

Thermoresponsive Copolymers with Well-Defined Composition and Phase Separation Via Semi-Batch Free-Radical Polymerization in a Non-Polar Medium

Gianmaria Gardoni, Riccardo Menegon, Mattia Sponchioni,* and Davide Moscatelli



Cite This: *ACS Appl. Polym. Mater.* 2024, 6, 616–626



Read Online

ACCESS |



Metrics & More

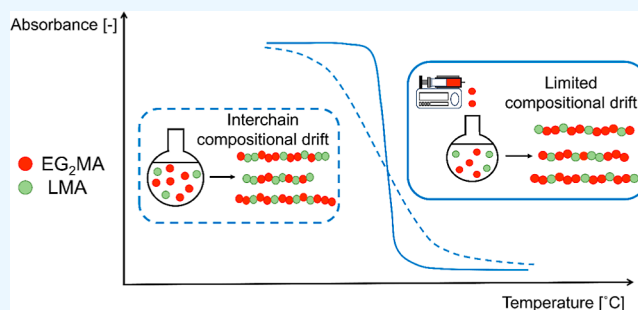


Article Recommendations



Supporting Information

ABSTRACT: Thermoresponsive polymers formulated in non-polar media are finding a plethora of applications in the oil and gas and lubricant sectors. Their great adaptability mainly comes from the possibility of tuning their cloud point (T_{cp}), which is achieved by copolymerizing two or more monomers. In this direction, good control over the copolymer composition is crucial to ensure a sharp phase separation and, as a consequence, a prompt and well-defined response. For this reason, controlled radical polymerizations (CRPs) are often used to synthesize these materials. However, these pseudoliving polymerization techniques are still far from industrial maturity because of their cost and low polymerization rate. On the other hand, free-radical polymerization (FRP) is notoriously affected by the compositional drift of the copolymer chains, which for thermoresponsive polymers is reflected in broad phase separations. To overcome the disadvantages of FRP and guarantee remarkable control of the copolymer composition typical of CRPs, in this work we develop a semibatch power feed process for the copolymerization of diethylene glycol methyl ether methacrylate (EG₂MA) and lauryl methacrylate in Dectol (i.e., a mixture of decane/toluene 50:50 v/v). First, their reactivity ratios were determined by analyzing the variation in the residual monomer phase composition over time at different initial molar ratios of the two monomers. These were subsequently employed for designing the inlet flow rate of the power feed strategy. Through this approach, we demonstrated for the first time that semibatch FRP is a valuable strategy to afford compositionally well-defined copolymers with a controllable upper critical solution temperature and sharp phase separations while maintaining high productivity and avoiding CRPs.



KEYWORDS: thermoresponsive polymers, nonpolar media, free-radical polymerization, power feed, UCST, reactivity ratios

1. INTRODUCTION

Thermoresponsive polymers have been extensively studied in the past three decades due to their ability to undergo phase separation in response to thermal stimuli.^{1,2} Indeed, these polymers are able to switch from solvophilic to solvophobic at a specific temperature, which is called cloud point (T_{cp}), as it is associated with a coil-to-globule transition, causing turbidity of the mixture. Two main behaviors have been reported, according to whether this sharp change in the solubility occurs by decreasing or increasing the environment temperature. In the former case, the binodal curve of the T_{cp} as a function of the polymer volume fraction in the mixture has a maximum defined upper critical solution temperature (UCST), while in the latter the binodal curve shows a minimum defined lower critical solution temperature (LCST).^{3–8} This smart and controllable behavior opened up a plethora of applications in sectors as diverse as oil and gas,^{9–11} sensors,^{12,13} and in particular biomedicine,^{14–16} where thermoresponsive polymers are enabling fascinating and previously unexplored possibilities in tissue engineering and regenerative medicine.

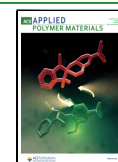
While the majority of the syntheses are performed in water due to its intrinsic safety and biocompatibility,^{17–19} in the last years thermoresponsive polymers in nonpolar media have started to see a rise in their appeal due to their direct application in the oil and gas sector, as lubricants,^{20–22} or o/w emulsifiers.^{11,23,24} In this case, the possibility of adapting the smart polymer to a specific application comes from the tunability of its LCST or UCST, most often through the copolymerization of two or more monomers. In fact, the copolymerization of a thermoresponsive monomer with a solvophilic comonomer allows either increasing the LCST or decreasing the UCST, while the incorporation of a solvophobic comonomer has the opposite effect.¹⁵ Then, proper control of

Received: September 20, 2023

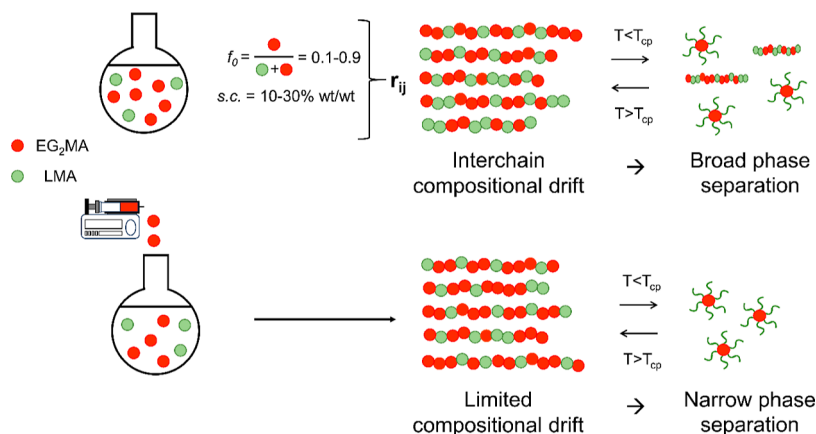
Revised: December 4, 2023

Accepted: December 5, 2023

Published: December 20, 2023



Scheme 1. Schematic Representation of the Synthesis of Thermoresponsive Copolymers Via FRP in Dectol. Batch syntheses were performed with different molar ratios between the thermoresponsive (EG₂MA, green dots) and solvophilic monomers (LMA, red dots) to determine the reactivity ratios. In the end, the reactivity ratios were exploited to perform a power feed semi-batch synthesis, which allowed to obtain copolymers with well-defined compositions and thermoresponsive behavior.



