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Coupled Stochastic Simulation of the Chain Length and Particle Size Distribution in Miniemulsion Radical Copolymerization of Styrene and N-Vinylcaprolactam

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Abstract

Kinetic Monte Carlo modeling is applied for the coupled simulation of the chain length and particle size distribution (CLD and PSD) in isothermal batch miniemulsion copolymerization of styrene and N-vinylcaprolactam (VCL), which is an interesting comonomer pair in view of thermoresponsive polymer nanoparticle applications. Considering a polymerization temperature of 333 K and the oil soluble initiator azobisisobutyronitrile (AIBN) it is shown that the disparate terminal monomer reactivity ratios induce a consecutive dominance of styrene and VCL incorporation, ultimately leading to a bimodal CLD with a relevance of the gel-effect. Moreover, the initial comonomer fractions are shown to effect the ability of growing oligomers to exit the particle in which they have been generated, thereby effecting the CLD evolution. A strong effect of the initial (Gaussian) PSD is also highlighted, with much higher polymerization rates if this PSD shifts to lower particles sizes. Overall, a very dynamic PSD evolution is simulated, with a negative skewing at low monomer conversions and a uniformization of the PSD as the monomer conversion increases. The current modeling platform can be further extended with additional reactions such as crosslinking on a longer term.

1. Introduction

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Thermoresponsive crosslinked polymer nanogels have unique capabilities for the controlled release of active ingredients at well-defined temperatures, a feature which can be exploited *e.g.* for drug delivery applications.^{1, 2} The most popular thermoresponsive polymers for nanogel application are poly(N-isopropylacrylamide), pNIPAM, and poly(N-vinylcaprolactam), pVCL.³⁻⁵ As such these polymers display a lower critical solution temperature (LCST) in water around body temperature, which implies that below this temperature they are water soluble and above that temperature phase segregation takes place.⁶⁻⁸ After crosslinking such polymers, the formed nanogels display a volume phase transition temperature (VPTT), *i.e.* the nanogels collapse upon switching the temperature from below to above VPTT, allowing the release of an active ingredient.

Recently, significant attention has been paid to the use of pVCL for nanogel production as this polymer has a better biocompatibility compared to pNIPAM.^{3, 9} The most frequently employed method for the synthesis of pVCL nanogels is dispersion/precipitation polymerization.¹⁰⁻¹² There one starts from a homogeneous mixture, *i.e.* the monomer N-vinylcaprolactam (VCL) dissolved in water. Chain growth is initiated by a water-soluble initiator (*e.g.* 2,2'-azobis(2-methylpropionamidine) dihydrochloride (AMPA)). As the growing oligomers become increasingly water insoluble precipitation takes place at low monomer conversions, leading to (precursor) particles that are dispersed in the water phase and can further grow by polymerization and aggregation. By adding a crosslinker to the initial reaction mixture, *e.g.* N,N-methylenebis-(acrylamide), chemically crosslinked nanoparticles result that can reversibly swell and collapse around the VPTT.^{11, 12}

Alongside dispersion/precipitation polymerization a limited number of studies¹³⁻¹⁵ have used mini- or microemulsion polymerization for the synthesis of pVCL nanogels, anticipating a better-defined particle growth due to a better initialization stage. For example, Medeiros *et al.*¹³

synthesized pVCL nanogels via water-in-oil, *i.e.* inverse, miniemulsion polymerization. By using hexadecane as the continuous phase, Span 80 (sorbitan monooleate) as oil soluble surfactant, NaCl salt as a lipophobe to prevent Ostwald ripening, and N,N-methylenebis-(acrylamide) as a crosslinker, nanogels with an average diameter in the range of *ca.* 200 – 600 nm were obtained. On the other hand, Crespy *et al.*¹⁴ performed conventional or direct oil-in-water miniemulsion polymerization of VCL with toluene as an organic solvent and sodium dodecyl sulfate (SDS) as surfactant. As a last example, Shah *et al.*¹⁵ synthesized stable non-crosslinked copolymer nanoparticles based on VCL and methyl methacrylate (MMA) with an average diameter less than 50 nm via oil-in-water microemulsion polymerization, thus starting from micelles and monomer droplets.

Crucial for nanogel production is the need for an on-spec (co)polymer composition, crosslinking density, and particle size distribution (PSD), as these properties determine key features such as the VPTT, the swelling degree (and hence the loading capacity), and the rheological behavior.^{1, 10, 16, 17} Limited focus has however been put on a systematic understanding of the relation of reaction conditions and the final nanogel properties. Most modeling studies are also focused on a limited number of experimental variables and responses, typically the (co)monomer conversion and neglecting the PSD evolution.^{12, 18, 19}

Due to the high number of process variables, specially under emulsion conditions, it is recommended to apply multi-scale modeling in which at the micro-scale the interplay of chemistry and viscosity is grasped in a given reaction locus (*e.g.* polymer particle) and at the meso-scale interphase mass phenomena (*e.g.* exit and entry of radicals) are included, see Figure 1.²⁰⁻²⁷ Ideally, micro- and meso-scale model parameters are respectively determined by careful parameter estimation to bulk and dispersed phase polymerization data.²⁸⁻³⁰ Recent work of Marien *et al.*³¹ on radical miniemulsion homopolymerization has indicated that advanced kinetic Monte Carlo (*k*MC) modeling is very promising to handle the interactive evolution of

the chain length distribution (CLD) and PSD in dispersed phase polymerization. Only by particle-by-particle tracking of the reaction and mass transfer events, as illustrated in Figure 1, it becomes possible to capture the correlation between chain and particle growth. Notably this work highlighted the limitations of the conventional Smith-Ewart approach³² to model miniemulsion polymerization kinetics. Monomer transport needs to be accounted for and an average monomer concentration per particle at each integration time step cannot be simply assumed as done in most modeling studies.³¹

Figure 1. Illustration of the application of the multi-scale kinetic Monte Carlo modeling tool to miniemulsion copolymerization of styrene and N-vinylcaprolactam (VCL) initiated by azobisisobutyronitrile (AIBN); 5 consecutive illustrative events are shown (starting at event i), namely initiator dissociation in particle 2, exit of an initiator radical from particle 3, chain initiation of an initiator radical with VCL in particle 4, initiator dissociation in the aqueous phase and termination in particle 2; each time a certain number of events (e.g. 1000) has taken place, net entry or exit of the initiator and comonomer molecules is for each particle accounted for; here only net entry to particle 4 leading to an increase in its particle diameter d_p and net exit from particle 5 leading to a decrease in its d_p are shown.

