parameters. Figure 13a shows the evolution of the droplet concentration as a function of time. The droplet shrinks with time



FIG. 13. (a) A time series showing the shrinkage of a polymeric droplet with an initial composition: $\{\bar{\phi}_p, \bar{\phi}_n, \bar{\phi}_s\} = \{0.2, 0.2, 0.6\}$. (b) The droplet radius as a function of time during the solvent/nonsolvent exchange process for the droplet shown in panel (a).

while maintaining a sharp interface between the droplet phase and the bath, while the polymer concentration increases. Figure 13b shows the droplet radius, which monotonically decreases until it reaches a steady state at long times.

To further quantify this exchange, we calculate the flow rate of solvent Q_s , nonsolvent Q_n , and polymer Q_p across the moving droplet interface. The details of the calculation of this flow rate are given in the Supplementary Information. The resulting flow rates and the total flow rate

$$Q_{\rm tot} = Q_s + Q_n + Q_p \tag{21}$$

are given in Figure 14 as a function of time for the same simulation discussed in Figure 13.

Figure 14 shows that $Q_s < 0$, meaning that solvent is leaving the droplet, while $Q_n > 0$, meaning nonsolvent is entering the droplet. Due to low diffusivity of the polymer, $Q_p \approx 0$. More solvent leaves than nonsolvent enters ($|Q_s| > |Q_n|$), meaning there is a net flux of material out of the droplet ($Q_{\text{tot}} < 0$). However, it is interesting to note that the magnitude of solvent and nonsolvent flows is considerably larger than the net flow Q_{tot} . The magnitude of all of the flows monotonically decreases, eventually reaching zero at long times as the droplet reaches an equilibrium size. Recall that the system

is incompressible, so as the droplet shrinks the low-mobility polymer is trapped and the polymer concentration inside the droplet necessarily increases. Note also that the analysis here is for a single droplet, and the magnitude (and possibly the direction) of these flows depends on the initial composition.



FIG. 14. The evolution of the polymer (Q_p) , the nonsolvent (Q_n) , the solvent (Q_s) , and the total (Q_{tot}) flow rates as a function of time across a moving control volume for the droplet specified in Figure 13.

Recently, there has been interest in characterizing the physics of the diffusion kinetics for NIPS-like systems.^{12,14,15,49} Classical diffusion of liquids follows Fick's law, where components freely mix in response to a concentration gradient. However, NIPS diffusion is characterized by a moving boundary between phases, typically a signal that such diffusion is non-Fickian.^{12,51} For example, in non-Fickian Case-II diffusion, mass transfer is completely controlled by the swelling/deswelling of the substrate matrix.⁵²

As seen in Figure 13, our simulations also contain a moving boundary so one may expect that this is an indication of non-Fickian diffusion. However, the phase-field model in Eq. 1 explicitly incorporates Fick's law. This apparent contradiction provides an excellent opportunity to examine whether the solvent/non-solvent exchange process in NIPS is necessarily non-Fickian due to the phase separation.

Accordingly, we use a power-law model to quantitatively characterize the diffusion kinetics in our simulations. Specifically, we employ the Peppas equation, a semiempirical power-law model often used in drug delivery applications.^{51,53,54} The Peppas equation

$$\frac{M}{M_{\infty}} = K \left(\frac{\mathscr{D}t}{a^2}\right)^n \tag{22}$$

relates M, the amount (mass) of a component released from the droplet, to time t with a power-law exponent n that is related to the diffusion mechanism. Additionally, in Eq. 22 M_{∞} is the amount of the component at $t \to \infty$ when equilibrium is reached, K is a constant, \mathcal{D} is the diffusion coefficient, and a is characteristic size of the droplet. Many researchers have used this or related models to study the release of a drug component from polymeric systems and other swellable and nonswellable devices. 51,53-61

Ritger and Peppas^{51,54} derived this model for non-swellable and swellable systems by combining the short-time solution of Fick's second law

$$\frac{M}{M_{\infty}} \sim t^{0.5} \tag{23}$$

and the solution for Case-II diffusion

$$\frac{M}{M_{\infty}} \sim t \tag{24}$$

for a planar geometry. Accordingly, the exponent *n* can be used to characterize the degree to which mass transfer has Fickian or Case-II like character, with a value of n = 0.5 indicating Fickian diffusion and n = 1 indicating Case-II diffusion for a planar system. Note that when fitting diffusion data to the semi-empirical Peppas equation, only the short-time data $M/M_{\infty} \lesssim 60\%$ should be used to find the exponent *n*, because of the use of the short-time approximation of Fick's second law in the derivation.