the copolymer composition is crucial to ensure the expected value of T_{cp} for all of the chains and hence sharp phase separations, allowing well-defined bulk responses to even small temperature gradients. To ensure this control, most of these materials are synthesized through controlled radical polymerization (CRP) techniques such as reversible addition-fragmentation chain transfer (RAFT) polymerization or atom transfer radical polymerization (ATRP).^{20,25–27} Indeed, the pseudoliving feature of CRPs is essential to reduce interchain compositional drifts.^{28–30} However, they suffer from high costs of the controlling agents and a low polymerization rate, which prevent their widespread diffusion on an industrial scale.^{31,32}

In this context, free-radical polymerization (FRP) is the preferred solution because of its low cost and simplicity, coupled to high reaction rates and poor sensitivity to the solvents and monomers used. These aspects have contributed to its ubiquitous use for the industrial production of a large variety of polymeric materials, such as adhesives, paints, and coatings.^{33–35}

Despite its advantages, the main drawback of FRP is the lack of control over the copolymer composition, especially for systems where the monomers are characterized by highly different reactivities. Indeed, in the case of the common batch syntheses, a compositional drift in the copolymer composition is always in place, following the behavior described by Mayo and Lewis and leading to an inhomogeneous material.^{36–38} This aspect is particularly of concern for thermoresponsive polymers, whose phase separation is highly sensitive to the copolymer chain composition. Indeed, this limitation is recognized in the literature, where FRP is mainly used to synthesize thermoresponsive homopolymers, which in turn prevent any control on the T_{cp} , or copolymers with broad phase separations.^{39–42}

To bridge this gap and combine the minimal compositional drift of CRPs with the advantages and scalability of FRP, in this work we develop a semibatch FRP process known as power feed^{43–45} for the synthesis of thermoresponsive copolymers with a narrow composition distribution in non-polar media. The study is focused on a binary monomer mixture including lauryl methacrylate (LMA) as a solvophilic monomer and di(ethylene glycol) methyl ether methacrylate (EG₂MA) showing an UCST behavior in a decane/toluene 50:50 v/v

mixture (Dectol), chosen as representative of both the paraffinic and aromatic fractions of crude oil. While in previous works the well-defined thermoresponsive behavior of these copolymers was obtained by controlling their structure via RAFT polymerization,^{20,25} in this work we demonstrate that the same effect can be achieved by tuning the copolymer composition through the implementation of a carefully designed power feed process. This requires loading the reactor with the whole mass of the less reactive monomer (LMA) and a portion of the most reactive monomer, followed by continuous feeding of the remaining fraction. The definition of the mass of the most reactive monomer to be charged in the reactor and the feeding policy require knowledge of the reactivities of the two monomers. Therefore, their reactivity ratios were first determined by analyzing the experimental evolution of the residual monomer phase composition during time in batch polymerizations through Skeist's equation at different initial mole ratios. The implementation of the power feed allowed obtaining copolymers with well-defined compositions and as a consequence sharp phase separation by simply choosing, through the system-specific Mayo–Lewis plot, the correct initial molar ratio between the solvophilic and the thermoresponsive units and the inlet flowrate for the LMA (Scheme 1). To the best of our knowledge, this is the first work demonstrating the possibility of controlling the cloud point of a thermoresponsive polymer and of decreasing the width of its phase separation by reducing the interchain compositional drift through semibatch FRP.

Once the efficacy and potentialities of this method were verified, the study was expanded to the use of poly(ethylene glycol) methyl ether methacrylates with longer side chains to add another degree of freedom and give the possibility to tune the final T_{cp} of the material in a wider temperature range.

Eventually, the possibility of producing thermoresponsive materials with well-defined properties through an easy and scalable process paves the way for their applicability also on an industrial scale, where these systems are scarcely implemented.

2. EXPERIMENTAL SECTION

2.1. Materials. Decane (Dec, $\geq 99\%$, MW = 142.28 g/mol, Sigma-Aldrich), toluene (Tol, $\geq 99.5\%$, MW = 92.14 g/mol, Sigma-Aldrich), di(ethylene glycol)methyl ether methacrylate (EG₂MA, MW = 188.2 g/mol, Sigma-Aldrich), poly(ethylene glycol)methyl ether methacry-

late (EG₄MA, MW = 300 g/mol, Sigma-Aldrich), poly(ethylene glycol)methyl ether methacrylate (EG₈MA, MW = 500 g/mol, Sigma-Aldrich), LMA (96%, MW = 254.41 g/mol), 2,2'-azobis(2-methylpropionitrile) (AIBN, ≥98%, MW = 164.21 g/mol, Sigma-Aldrich), tetrahydrofuran (THF, 99.9%, MW = 72.11 g/mol, Sigma-Aldrich), and chloroform-*d* (CDCl₃, ≥99.8%, MW = 120.38 g/mol, Sigma-Aldrich) were of analytical-grade purity and used as received unless otherwise noted.