A next logical step is to evaluate if the developed kMC model can also be applied for radical miniemulsion copolymerization and can support on a longer term the design of nanogel synthesis in which additionally crosslinking takes place. In the present work, the main characteristics of isothermal batch miniemulsion copolymerization of VCL with a hydrophobic comonomer are therefore simulated. Focus is on a polymerization temperature of 333 K and the

oil soluble initiator azobisisobutyronitrile, AIBN. In view of not overloading the complexity the addition of the crosslinker is not included as well as the presence of a costabilizer. All model parameters are literature based, with some simplifications due to lack of complete literature data for VCL kinetics. Incorporation of certain amounts of the hydrophobic comonomer allows to tune the VPTT and to facilitate the miniemulsion formation. For illustration purposes, styrene is considered as a hydrophobic comonomer in view of the availability of benchmarked model parameters for styrene.

It is theoretically shown that the disparate monomer reactivity ratios of styrene and VCL lead to a consecutive dominant consumption of styrene and VCL. Moreover, it is demonstrated that the initial comonomer fractions determine the probability that an oligomeric species exits the particle in which it was generated, thereby affecting the evolution of the CLD in general and the average chain length in particular. A strong effect of the initial (Gaussian) PSD on the miniemulsion copolymerization kinetics is also observed, with higher polymerization rates if this initial PSD shifts to lower particles sizes. Overall, a very dynamic PSD evolution is simulated, with a negative skewing at low monomer conversions and a uniformization of the PSD as the monomer conversion further increase. The reported results open the pathway to tackle in the future the additional complexity of the presence of crosslinker, uniquely covering the interplay between micro- and meso-scale phenomena.

2. Model development

In the present work, the kinetic Monte Carlo (*k*MC) model developed by Marien *et al.*³¹ allowing to track particle-by-particle reaction and interphase mass transfer events in miniemulsion free radical homopolymerization is extended to copolymerization. Focus is on copolymerization of styrene and VCL at 333 K, for which for simplicity a terminal model is assumed, *i.e.* the reactivity of a radical is assumed to depend only on the terminal unit.^{33, 34} Azobisisobutyronitrile, AIBN, is used as an oil soluble radical initiator. The simulated number

of particles (127 in case of an initial PSD with a volume-average diameter $\bar{d}_{p,0}$ equal to 100 nm, 63 in case $\bar{d}_{p,0} = 200$ nm) and the corresponding number of molecules are sufficiently high for numerical accuracy in agreement with earlier work for k MC modeling of miniemulsion homopolymerization³¹ and k MC modeling in general, which included benchmarking to deterministic solvers and convergence testing via the gradual increase of the simulation volume.³⁵⁻³⁷

A listing of all reaction and mass transfer events considered in the k MC model and their corresponding rate coefficients is shown in Table 1, with the label A referring to styrene and B to VCL and for particle size dependent coefficients the value at 100 nm reported. It follows that a basic FRP reaction scheme, consisting of dissociation, chain initiation, propagation, chain transfer to monomer, and termination (by recombination), is considered with a further distinction based on the reaction locus being the organic phase or water.

It should be noted that limited kinetic information is available for radical polymerization of VCL. In particular, to the best of our knowledge, no absolute homopropagation rate coefficients are available for VCL. Hence, homopropagation rate coefficients for VCL are approximated by the ones reported for N-vinylpyrrolidone,³⁸ which belongs to the same family of vinyl lactams. Notably N-vinylpyrrolidone has a pronounced solvent effect attributed to intermolecular interactions leading to a hindered internal rotational motion in the transition structure. A 20-fold increase in the homopropagation rate coefficient is for instance observed at 303 K from bulk to dilute aqueous solution conditions.³⁸ This solvent effect is reflected in the current work, as envisaged by the higher propagation rate coefficients for VCL in the aqueous phase compared to the ones for the organic phase (Table 1).

Cross-propagation rate coefficients are calculated from literature data³⁹ on the terminal reactivity ratios ($r_A = k_{p,AA}/k_{p,AB} = 21.2$; $r_B = k_{p,BB}/k_{p,BA} = 0.026$). Due to the lack of literature

data, homo-chain transfer to monomer coefficients (or the ratio of chain transfer to monomer rate coefficients to propagation rate coefficients) for VCL are approximated by the ones for N-vinylpyrrolidone.⁴⁰ Cross-chain transfer coefficients follow for simplicity from a geometric mean calculation (see footnote *d* in Table 1).

Table 1. Reactions and phase transfer events for the simulation of batch isothermal ($T = 333$ K) miniemulsion copolymerization of styrene ('A' label) and N-vinylcaprolactam ('B' label) initiated by azobisisobutyronitrile, AIBN; the reported k values for entry and exit events correspond to a particle diameter of 100 nm; 200 nm values: see Table S1 in the SI; other particle sizes: see formulas footnotes.