In addition, the analysis is slightly more complicated when the system is non-planar, because the release equation depends on the surface area where diffusion takes place.⁵¹ We assume that a 2D particle is equivalent to a 3D cylinder, which corresponds to the cylindrical Peppas equation

$$\frac{R_{\infty}^2}{R^2} = K \left(\frac{t}{\tau}\right)^n \tag{25}$$

where *R* is the instantaneous droplet radius at time *t*, R_{∞} is the equilibrium radius, *K* is a constant, and τ is the characteristic diffusion time. In Eq. 25, the exponent n = 0.45 corresponds to the limit for Fickian diffusion and n = 0.89 corresponds to Case-II diffusion.⁵¹ A value in between those limits is considered to have both Fickian diffusion and Case-II-like swelling effects, and this case of non-Fickian diffusion is called anomalous diffusion.⁶¹

To evaluate the exponent for droplet shrinkage in our model, we simulated droplets with a range of initial sizes $R_0 \in [12.8, 32]$ undergoing solvent non-solvent exchange with a starting initial composition $\{\bar{\phi}_p, \bar{\phi}_n, \bar{\phi}_s\} = \{0.2, 0.2, 0.6\}$, which is the same as the droplet in Figure 13. The raw data for these droplets are provided in Figure S7 in the Supplementary Information. Scaling this data according to the dimensionless groups in Eq. 25 causes them to collapse to the single master curve shown in Figure 15. A fit to the data for $R^2/R_{\infty}^2 \leq 0.6$) gives n = 0.55, which lies in between the limiting cases of Fickian diffusion (n = 0.45) and Case-II diffusion (n = 0.89), but closer to the Fickian limit.

With n = 0.55, we conclude that the physical behavior of our model is nearly Fickian. We hypothesize that the deviation from pure Fickian diffusion is due to the difference in diffusivity between the low-mobility polymer-rich phase and the high-mobility nonsolvent bath. By comparison, experiments of solvent extraction of polymeric droplets show a much larger deviation from Fickian diffusion for deswelling particles.^{11–15}



FIG. 15. Diffusion kinetics of droplets extraction implementing the power law model.

We attribute this difference to the vitrification of the polymerrich phase that occurs in experimental systems when the polymer concentration crosses a glass transition. Additionally, before the glass transition, the polymer-rich phase will also have a larger viscosity, further hindering solvent diffusion in this phase. As previously discussed, the present model does not contain a mechanism for vitrification or elasticity.

IV. CONCLUSION

In this paper, we have studied the process parameters controlling the production of polymeric particles via a phase-field model of nonsolvent-induced phase separation (NIPS). We have focused on the effects of droplet size, droplet composition, and solvent/nonsolvent miscibility on the microstructure and mass transfer kinetics of particles during NIPS. We found it useful to divide our analysis into two parts: (a) phase separations initiating inside the two-phase gap (initially unstable conditions), and (b) phase separations initiating outside the two-phase gap (initially stable conditions). The former permits a study of the influence of finite droplet size on microstructure evolution, while the latter isolates the effects of droplet size on solvent/nonsolvent mass transfer.

In the first section, we found evidence for two modes of spinodal decomposition: (i) surface-directed spinodal decomposition (SDSD), and (ii) isotropic, bulk spinodal decomposition (IBSD). SDSD has some influence on droplets with a large initial polymer concentration (on the left of the static symmetry line) and produces porous ("inverted") polymeric structures. By contrast, IBSD dominates for droplets with a small initial polymer composition (on the right of the SSL) and produces smaller droplets. Near the SSL, both SDSD and IBSD influence the morphology, and we observe elongated, nearly bicontinuous structures. Simulations of droplets of various sizes and shapes revealed minor effects on the morphology. However, at larger polymer concentrations, SDSD in smaller droplets appears to lead to faster phase separation kinetics than occurs in larger droplets.