2.2. Synthesis of Thermoresponsive Copolymers Via Batch FRP. EG₂MA, EG₄MA, and EG₈MA were polymerized with LMA via FRP to produce thermoresponsive polymers with different cloud points according to their composition.

In particular, the reactions were performed changing three parameters, namely, the solid content (15, 20 and 30% w/w), the initial mole fraction of the thermoresponsive monomer in the monomer mixture f_0 (0.1, 0.3, 0.5, 0.7, and 0.9), and the molecular weight of the poly(ethylene glycol)methyl ether methacrylate (EG₂MA, EG₄MA, and EG₈MA) used.

As an example, to synthesize an EG₂MA–LMA copolymer with $f_0 = 0.7$ and 15% w/w of solid content, 1.84 g of LMA and 3.17 g of EG₂MA were dissolved in 26.62 g of Dectol in a 100 mL round-bottom flask sealed with a rubber stopper. Then, the solution was purged with nitrogen for 20 min at room temperature and put in an oil bath at 80 °C under magnetic stirring. To initiate the reaction, 50 mg of AIBN was dissolved in 2 g of Dectol, purged with nitrogen, and injected with a syringe into the flask. The mixture was then left to react for 21 h. Along the reaction time, small aliquots (0.1 mL) were withdrawn from the system and immediately quenched by cooling them down in a water/ice mixture. The sampling was designed in order to impact the reaction volume by less than 3%. After 21 h, the samples were left to equilibrate in a bath of ice and tap water up to room temperature.

The copolymers were characterized via proton nuclear magnetic resonance (¹H NMR) spectroscopy by dissolving 10 mg of the polymer/solvent mixture in 0.7 mL of CDCl₃ to determine the monomer conversion. The analysis was performed on a Bruker 400 MHz spectrometer with 64 scans per measurement. Peak integration was performed using MestReNova software. A typical spectrum for the copolymer with peak recognition is shown in Figure 1. For a direct comparison, the NMR spectra of the two monomers LMA and EG₂MA recorded under the same conditions are reported in Figure S1a,b, respectively.

First of all, the following parameters were defined in order to facilitate the calculations

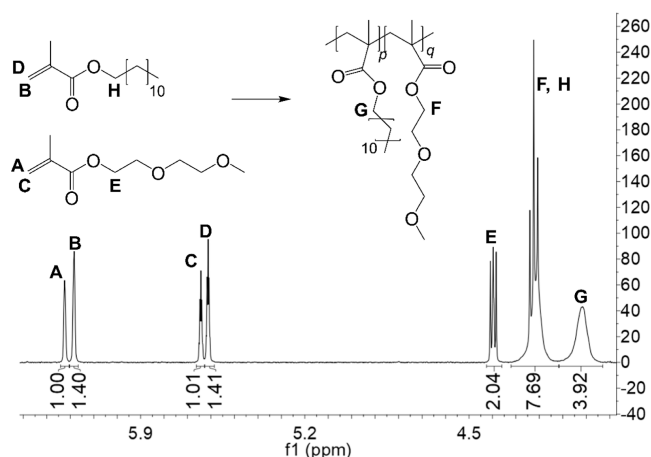


Figure 1. ¹H NMR spectrum of a copolymer with $f_0 = 0.5$ after 2 h of reaction at 80 °C and the corresponding peak recognition. The reaction was performed with EG₂MA as thermoresponsive monomer, but the analysis can also be applied to the cases with EG₄MA and EG₈MA.

$$\alpha = \frac{A + C}{2} \quad (1)$$

$$\beta = \frac{B + D}{2} \quad (2)$$

$$\gamma = \frac{F + H - 2\beta}{2} \quad (3)$$

$$\delta = \frac{G}{2} \quad (4)$$

where A , C and B , D are the areas of the peaks related to the vinyl hydrogens of EG_{*n*}MA and LMA, respectively, while F and G are the peaks associated to the hydrogens near the ester groups in the EG_{*n*}MA and LMA polymers, in agreement with the labeling in Figure 1.

The EG_{*n*}MA mole fraction in the residual monomer mixture was determined according to eq 5.

$$f_{\text{EG}_n\text{MA}} = \frac{\alpha}{\alpha + \beta} \quad (5)$$

The monomer conversions, as well as the overall conversion, can be evaluated by eqs 6–8.

$$\chi_{\text{EG}_n\text{MA}} = \frac{\gamma}{\gamma + \alpha} \quad (6)$$

$$\chi_{\text{LMA}} = \frac{\delta}{\delta + \beta} \quad (7)$$

$$\chi = \frac{\gamma + \delta}{\gamma + \alpha + \delta + \beta} \quad (8)$$

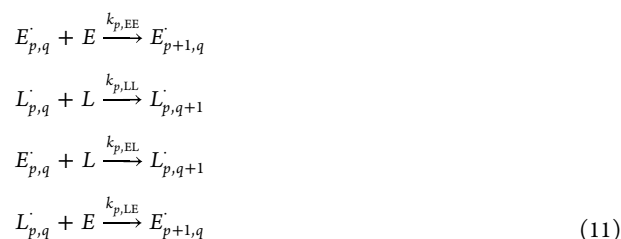
where $\chi_{\text{EG}_n\text{MA}}$ and χ_{LMA} are the EG_{*n*}MA and LMA conversions, respectively, and χ is the overall monomer conversion. On the other hand, the cumulative copolymer composition was estimated according to eq 9 in terms of the EG_{*n*}MA mole fraction $F_{\text{EG}_n\text{MA}}$.