Event	Equation	k ($d_p = 100$ nm)	Ref.
Reactions in particles			
Dissociation ^a	$I_{2,p} \xrightarrow{f_p k_{d,p}} 2 I_p$	$1.3 \times 10^{-5} \text{ s}^{-1}$	41
Chain initiation	$I_p + M_{A,p} \xrightarrow{k_{iIA,p}} R_{1,A,p}$	$3.4 \times 10^3 \text{ L mol}^{-1} \text{ s}^{-1}$	b,42
	$I_p + M_{B,p} \xrightarrow{k_{iIB,p}} R_{1,B,p}$	$2.2 \times 10^4 \text{ L mol}^{-1} \text{ s}^{-1}$	b,38
	$M_{A,p}^* + M_{A,p} \xrightarrow{k_{iMA,p}} R_{1,A,p}$	$3.4 \times 10^3 \text{ L mol}^{-1} \text{ s}^{-1}$	b,38
	$M_{A,p}^* + M_{B,p} \xrightarrow{k_{iMA,B,p}} R_{1,B,p}$	$1.6 \times 10^2 \text{ L mol}^{-1} \text{ s}^{-1}$	b,39, 42
	$M_{B,p}^* + M_{A,p} \xrightarrow{k_{iMB,A,p}} R_{1,A,p}$	$8.5 \times 10^6 \text{ L mol}^{-1} \text{ s}^{-1}$	b,38, 39
	$M_{B,p}^* + M_{B,p} \xrightarrow{k_{iMB,B,p}} R_{1,B,p}$	$2.2 \times 10^4 \text{ L mol}^{-1} \text{ s}^{-1}$	b,38
Propagation	$R_{i,A,p} + M_{A,p} \xrightarrow{k_{pAA,p}} R_{i+1,A,p}$	$3.4 \times 10^2 \text{ L mol}^{-1} \text{ s}^{-1}$	42
	$R_{i,A,p} + M_{B,p} \xrightarrow{k_{pAB,p}} R_{i+1,B,p}$	$1.6 \times 10^1 \text{ L mol}^{-1} \text{ s}^{-1}$	c,39, 42
	$R_{i,B,p} + M_{A,p} \xrightarrow{k_{pBA,p}} R_{i+1,A,p}$	$8.5 \times 10^4 \text{ L mol}^{-1} \text{ s}^{-1}$	c,38, 39
	$R_{i,B,p} + M_{B,p} \xrightarrow{k_{pBB,p}} R_{i+1,B,p}$	$2.2 \times 10^3 \text{ L mol}^{-1} \text{ s}^{-1}$	38
Chain transfer to monomer	$R_{i,A,p} + M_{A,p} \xrightarrow{k_{trMAA,p}} P_{i,p} + M_{A,p}^*$	$1.8 \times 10^{-2} \text{ L mol}^{-1} \text{ s}^{-1}$	d,43
	$R_{i,A,p} + M_{B,p} \xrightarrow{k_{trMAB,p}} P_{i,p} + M_{B,p}^*$	$1.4 \times 10^{-1} \text{ L mol}^{-1} \text{ s}^{-1}$	d,40, 43
	$R_{i,B,p} + M_{A,p} \xrightarrow{k_{trMBA,p}} P_{i,p} + M_{A,p}^*$	$1.4 \times 10^{-1} \text{ L mol}^{-1} \text{ s}^{-1}$	d,40, 43
	$R_{i,B,p} + M_{B,p} \xrightarrow{k_{trMBB,p}} P_{i,p} + M_{B,p}^*$	$1.1 \times 10^0 \text{ L mol}^{-1} \text{ s}^{-1}$	d,40
Termination	$R_{i,p} + R_{j,p} \xrightarrow{k_{t,app,p,i,j}} P_{i+j,p}$	$1.0 \times 10^9 \text{ L mol}^{-1} \text{ s}^{-1}$	e,44
Reactions in water			
Dissociation ^a	$I_{2,w} \xrightarrow{f_w k_{d,w}} 2 I_w$	$1.3 \times 10^{-5} \text{ s}^{-1}$	41
Chain initiation	$I_w + M_{A,w} \xrightarrow{k_{iIA,w}} R_{1,A,w}$	$3.4 \times 10^3 \text{ L mol}^{-1} \text{ s}^{-1}$	b,42
	$I_w + M_{B,w} \xrightarrow{k_{iIB,w}} R_{1,B,w}$	$3.3 \times 10^5 \text{ L mol}^{-1} \text{ s}^{-1}$	b,38
	$M_{A,w}^* + M_{A,w} \xrightarrow{k_{iMA,w}} R_{1,A,w}$	$3.4 \times 10^3 \text{ L mol}^{-1} \text{ s}^{-1}$	b,38
	$M_{A,w}^* + M_{B,w} \xrightarrow{k_{iMA,B,w}} R_{1,B,w}$	$1.6 \times 10^2 \text{ L mol}^{-1} \text{ s}^{-1}$	b,39, 42
	$M_{B,w}^* + M_{A,w} \xrightarrow{k_{iMB,A,w}} R_{1,A,w}$	$1.3 \times 10^7 \text{ L mol}^{-1} \text{ s}^{-1}$	b,38, 39
	$M_{B,w}^* + M_{B,w} \xrightarrow{k_{iMB,B,w}} R_{1,B,w}$	$3.3 \times 10^5 \text{ L mol}^{-1} \text{ s}^{-1}$	b,38
Propagation	$R_{i,A,w} + M_{A,w} \xrightarrow{k_{pAA,w}} R_{i+1,A,w}$	$3.4 \times 10^2 \text{ L mol}^{-1} \text{ s}^{-1}$	42
Table 1 continued	$R_{i,A,w} + M_{B,w} \xrightarrow{k_{pAB,w}} R_{i+1,B,w}$	$1.6 \times 10^1 \text{ L mol}^{-1} \text{ s}^{-1}$	c,39, 42