Additionally, we investigated the effect of solvent/nonsolvent miscibility (via χ_{ns}) on the microstructure. We observed the same sequence of morphologies relative to the SSL for all values of χ_{ns} . We concluded that the morphology pattern of the droplets is highly dependent on the initial composition rather than the miscibility parameter.

In the second section, we studied the phase separation dynamics from initially stable conditions driven by solvent/nonsolvent exchange. Consistent with previous work³, this process results in early-time and late-time kinetic Regimes with three classes of behavior: (I) absence of phase separation, (II) phase separation with a sharp front, and (III) an rapid decomposition of the droplet. Solvent/nonsolvent miscibility has an important effect on these kinetics. Decreasing solvent/nonsolvent miscibility (increasing χ_{ns}) competes with the drive for the polymer to phase separate, reducing or eliminating rapid decomposition behavior. This was evident at early and late times by the decrease in the occurrence of Regime III and increase of Regime II dominance for most of the composition space.

Using an example of a droplet from the dominant Regime II, we examined the mass transfer kinetics that leads to droplet shrinkage. We characterized the diffusion physics using a semi-empirical power law model whose exponent provides a measure of the non-Fickian character of diffusion. Fits to the change in radius of the simulated droplet gave an exponent that is "close to Fickian". We attributed this minor deviation from Fickian behavior to the difference in diffusivity between the polymer-rich droplet phase and the bath.

Looking forward, it is clear that there is more work to be done to fully understand the NIPS process in droplets. The current model would clearly benefit from additional physics, including the addition of thermal noise, models of vitrification and/or viscoelasticity, and the extension to three dimensions. Furthermore, there is much work that could be done with more complex polymer models, including those containing block polymers.⁶² Some of these features have been already added to simulations of planar films^{4,20,62}, but there are some important trade-offs in computational demands and methodological complexity.

Similarly, the model used here relies on polymers with a small degree of polymerization. The corresponding radius of gyration $R_g \approx 2$ nm is small compared to, for example, the experimental work by Udoh et. al whose polymers have an $R_g = 10.6$ nm.¹⁵ This results in a relatively small simulation length and time scale, though this could be mitigated by properly tuning the dimensionless parameters in the simulation.² While certainly desirable, pushing the ability of the models to reach more realistic parameters may require innovative numerical methods.

Additionally, methodological innovations that allow for larger domain sizes or more complex boundary conditions would permit one to probe longer time-scale dynamics. Such simulations would permit a deeper investigation into the impact of finite droplet sizes on coarsening scaling laws, both with and without kinetic arrest. More could also be done to study the coupling between morphology and changing droplet shape due to mass transfer.³⁴ Also, there could be interesting behavior when the demixing length scale is commensurate with the droplet size at late times.²⁷

Finally, a high priority for future work should certainly be a more rigorous and quantitative comparison to experiments.^{14,15,63,64} Careful and accessible measurements of phase diagrams, morphologies, diffusion coefficients, viscosities, and/or glass transition behavior that can be directly compared to simulations would be most welcome.

Despite these wishes for the future, much progress has already been made in recent years to model NIPS processes and put them on a rigorous theoretical footing. In the present work, we have extended this effort to finite-sized polymeric droplets that contain non-ideal solvent/nonsolvent interactions. We anticipate that future researchers will build on these and other results to create better, cheaper, more useful, and more environmentally sustainable microstructured polymeric particles.

SUPPLEMENTARY MATERIAL

The supplementary material contains additional methods and results supporting the material described in this manuscript. Additional methods include a derivation of the proper off-diagonal gradient terms in the phase-field model, equations and numerical procedures for producing ternary phase diagrams, and a description of the differences between 1D and 2D simulations. Additional results and discussion include ternary phase diagrams with tie lines, plots of phase seprated states in composition space, calculations of the demixing length scale, simulations of the phase separation of non-circular droplets, early-time separation regimes as a function of χ_{pn} , and details relating to droplet shrinkage calculations.

ACKNOWLEDGMENTS

We would like to acknowledge financial support from Brigham Young University and computational resources from the BYU Office of Research Computing.

CONFLICT OF INTEREST

The authors have no conflicts to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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