$$F_{\text{EG}_n\text{MA}} = \frac{\gamma}{\gamma + \delta} \quad (9)$$

The residual monomer mixture composition was correlated to the overall conversion through eq 10 (Skeist's equation).

$$\frac{df_{\text{EG}_n\text{MA}}}{d\chi} = \frac{F_{\text{EG}_n\text{MA}} - f_{\text{EG}_n\text{MA}}}{\chi - 1} \quad (10)$$

The integration of this differential equation allowed the determination of the reactivity ratios for the two monomers. In fact, assuming the validity of the terminal model, the evolution of the copolymer composition can be described by the four propagation reactions shown in eq 11.



where $E_{p,q}$ and $L_{p,q}$ are active polymer chains with a terminal EG₂MA or LMA unit, respectively, and with p units of EG₂MA and q units of LMA randomly distributed along the chains. $k_{p,ij}$ is the rate coefficient for the propagation between radical $i_{p,q}$ and monomer j . From this, the well-known definition of reactivity ratio, as the probability of homopropagation with respect to cross-propagation, can be obtained as reported in eqs 12 and 13.

$$r_{EG_2MA} = \frac{k_{p,EE}}{k_{p,EL}} \quad (12)$$

$$r_{LMA} = \frac{k_{p,LL}}{k_{p,LE}} \quad (13)$$

By combining the Skeist's equation with the Mayo–Lewis equation based on the kinetic scheme shown above (eq 14), the following differential eq 15, which links the composition of the residual monomer phase to the monomer conversion can be derived

$$F_{EG_2MA} = \frac{r_{EG_2MA}f_{EG_2MA}^2 + f_{EG_2MA}f_{LMA}}{r_{EG_2MA}f_{EG_2MA}^2 + 2f_{EG_2MA}f_{LMA} + r_{LMA}f_{LMA}^2} \quad (14)$$

$$\frac{df_{EG_2MA}}{d\chi} = \frac{\frac{r_{EG_2MA}f_{EG_2MA}^2 + f_{EG_2MA}f_{LMA}}{r_{EG_2MA}f_{EG_2MA}^2 + 2f_{EG_2MA}f_{LMA} + r_{LMA}f_{LMA}^2} - f_{EG_2MA}}{\chi - 1} \quad (15)$$

where $f_{LMA} = 1 - f_{EG_2MA}$ for a binary mixture. In Skeist's equation, the only parameters appearing are the reactivity ratios of the two monomers.

These were determined through a two-dimensional optimization performed in Matlab. In particular, batch experiments at $f_0 = 0.1, 0.3, 0.5, 0.7,$ and 0.9 were performed, and the residual monomer phase composition was tracked via NMR as a function of conversion. The reactivity ratios were obtained as those values that minimized the difference between the experimental evolution of the monomer mixture composition and that predicted by integration of eq 15. The minimization was obtained by exploiting the genetic algorithm routine in Matlab (*ga*) followed by the *lsqnonlin* algorithm for the determination of the absolute minimum.

Finally, the molecular weight distribution (MWD) of the copolymers was analyzed via gel permeation chromatography (GPC) on a Jasco LC-2000Plus apparatus. For GPC analysis, 4 mg of polymer was dissolved in 1 mL of THF and filtered through a 0.45 μm polytetrafluoroethylene (PTFE) membrane before injection. The instrument comprised three styrene/divinylbenzene columns (Polymer Standard Service; pore sizes $10^3, 10^5,$ and 10^6 Å; 300 mm length and 8 mm internal diameter) and a precolumn (50 mm length and 8 mm internal diameter), paired with a refractive index (RI) detector to record the signal. The separation was performed using THF as eluent at 35 °C with a flow rate of 1 mL/min. Through GPC analysis, it was possible to assess the MWD based on a calibration made with polystyrene standards from 580 to 3,250,000 Da (Polymer Laboratories).

2.3. Synthesis of Thermoresponsive Copolymers Via Semi-Batch FRP. To control the copolymer composition and avoid interchain drifts, once the reactivity ratios were known, the semibatch FRP named power feed was run. To do so, once the desired copolymer composition ($F_{\text{Mayo-Lewis}}$) was chosen, the f_0 value was determined from the Mayo–Lewis plot. Based on this, the desired amount of the less reactive monomer (LMA) was charged in the reactor together with an amount of the most reactive monomer (EG_2MA) to meet the required f_0 . Finally, the feed flow rate (q_{EG_2MA}) for the residual portion of EG_2MA has been calculated by eq 16.

$$q_{EG_2MA} = \frac{dP}{dt} \times \frac{\hat{q}_{EG_2MA} \times MW_{EG_2MA}}{\rho_{EG_2MA}} \quad (16)$$

where MW_{EG_2MA} and ρ_{EG_2MA} are the molecular weight and density of EG_2MA , respectively. dP/dt is the polymer accumulation rate calculated by interpolating the batch conversion data. Finally, \hat{q}_{EG_2MA} is derived from eq 17 by knowing the reactivity ratios.

$$\hat{q}_{EG_2MA} = \frac{F_{EG_2MA} - f_{EG_2MA}}{1 - f_{EG_2MA}} \quad (17)$$

This equation leads to an EG_2MA flow rate decreasing with monomer conversion. This function was approximated in practice through a series of steps at constant flow rate, adjusted every 15 min. For the feed during the first 4 h, we employed the kinetic data for the preliminary experiments, where the samples were taken every hour. On the other hand, for the fourth and eighth hours of reaction, a constant rate was adopted, chosen by simply dividing the residual monomer to be fed by the remaining 4 h.