	$R_{i,B,w} + M_{A,w} \xrightarrow{k_{pBA,w}} R_{i+1,A,w}$	$1.3 \times 10^6 \text{ L mol}^{-1} \text{ s}^{-1}$	c,38, 39
	$R_{i,B,w} + M_{B,w} \xrightarrow{k_{pBB,w}} R_{i+1,B,w}$	$3.3 \times 10^4 \text{ L mol}^{-1} \text{ s}^{-1}$	38
Chain transfer to monomer	$R_{i,A,w} + M_{A,w} \xrightarrow{k_{trMA,w}} P_{i,w} + M_{A,w}^*$	$1.8 \times 10^{-2} \text{ L mol}^{-1} \text{ s}^{-1}$	d,43
	$R_{i,A,w} + M_{B,w} \xrightarrow{k_{trMA,w}} P_{i,w} + M_{B,w}^*$	$5.3 \times 10^{-1} \text{ L mol}^{-1} \text{ s}^{-1}$	d,40, 43
	$R_{i,B,w} + M_{A,w} \xrightarrow{k_{trMB,w}} P_{i,w} + M_{A,w}^*$	$5.3 \times 10^{-1} \text{ L mol}^{-1} \text{ s}^{-1}$	d,40, 43
	$R_{i,B,w} + M_{B,w} \xrightarrow{k_{trMB,w}} P_{i,w} + M_{B,w}^*$	$1.6 \times 10^1 \text{ L mol}^{-1} \text{ s}^{-1}$	d,40
Termination	$R_{i,w} + R_{j,w} \xrightarrow{k_{t,app,w}^{i,j}} P_{i+j,w}$	$1.0 \times 10^9 \text{ L mol}^{-1} \text{ s}^{-1}$	e,44
Phase transfer events			
Entry of I_2	$I_{2,w} \xrightarrow{k_{entry,I}} I_{2,p}$	$6.0 \times 10^6 \text{ L mol}^{-1} \text{ s}^{-1}$	f
Entry of I	$I_w \xrightarrow{k_{entry,I}} I_p$	$6.0 \times 10^6 \text{ L mol}^{-1} \text{ s}^{-1}$	f
Entry of M_A	$M_{A,w} \xrightarrow{k_{entry,M_A}} M_{A,p}$	$6.0 \times 10^6 \text{ L mol}^{-1} \text{ s}^{-1}$	f
Entry of M_B	$M_{B,w} \xrightarrow{k_{entry,M_B}} M_{B,p}$	$6.0 \times 10^6 \text{ L mol}^{-1} \text{ s}^{-1}$	f
Entry of M_A^*	$M_{A,w}^* \xrightarrow{k_{entry,M_A^*}} M_{A,p}^*$	$6.0 \times 10^6 \text{ L mol}^{-1} \text{ s}^{-1}$	f
Entry of M_B^*	$M_{B,w}^* \xrightarrow{k_{entry,M_B^*}} M_{B,p}^*$	$6.0 \times 10^6 \text{ L mol}^{-1} \text{ s}^{-1}$	f
Entry of R_i	$R_{i,w} \xrightarrow{k_{entry,R}} R_{i,p}$	$6.0 \times 10^6 \text{ L mol}^{-1} \text{ s}^{-1}$	f
Exit of I_2	$I_{2,p} \xrightarrow{k_{exit,I_2}} I_{2,w}$	$1.7 \times 10^{-1} \text{ s}^{-1}$	g
Exit of I	$I_p \xrightarrow{k_{exit,I}} I_w$	$2.4 \times 10^0 \text{ s}^{-1}$	g
Exit of M_A	$M_{A,p} \xrightarrow{k_{exit,M_A}} M_{A,w}$	$7.0 \times 10^{-2} \text{ s}^{-1}$	g
Exit of M_A^*	$M_{A,p}^* \xrightarrow{k_{exit,M_A^*}} M_{A,w}^*$	$7.0 \times 10^{-2} \text{ s}^{-1}$	g
Exit of M_B	$M_{B,p} \xrightarrow{k_{exit,M_B}} M_{B,w}$	$7.6 \times 10^{-1} \text{ s}^{-1}$	g
Exit of M_B^*	$M_{B,p}^* \xrightarrow{k_{exit,M_B^*}} M_{B,w}^*$	$7.6 \times 10^{-1} \text{ s}^{-1}$	g
Exit of R_i ($i \leq i_{sol}$)	$R_{i,p} \xrightarrow{k_{exit,R}} R_{i,w}$	$2.4 \times 10^0 \text{ s}^{-1}$ c	g

^a Initiator efficiency f ; for illustration purposes, a constant value equal to 0.6 is used for all reaction loci.⁴⁵

^b Chain initiation rate coefficient assumed 10 times higher than the long chain limit for macroradical propagation.⁴⁶

^c Terminal reactivity ratios $r_A = k_{p,AA}/k_{p,AB} = 21.2$, $r_B = k_{p,BB}/k_{p,BA} = 0.026$.³⁹

^d Same chain transfer to monomer ratios $C_{trM} = k_{trM}/k_p$ assumed for the organic and aqueous phase; hence, higher chain transfer to monomer rate coefficients for VCL in the aqueous phase as higher propagation rate coefficient due the reported solvent effect for the analogue N-vinylpyrrolidone,³⁸ $C_{trM,AA} = k_{trM,AA}/k_{p,AA} = 5.3 \times 10^{-5}$ (ref.⁴³); $C_{trM,BB} = k_{trM,BB}/k_{p,BB} = 4.8 \times 10^{-4}$ (ref.⁴⁰); $k_{trM,AB} = k_{trM,BA} = (k_{trM,AA} k_{trM,BB})^{0.5}$

^e Chain length and monomer conversion dependent termination rate coefficients are considered to account for a gel-effect,⁴⁴ see Equations (S1)-(S5) in the Supporting Information; $k_{t,app}$ (1,1) only reported here; due to lack of literature data for VCL termination rate coefficients, the termination reactivity is assumed independent of the terminal unit.