Through this approach, copolymers were synthesized using EG_2MA with n equal to 2, 4, and 8 as thermoresponsive monomers. As an example, to synthesize a copolymer with EG_2MA as a thermoresponsive unit and with $F_{\text{Mayo-Lewis}} = 0.75$, 11.30 g of EG_2MA and 6.36 g of LMA were weighted in separated containers ($f_0 = 0.706$ and solid content 15% w/w). The less reactive monomer (i.e., LMA) was directly charged in a 250 mL round-bottom flask together with 8.48 g of EG_2MA and 116 g of Dectol. The remaining 2.82 g of EG_2MA were fed with a Harvard apparatus 33 syringe pump. The flow rate of the EG_2MA addition was changed in time according to Table S1.

The solution was purged for 30 min at room temperature and put in a heating bath at 80 °C, before starting the addition of EG_2MA . The initiator (0.21 g, 1% w/w with respect to the total monomer mass) was bubbled with nitrogen for 5 min and added all at once to the solution once it reached the reaction temperature through the rubber stopper. Aliquots of the reaction mixture were withdrawn and quenched in an ice bath to stop the polymerization process. Then, the samples were dried and dissolved in $CDCl_3$ with a concentration of 10 mg/mL to perform NMR analysis and determine the conversion and composition of the monomer mixture and copolymer.

2.4. Cloud Point Measurement. The cloud points of the copolymers were determined by turbidity studies. The samples were diluted with Dectol to 1% w/w in each case and heated to 90 °C in an oven or cooled to -20 °C in a freezer. A Jasco V-630 UV spectrophotometer was used to record the absorbance at a fixed wavelength equal to 500 nm while the samples were cooled or heated to a stable room temperature. By tracking the temperature with a type K thermocouple every 1 s, it was finally possible to obtain the absorbance vs temperature plot and determine the T_{cp} of every copolymer as the mean value of temperature at 10 and 90% of relative absorbance.

For each sample, the temperature transition range $\Delta T_{\text{transition}}$ defined as the difference between the value of temperature at 10 and 90% of relative absorbance, was also calculated, which is a parameter useful to determine the broadness of the phase separation.

3. RESULTS AND DISCUSSION

3.1. Thermoresponsive Polymers Via Batch FRP. First, we synthesized thermoresponsive EG_2MA –LMA copolymers via batch FRP at 15% w/w of solid content, varying the parameter f_0 , defined as the initial mole fraction of EG_2MA in the monomer mixture, between 0.1 and 0.9. The products were characterized via GPC and NMR to determine the MWD, conversion, and copolymer composition.

The results of GPC (Table S2 and Figure S2) show the formation of copolymers with similar MWD, regardless of the initial monomer mixture composition. On the other hand, the NMR analyses confirmed that the syntheses are efficient and allow to obtain copolymers with a conversion of both monomers higher than 80% after 21 h, as summarized in Table S2 and shown in Figure S3 for the synthesis with $f_0 = 0.7$, as an example. However, a difference in the reactivity between the two monomers is clearly visible, with EG_2MA converted faster than LMA.

This difference in reactivity is reflected in EG_2MA mole fractions in the copolymer (F_{EG_2MA} in Table S2) always being higher than the corresponding f_0 , confirming the difficulty in

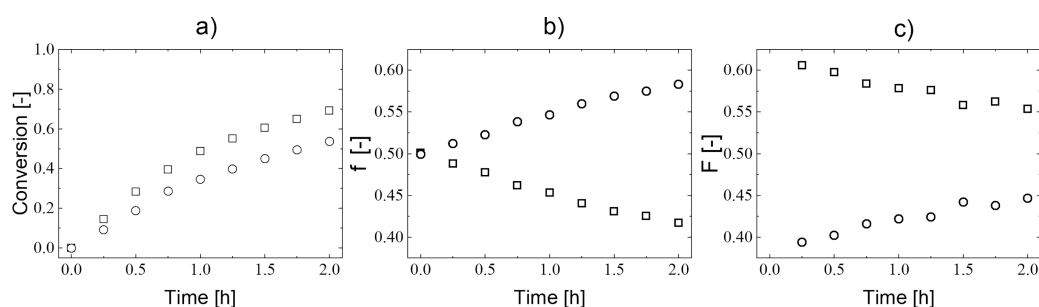


Figure 2. Instantaneous conversion (a), residual monomer mixture molar composition f (b), and cumulative copolymer composition F (c) during time for EG₂MA (squares) and LMA (circles). The data were determined via NMR for a copolymer with a starting composition $f_0 = 0.5$.

properly controlling the copolymer composition via batch FRP.

To validate this finding, for the reaction at $f_0 = 0.5$ and 15% w/w solid content, the monomer conversion and composition of both the residual monomer mixture and of the copolymer were tracked in the first 2 h of the reaction, as shown in Figure 2.

Considering the instantaneous conversions (Figure 2a), it can be seen that EG₂MA has a higher reactivity than LMA, as its conversion is always higher. As a result of this faster consumption, the monomer mixture is depleted in EG₂MA and enriched in LMA (Figure 2b). This is reflected in a compositional drift in the copolymer as the reaction progresses, as at the beginning it is richer in EG₂MA, the most reactive component, while it incorporates more LMA units toward the end of the reaction, where most of the EG₂MA is already consumed (Figure 2c). This phenomenon leads to the formation of copolymer chains with a wide variety of compositions. This interchain heterogeneity is particularly detrimental in the case of thermoresponsive polymers, since the transition between the soluble and insoluble states is strictly related to the composition of the copolymer. This is then expected to lead to copolymers with a broad range of T_{cp} .

In the end, the thermoresponsive behavior was also assessed. The samples reported in Table S2 (f_0 from 0.1 to 0.9) were analyzed in a temperature range between -20 and 100 °C to determine if they were able to undergo a temperature-driven phase separation. As reported in Section 2.4, the thermoresponsive behavior was evaluated by tracking the mixture absorbance at 500 nm with temperature.²⁴ It was noted that the samples with a content of EG₂MA lower than 0.7 were always transparent (i.e., low absorbance), meaning that the T_{cp} of the copolymers was below -20 °C. On the other hand, the sample with the highest content of EG₂MA was turbid (i.e., high absorbance) in the whole range of temperatures considered. In the end, the sample with f_0 equal to 0.8 was the only one to show a transition between turbid and transparent at fairly high temperatures, around 90 °C. A visual representation of this behavior can be seen in Figure S4.

The wide difference in T_{cp} following a little variation in the copolymer composition is an element usually not found in the thermoresponsive polymers made via CRP. Therefore, these findings were further investigated. In particular, we synthesized copolymers with 15% w/w of solid content and different f_0 between 0.7 and 0.8. The phase separation for these samples is shown in Figure 3, where the sharp decrease in the mixture absorbance when the temperature is increased confirms the solubilization of the copolymer.

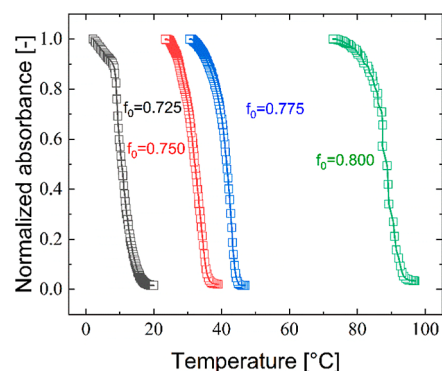


Figure 3. Absorbance ($\lambda = 500$ nm) normalized with respect to its maximum value against temperature for EG₂MA–LMA copolymers with 15% w/w solid content and different f_0 (black: $f_0 = 0.725$; red: $f_0 = 0.750$; blue: $f_0 = 0.775$; green: $f_0 = 0.800$). The curves were used to determine the T_{cp} for each copolymer.

The T_{cp} was calculated from these curves as the mean temperature between 10 and 90% absorbance and is reported in Table 1. This parameter increased with f_0 , confirming the

Table 1. Initial Monomer Mixture Composition and Mole Fraction of EG₂MA (F_{EG_2MA}) in the Copolymer at the End of the Reaction as Measured Via NMR for EG₂MA–LMA Copolymers^a

f_0 [–]	F_{EG_2MA} [–]	T_{cp} [°C]	$\Delta T_{transition}$ [°C]
0.700	0.74	out of range	
0.725	0.76	7.5	9.6
0.750	0.78	31.3	7.8
0.775	0.80	39.9	7.8
0.800	0.84	87.3	10.8

^aThe T_{cp} and the temperature transition range were determined via UV as explained in Section 2.4.

possibility of synthesizing materials with tunable thermoresponsive behavior by acting on the initial molar ratios of the two monomers. At the same time, these copolymers have comparable MWDs (Table S2 and Figure S2); therefore, their difference in T_{cp} can be ascribed only to their different compositions. Interestingly, this increase is not linear with the content of thermoresponsive monomer, as reported instead for copolymers synthesized via RAFT polymerization.^{20,25} Moreover, as testified by $\Delta T_{transition}$, the samples undergo the coil-to-globule transition in a wide temperature range, probably due to the broad copolymer composition distribution.