^f $k_{entry,Z} = C_{entry,Z} N_A D_{Z,w} d_p$ (references⁴⁷⁻⁵³) with $Z = I_2, I, M_A, M_B, M_A^*, M_B^*,$ or R and $C_{entry,Z} = 10^{-4}$ and $D_{I_2/I/M/M^*} = D_{R,w}$ ($i = 1$) = $10^{-7} \text{ dm}^2 \text{ s}^{-1}$; $D_{R,w}(i)$: Eq (S6) in the Supporting Information (ref.⁵⁴); here only value at $i=1$ reported; diffusivity is formally described based on styrene units for the whole chain; update of monomer and initiator molecules for each particle only after 1000 events have taken place; net amount of monomer and initiator molecules entering (or exiting) a particle during this time is calculated via Equation (S7)-(S11) in the Supporting Information.

^g $k_{exit,Z} = C_{exit,Z} D_{Z,p} d_p^{-2}$ with $C_{exit,Z} = 6 C_{entry,Z} D_{Z,w} \pi^{-1} \Gamma_Z^{-1} D_{Z,p}^{-1}$ (references⁴⁷⁻⁵³); $D_{R,p}(i = 1) = 10^{-7} \text{ dm}^2 \text{ s}^{-1}$; $D_{R,p}(i)$: Eq (S6) in the Supporting Information (ref.⁵⁴); here only value at $i=1$ reported; diffusivity is again described based

on styrene units; lumped update of net exit (or entry) of monomer and initiator molecules via Equation (S7)-(S11) in the Supporting Information; Partitioning coefficients (organic over water): $\Gamma_{I_2} = 115$, $\Gamma_I = 8$ (intermediate literature value⁵⁵), $\Gamma_{M_A} = \Gamma_{M_A^*} = 273$, $\Gamma_{M_B} = \Gamma_{M_B^*} = 25$, $\Gamma_{R_i}(i \leq i_{sol}) = 8$, $\Gamma_{R_i}(i > i_{sol}) = \infty$; $i_{sol} = 7$ (intermediate value for styrene⁵⁶ and VCL¹²).

To account for a representative description of the gel-effect apparent chain length and monomer conversion dependent termination rate coefficients pertaining to standard styrene homopolymerization are used in all cases, again bearing in mind that with VCL such parameters are lacking. The apparent termination rate coefficients are explicitly linked to each termination couple taking into account the actual chain lengths of the two radicals and the polymer mass fraction corresponding to the reaction locus in which the two radicals reside, *i.e.* no average termination rate coefficient $\langle k_{t,app} \rangle$ is used. The individual apparent termination coefficients are calculated using Equation (S1)-(S5) in the Supporting Information.⁵⁷ For simplicity the cage and glass effect, which are more likely at the very high monomer conversions, are not accounted for.

Entry and exit rate coefficients are calculated in agreement with the emulsion field⁴⁷⁻⁵³ (formulas: see footnotes Table 1). In agreement with Marien *et al.*³¹ entry and exit phenomena of the comonomers and initiator are described via lumped events per particle, see Equation (S7)-(S11) in the Supporting Information. Globally these equations highlight that the system strives for the establishment of equilibrium. The latter is reflected by partitioning coefficients (Γ values; organic over water) for which literature based data are considered.^{12, 55} Moreover, potential diffusional limitations on entry and exit of oligomers are accounted for via Equation (S6) in the Supporting Information with parameters based on styrene based chains.⁵⁴ For simplicity density differences due to polymerization are ignored and the initial volume weighted PSD is of a Gaussian nature with a standard deviation of 25 nm. Note that, for illustration purposes, the choice of a volume-weighted PSD allows a more facile interpretation of the simulation results than an intensity-based PSD. As indicated above, the initial average particle

diameter ($\overline{d_{p,0}}$) is either 100 or 200 nm. In all simulations, the volume fraction of the aqueous phase is equal to 0.3.

It should be stressed that the scope of the current work is to theoretically highlight the strength of developed kinetic modeling platform for copolymerization miniemulsion. The current results must be only interpreted in the following way: if the model parameters in Table 1 are considered and the previously discussed assumptions are made then the model outcome is as predicted in the present work. The further tuning of the model parameters and the further refinement of the model itself (*e.g.* consideration of the cage and glass effect) will be covered in future work.

3. Results and Discussion

In this section, attention is focused on the potential of *k*MC modeling to understand CLD and PSD variations in miniemulsion radical copolymerization, starting from the reaction scheme and mass transfer events in Table 1. Central in the discussion are the relevance of the initial average particle size and the initial comonomer feed composition. The modeling framework is illustrated selecting styrene and VCL as comonomers to enable a direct link to future work with *e.g.* crosslinking as additional reaction possibility in view of nanogel synthesis.

3.1 Main characteristics for $f_{A,0} = 0.5$ and $\overline{d_{p,0}} = 100$ nm

The evolution of the conversion of monomer A (styrene; full blue line; X_A), monomer B (VCL; dotted red line; X_B) and the total monomer conversion (*i.e.* based on both monomer A and B; dashed black line; X_{tot}) for an initial volume average diameter $\overline{d_{p,0}}$ equal to 100 nm and an initial feed composition for monomer A, $f_{A,0}$, equal to 0.5 are shown in Figure 2 (a). A faster increase of X_A is observed, in agreement with the high value of r_A ($r_A = k_{p,AA}/k_{p,AB} = 21.2$) and the low value of r_B ($r_B = k_{p,BB}/k_{p,BA} = 0.026$). Such reactivity ratios imply that radicals with both a terminal A and B unit preferentially add to monomer A, hence, most radicals have a terminal A unit and mostly homopropagation of A occurs, leading to the formation of copolymer chains

with a dominant presence of A segments as long as monomer A is present. At high reaction times ($t > 400$ min), a pronounced increase in X_B is observed as almost all of monomer A has been consumed and homopropagation of B becomes therefore the dominant propagation mode, leading to the formation of pseudo homopolymer chains of type B. Due to the higher value of $k_{p,BB}$ compared to $k_{p,AA}$ and the unavoidable gel-effect, although slight in this case, a faster increase in X_{tot} is observed for these high reaction times ($t > 400$ min).