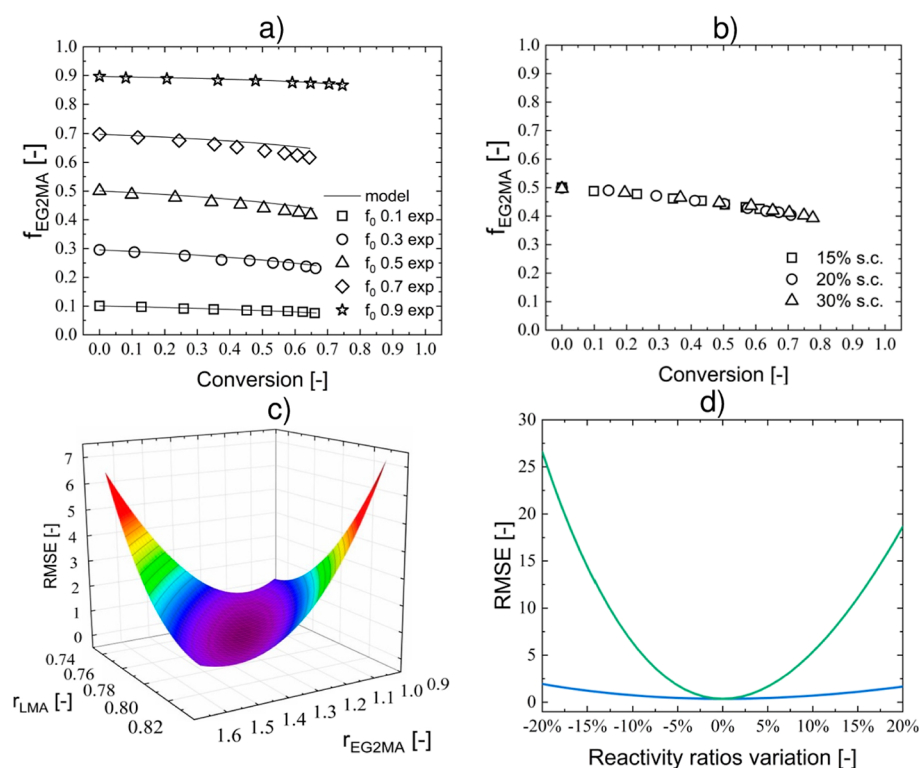


Figure 4. EG₂MA mole fraction in the residual monomer mixture as a function of the overall conversion for EG₂MA–LMA samples with (a) variable f_0 and 15% w/w solid content and (b) variable solid content and fixed $f_0 = 0.5$. The continuous curves refer to the integration of the Skeist's equation using $r_{EG_2MA} = 1.24$ and $r_{LMA} = 0.77$. (c) 3D plot of the RMSE between the integrated Skeist's equation and the experimental data, measured at increasing mole fraction of EG₂MA in the monomer mixture at different reactivity ratios. (d) RMSE as a function of an imposed variation to the optimal values of the reactivity ratios of EG₂MA (light-blue line) and LMA (green line).

Overall, FRP has shown to be a suitable technique to produce copolymers with variable T_{cp} . However, the copolymers obtained via batch FRP have a hardly controllable thermoresponsive behavior, as confirmed by the broad transition and the strong dependence of T_{cp} from the mole fraction of EG₂MA in the copolymer. These issues represent a big obstacle for the use of these materials in advanced applications, where a sharp and precisely defined transition is required.

To solve these problems and expand the application of FRP to the synthesis of tunable thermoresponsive polymers, the precise control of the copolymer composition becomes crucial, as it ensures sharp phase separations and controllable cloud points.

To better control the composition of a copolymer made from monomers with different reactivities, two different strategies can be implemented. The first one is based on starved monomer conditions, which means that the monomer mixture with the desired composition is fed to the reactor with a feeding time much higher than the one required for their polymerization. In this way, the monomers ideally react as soon as they are fed to the system, producing a copolymer with a fixed composition equal to that of the initial monomer mixture. From one side, this strategy reduces the monomer holdup in the reactor and, as a consequence, the risk associated with thermal runaway.^{46,47} Nonetheless, this method requires very long feeding times and is characterized by poor productivity.^{48,49}

The second possibility is called power feed and consists of charging the whole amount of the less reactive monomer at the

beginning of the process together with a fraction of the most reactive one while feeding the remaining part in semibatch mode to prevent chain compositional drift. Owing to its high productivity, we decided to pursue the power feed approach, although it requires detailed knowledge of the reactivity of the system. Hence, we first estimated the reactivity ratios of the two monomers.⁵⁰

3.2. Determination of the EG₂MA and LMA Reactivity Ratios. To determine the reactivity ratios for the binary mixture EG₂MA–LMA, we synthesized different copolymers with variable f_0 (i.e., 0.1, 0.3, 0.5, 0.7, and 0.9) at 15% w/w solid content. For each reaction condition, the composition of the residual monomer phase as well as the cumulative copolymer composition were tracked every 15 min via NMR and related to the overall monomer conversion, as shown in Figure 4a. These experimental data were fitted with the integrated Skeist's equation (see eq 15) and the reactivity ratios determined by minimization of the error between the experimental monomer phase composition and the simulated one, as already reported in other works.^{28,51} We found the optimal reactivity ratios to be 1.24 for EG₂MA (r_{EG_2MA}) and 0.77 for LMA (r_{LMA}). These values confirmed the experimental evidence of a higher reactivity of EG₂MA compared to LMA.

In addition, the same values were able to predict the evolution of the monomer phase composition with the overall conversion at different solid contents, from 15 to 30% w/w (see Figure 4b), confirming that the reactivity ratios are influenced only by the chemical nature of the monomers involved and not by the solid content. This, in turn, has only

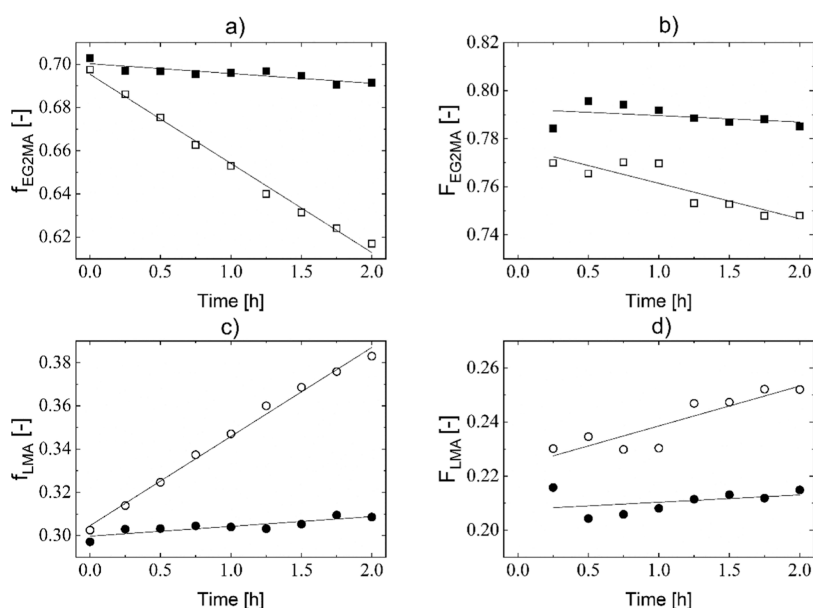


Figure 5. Comparison between residual monomer mixture composition (a,c) and copolymer composition (b,d) for semibatch (full symbols) and batch (empty symbols) processes at 15% w/w and $f_0 = 0.7$. EG₂MA is represented by squares, while LMA is represented by circles.

the effect of increasing the polymerization rate, as confirmed by higher conversions reached at a given time (Figure S5).