The associated evolution of the average number of macroradicals per particle, $\bar{n}_R$, is given in Figure 3. In this figure, a further distinction is made between macroradicals with a terminal A ($\bar{n}_A$) and B ($\bar{n}_B$) unit. It follows that at (very) low reaction times $\bar{n}_R$ increases to a value of *ca.* 0.1 which is a typical value for minemulsion polymerizations initiated by an oil soluble initiator and with a relevance of radical exit and entry.^{45, 58} Consistent with the monomer conversion changes - for low reaction times ($t < 400$ min) - almost all macroradicals have a terminal A unit, as envisaged by the almost coinciding full black and dashed blue line ($\bar{n}_R \approx \bar{n}_A$; $\bar{n}_B \approx 0$). At *ca.* $t = 400$ min a rapid decrease of $\bar{n}_A$ and a strong increase of $\bar{n}_B$ to approximately $\bar{n}_R$ is observed, as monomer A has disappeared. At even larger reaction times ($t > 450$ min) an increase in $\bar{n}_B$ and $\bar{n}_R$ is observed which is attributed to a gel-effect and a changing radical entry and exit pattern due to the varying average radical chain lengths as a switch to pseudo-VCL-homopolymerization has been made. Finally, for $t > 500$ min a decrease in $\bar{n}_B$ and $\bar{n}_R$ is observed as both monomer types have been consumed and, hence, macroradicals are no longer generated as chain initiation can no longer take place. For completeness the reader is referred to Figure S1 for the evolution of the distribution of particles possessing zero, one, or two or more macroradicals, from which it can be observed that on average the fraction of particles having two or more radicals is very low.

Figure 1. Simulation results for the batch isothermal miniemulsion copolymerization of styrene (A; molar fraction at start $f_{A,0} = 0.5$) and N-vinylcaprolactam (B; molar fraction at start $f_{B,0} = 0.5$) initiated by azobisisobutyronitrile, AIBN; initial PSD and its evolution: see Figure 3 (case of initial volume average diameter $d_{p,0}$ equal to 100 nm); (a) conversion of monomer A (full blue line), monomer B (dotted red line) and the total monomer conversion (*i.e.* based on both A and B; dashed black line); (b) fraction of monomer molecules of type A (f_A ; full blue line) and type B (f_B ; full red line); (cumulative) fraction of units on average in the ‘dead’ polymer of type A (F_A ; dashed blue line) and type B (F_B ; dashed red line); (c) number (x_n ; full purple line) and mass (x_m ; dashed black line) average chain length of the ‘dead’ polymer and the corresponding dispersity (x_m/x_n ; dotted green line); (d) final chain length distribution (CLD) and related cumulative distribution; Initial conditions: $T = 333$ K, $[AIBN]_{p,0} = 1.0 \cdot 10^{-2}$ mol L $^{-1}$, $[AIBN]_{w,0} = 8.7 \cdot 10^{-5}$ mol L $^{-1}$, $[A]_{p,0} = 4.3$ mol L $^{-1}$, $[A]_{w,0} = 2.9 \cdot 10^{-2}$ mol L $^{-1}$, $[B]_{p,0} = 4.1$ mol L $^{-1}$, $[B]_{w,0} = 3.5 \cdot 10^{-1}$ mol L $^{-1}$; volume fraction aqueous phase: 0.3; model parameters: Table 1; simulated number of particles: 127.

The evolution of the fraction of monomer A (f_A ; full blue line) and B (f_B ; full red line) are shown in Figure 2 (b) together with the evolution of the (cumulative) fraction of monomer units incorporated on average in the ‘dead’ polymer of type A (F_A ; dashed blue line) and B (F_B ; dashed red line). In agreement with the faster increase in X_A for $t < 400$ min (Figure 2 (a)), F_A is much higher than F_B for $t < 400$ min and a decrease of f_A and increase of f_B are observed for

these reactions times. Once almost all of monomer A has been consumed ($t > 400$ min), the fraction of B incorporated on average in the ‘dead’ polymer increases to its final value, with as expected $F_B = F_A = f_{A,0} = f_{B,0} = 0.5$ as this is theoretically allowed based on the model assumptions in the present work.

Figure 3. Averaged profile of the average number of macroradicals per particle ($\bar{n}_R$; full black line) corresponding to Figure 2 ($f_{A,0} = 0.5$, $\bar{d}_{p,0} = 100$ nm). A distinction between macroradicals having a terminal A unit ($\bar{n}_A$, dashed blue line) and B unit ($\bar{n}_B$; dotted red line) is also made. Initial conditions: caption Figure 2; model parameters: Table 1. The corresponding evolution of the distribution of particles possessing zero, one, or two or more radicals is shown in Figure S1 of the Supporting Information; smoothed line.

Figure 2 (c) shows the evolution of the ‘dead’ polymer number (x_n ; full purple line) and mass (x_m ; dashed black line) average chain length and the corresponding dispersity (x_m/x_n ; dotted green line). In agreement with work on the modeling of free radical homopolymerization under miniemulsion conditions,³¹ a maximum in x_n and x_m is observed for low reaction times. At very low reaction times the only termination events taking place are between radicals originating from the same particle (*cf.* oil soluble initiator). Hence, due to a strong confined space effect,⁵⁹⁻⁶² initially only ‘dead’ polymers of very short chain length are formed. For somewhat larger but still rather low times, also termination after entry of a radical to a particle containing a single

radical can take place, leading to the formation of 'dead' polymer with much higher chain lengths and an increase of the (cumulative) x_n value. This increase in x_n is however counteracted by the decreasing comonomer concentrations (*cf.* Figure 2 (a)), which lowers the propagation rate, and, hence, the lengths of the chains formed additionally, explaining the observed maximum. It can be further noted that the shift from initially forming only very short 'dead' polymer chains to also forming longer 'dead' polymer chains also leads to a maximum in the dispersity (full green line). Closer inspection reveals that a strong variation in the dispersity values is obtained, highlighting the relevance of the developed model which fully reflects time dependencies. Furthermore, a slight increase in x_n and x_m can be observed at high reaction times ($t > 400$ min), which can be again explained by the depletion of almost all of monomer A at these reaction times and the higher value of $k_{p,BB}$ compared to $k_{p,AA}$.

Figure 2 (d) shows the number CLD (full blue line) and its cumulative distribution (dotted blue line) at the end of the polymerization ($X_{tot} = 1$). Due to a strong confined space effect at low times⁵⁹⁻⁶² and the final terminations taking place by definition with very low monomer amounts, a large fraction (*ca.* 20%) of the 'dead' polymer chains has a very short chain length (< 10). In particular, there is a dominant contribution of chain length 2 and 4, as can be envisaged from the two peaks defining the bimodality of the number CLD. The fraction of large polymer chain lengths (chain length 100-10000) can be attributed to particles in which a single radical grows to a high chain length due to a long absence of a second radical, delaying termination.^{31, 59} Note that the CLD has a pronounced tail, which can be most easily realized upon evaluating the cumulative subplot. This further highlights the need of advanced modeling tools such as the one presented in this work to fully understand the relation between reaction conditions and final product properties.

Figure 4. Evolution of the particle size distribution (PSD) corresponding to Figure 2, so at the reaction temperature; volume-weighted PSD at a total monomer conversion (*i.e.* based on both comonomers) of 0% (*i.e.* the initial PSD; top left; Gaussian; case of initial volume average diameter $d_{p,0}$ equal to 100 nm), 25% (top right), 50% (bottom left) and 100% (*i.e.* the final PSD; bottom right); initial conditions: see caption Figure 2; model parameters: see Table 1; corresponding overall chain length distributions (CLDs) at $X_M = 1$ is shown in Figure 2 (d).

The evolution of the volume weighted PSD corresponding to the conditions of Figure 2 is shown in Figure 4. In agreement with Jansen *et al.*,⁶³ at X_{tot} equal to 0.25, a negatively skewed distribution is observed. This skew is due to the presence of droplets/particles which did not undergo any significant polymerization and, hence, only supplied monomer to other particles, which leads to particles with sizes larger than initially present (Figure 4; top left vs. top right). As the polymerization rate is lower in larger particles,³¹ the large particles eventually supply monomer to particles of small and intermediate size in which polymerization is faster, leading to a narrowing of the PSD when X_{tot} further increases to 0.50 (Figure 4; bottom left) and 1 (Figure 4; bottom right).

Figure 5. Effect of the initial comonomer fractions; initial conditions: caption Figure 2; model parameters: Table 1.

3.2 Effect of $f_{A,0}$ at $\overline{d_{p,0}} = 100 \text{ nm}$

The effect of the initial comonomer fractions on the characteristics covered in Figure 2 is investigated in Figure 5 and Figure 6. Compared to Figure 2 ($f_{A,0} = 0.5$) a lowering of $f_{A,0}$ to 0.2 (so less styrene) is considered in Figure 5 whereas in Figure 6 an increase of $f_{A,0}$ to 0.8 (so more styrene) is focused on. As illustrated by the full light blue (X_A evolution) and dashed orange (X_B evolution) line in Figure 5 (a) and Figure 6 (a), also in the cases $f_{A,0} = 0.2$ and $f_{A,0} = 0.8$ styrene homopolymerization is the dominant propagation mode in a first stage. Later on when almost all styrene (monomer A) has been consumed (*ca.* $t > 225 \text{ min}$ for $f_{A,0} = 0.2$ and *ca.* $t >$

700 min for $f_{A,0} = 0.8$), VCL homopropagation becomes dominant. Due to the higher homopropagation rate coefficient for VCL than for styrene, full monomer conversion is obtained faster in case of a lower $f_{A,0}$ (Figure 5 (a)) and slower for a higher $f_{A,0}$ (Figure 6 (a)). Moreover, due to the law of mass action, the dominance of styrene homopolymerization in the first stage is less pronounced for a lower $f_{A,0}$ (Figure 5 (b)), as can also be observed from the lower values of F_A in this stage (dark versus light blue dashed line). Analogously, a more pronounced dominance of styrene homopolymerization is observed in a first stage for a higher $f_{A,0}$ (Figure 6 (b)), consistent with the higher values of F_A in this stage (dark versus light blue dashed line). Furthermore, the final value of F_A ($f_{A,0}$) and the final value of F_B ($f_{B,0}$) is detectable with this final value obtained faster for a lower $f_{A,0}$ (Figure 5 (b)) and slower for a higher $f_{A,0}$ (Figure 6 (b)).

Since for a lower $f_{A,0}$ higher polymerization rates are obtained in the first stage (*cf.* higher chain initiation and propagation rate coefficients for VCL (monomer B) and law of mass action), the average time to reach the critical chain length above which an oligoradical no longer undergoes exit is smaller. For a lower $f_{A,0}$, radical exit thus occurs less and the confined space effect gains in importance with consequently smaller 'dead' polymer chain lengths observed in a first stage, explaining the lower initial x_n values in Figure 5 (c). This effect is however counteracted at larger times by the longer period of a dominant VCL homopolymerization. In this period, longer 'dead' polymer chains are formed than in the period of a dominant styrene homopolymerization. As a result similar average chain lengths are obtained at the end of the polymerization for $f_{A,0} = 0.2$ and 0.5 , consistent with the relatively similar number CLDs (Figure 5 (d)). The opposite reasoning is valid for a higher $f_{A,0}$ as can be observed in Figure 6 (c) and (d)) with first higher values and then similar ones as in the 0.5 case.

Figure 6. Effect of the initial comonomer fractions; initial conditions: caption Figure 2; model parameters: see Table 1.

3.3 Effect of $\overline{d_{p,0}}$ for $f_{A,0} = 0.5$

The effect of the initial PSD on the evolution of the copolymerization characteristics of Figure 2 is studied in Figure 7 by considering a Gaussian initial PSD with average diameter $\overline{d_{p,0}} = 200$ nm (Figure 8; top left) instead of $\overline{d_{p,0}} = 100$ nm as before (Figure 2 and 4). For $\overline{d_{p,0}} = 200$ nm the (co)monomer conversions (Figure 7 (a)) show a similar trend as for $\overline{d_{p,0}} = 100$ nm (same lines as in Figure 2). However, a significantly slower increase in (co)monomer conversion is observed, in agreement with the larger time scale for radical entry and larger time between two dissociation events for smaller particles, leading to a delayed termination. This is also consistent

with the overall increase in $\bar{n}_R$ being less pronounced than the increase in the average particle volume when going from $\bar{d}_{p,0} = 100$ nm (Figure 3) to $\bar{d}_{p,0} = 200$ nm (Figure S2 in the Supporting Information; corresponding fraction of particles possessing zero, one, or two or more radicals shown in Figure S3 of the the Supporting Information).

Figure 7. Effect of the initial PSD on the simulation results of Figure 2; cases of initial volume average diameter $\bar{d}_{p,0}$ equal to 100 and 200 nm; initial conditions: see caption Figure 2; model parameters: see Table 1; simulated number of particles equal to 127 for the case $\bar{d}_{p,0}=100$ nm and 63 for the case $\bar{d}_{p,0} = 200$ nm.

Analogously, a similar but slower evolution of f_A, f_B, F_A and F_B is observed in Figure 7 (b). As can be envisaged from Figure 7 (c), a more pronounced maximum for x_n and x_m at low reaction times (< 100 min) is observed for the initialization with the smaller particles. The difference

between the average chain length characteristics however narrows as the reaction time increases, as is also the case under homopolymerization conditions.³¹ A significant effect of the initial PSD can however still be observed for the final CLD, as shown in Figure 7 (d). Consistent with a delayed termination in smaller particles, a higher contribution of high chain length product is observed for $\overline{d_{p,0}} = 100$ nm (dotted blue line), as can be envisaged from the lower cumulative number fraction at a chain length of *e.g.* 100.

Figure 8. Evolution of the particle size distribution (PSD) corresponding to Figure 7 (the case of a Gaussian initial PSD with average diameter $\overline{d_{p,0}} = 200$ nm; again at the reaction temperature); volume-weighted PSD at a total monomer conversion (*i.e.* based on both comonomers) of 0% (*i.e.* the initial PSD; top left), 25% (top right), 50% (bottom left) and 100% (*i.e.* the final PSD; bottom right); initial conditions: see caption Figure 2; model parameters: see Table 1.

For completeness, the evolution of the PSD corresponding to Figure 7 (case with $\overline{d_{p,0}} = 200$ nm) is shown in Figure 8, again at 4 distinct monomer conversions. As in Figure 4, a negative skewing is observed at low (Figure 8; top right) and intermediate (Figure 8; bottom left)

monomer conversions and a uniformization occurs toward high monomer conversion (Figure 8; bottom right).

4. Conclusions

A kinetic Monte Carlo model for the simulation of isothermal batch miniemulsion copolymerization has been developed. Reaction and interphase mass transfer events of initiator, monomer, and initiator-derived, monomeric and oligomeric radicals are tracked particle by particle, considering a terminal model for the intrinsic reactivities, diffusional limitations on termination, and radical entry/exit. The model allows the interactive and joint simulation of the micro-scale characteristics such as the chain length distribution (CLD) and copolymer composition and meso-scale characteristics such as the particle size distribution (PSD).

Miniemulsion radical copolymerization of styrene and N-vinylcaprolactam (VCL) initiated by azobisisobutyronitrile has been selected to demonstrate the potential of the copolymerization modeling tool, bearing in mind the opportunities VCL copolymer nanoparticles offer for the controlled release of active substances at well-defined temperatures. It is shown that the evolution of the (co)monomer conversions, the fractions of the comonomers in the reaction mixture, the average number of radicals per particle, the fractions of the comonomers incorporated on average in the polymer chains, and the number and mass average chain lengths are consistent with the disparate monomer reactivity ratios of styrene and VCL. Ultimately a bimodal CLD results due to the occurrence of fast terminations in particular at very low and high reaction times. For the latter times and higher chain lengths, also diffusional limitations on termination play a small role. The final CLD has a pronounced tail, indicative of the relevance of exit/entry phenomena and therefore the need for advanced multi-scale modeling tools covering also the aspect of interphase mass transfer events.

The effect of the initial PSD has been studied by comparing the evolution of the copolymerization characteristics obtained with an initial Gaussian PSD with a volume-average diameter of 100 nm and 200 nm. Similar but much slower evolving trends for the monomer conversions and copolymer compositions are obtained for the latter case, highlighting the strong interaction between the PSD (meso-scale) and the polymerization kinetics (micro-scale). This interaction is related to the delayed termination for smaller particles containing a single radical due the larger time scale for radical entry and the larger time between two dissociation events. Furthermore, a negative skewing of the PSD is highlighted at low and intermediate monomer conversions as monomer droplets/polymer particles that did not undergo any significant polymerization supplied monomer to the other particles. Toward higher monomer conversions, a more uniform PSD is obtained.

The presented modeling tool will enable dedicated insights into dispersed phase copolymerization and will help the design of tailored nanoparticles for *e.g.* drug delivery applications on a longer term. Crucial extensions are here the reflection of the crosslinking kinetics and morphological changes, which will be covered in future work as well as a detailed experimental validation.

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