The sensitivity of the results by imposing specific variations on each reactivity ratio and evaluating the root-mean-square error (RMSE, Figure 4c,d) between the experimental data and the simulated ones has been verified.

From Figure 4c, it is possible to observe that $r_{EG_2MA} = 1.24$ and $r_{LMA} = 0.77$ are the values leading to a minimum in the RMSE. This is then more affected by a change in r_{LMA} , whose slight variation causes a significant deviation of the model from the experimental data, as confirmed in Figure 4d. On the other hand, the system is less sensitive to r_{EG_2MA} , which only causes an increase in the RMSE of 2% when $\pm 20\%$ variations are imposed.

In the end, the r_i values were used to obtain the Mayo–Lewis diagram (Figure S6), which gives information about the deviation of the polymer composition from the monomer mixture. Although a limited deviation from the diagonal was observed, this is sufficient to cause an important compositional drift in the copolymer, thus making the control over the thermoresponsive behavior critical.

3.3. Thermoresponsive Polymers Via Power Feed FRP. After having determined the reactivity ratios for the system EG₂MA–LMA, we investigated the implementation of the power feed method to synthesize thermoresponsive copolymers with a well-defined composition and T_{cp} . Even if this method adds complexity with respect to the batch process, it allows control of the composition of the copolymer while maintaining high productivity, which is essential from an industrial point of view.

The synthesis of EG₂MA–LMA copolymers with a solid content of 15% w/w and f_0 in the range 0.7–0.8 has been performed, in order to be able to directly compare the T_{cp} of the materials prepared with the batch and semibatch process.

The conversion of the two monomers followed a trend similar to the batch cases (Figure S7), reaching high values after 21 h (Figure S8).

As expected, the conversion of the most reactive monomer is lower in the semibatch case than in the batch one, since this feeding strategy allows to decrease the EG₂MA polymerization rate and to make it more similar to the one of LMA.

As a result, the power feed process was able to efficiently compensate for the rapid depletion of EG₂MA experienced during the batch FRP (Figure 5a). This was reflected in a constant copolymer composition over time, preventing the compositional drift observed for the batch synthesis, as shown in Figure 5b. The same discussion can be applied to LMA. In this case, the power feed prevented the enrichment of this monomer during time (Figure 5c) and ensured its constant mole fraction in the copolymer (Figure 5d).

The properties of the copolymers synthesized through the power feed process at different f_0 are summarized in Table 2, highlighting the proximity of the experimental copolymer composition ($F_{Power\ Feed}$) to the one expected from the Mayo–Lewis plot ($F_{Mayo-Lewis}$).

Table 2. Properties of the copolymers synthesized via power feed process at different initial EG₂MA mole fraction in the monomer mixture (f_0) in terms of EG₂MA mole fraction in the copolymer predicted by the Mayo–Lewis plot ($F_{Mayo-Lewis}$) and obtained experimentally ($F_{Power\ Feed}$), T_{cp} , and temperature transition range ($\Delta T_{transition}$) determined as described in Section 2.4

f_0 [—]	$F_{Mayo-Lewis}$ [—]	$F_{Power\ Feed}$ [—]	T_{cp} [°C]	$\Delta T_{transition}$ [°C]
0.76	0.800	0.83	5.1	5.3
0.79	0.825	0.85	26.8	2.1
0.82	0.850	0.88	48.2	5.2

In the end, the beneficial effect of a limited compositional drift of the copolymer in guaranteeing a tunable thermoresponsive behavior, both in terms of T_{cp} and width of temperature transition range ($\Delta T_{transition}$ in Table 2), was verified. The normalized absorbance as a function of temperature for the samples produced via the power feed

process is compared to those samples produced in batch in Figure 6.

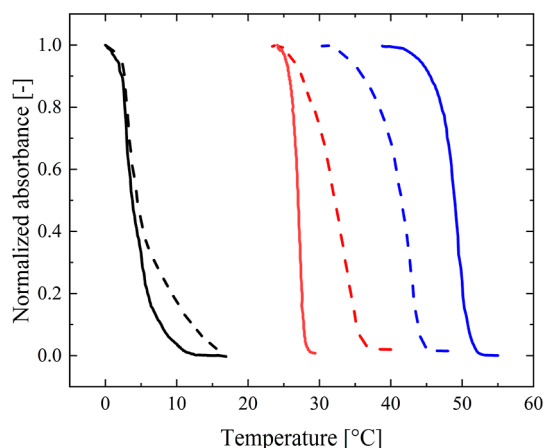


Figure 6. Normalized absorbance ($\lambda = 500$ nm) as a function of temperature for EG₂MA–LMA copolymers synthesized through the power feed method (continuous lines) or batch FRP (dashed lines). The semibatch syntheses were performed at 15% w/w solid content and different $F_{\text{Mayo-Lewis}}$ values (black: $F_{\text{Mayo-Lewis}} = 0.800$; red: $F_{\text{Mayo-Lewis}} = 0.825$; blue: $F_{\text{Mayo-Lewis}} = 0.850$).

In addition to the possibility of regulating the T_{cp} , it is interesting to notice that the phase separation for copolymers obtained via power feed is much sharper than the one for copolymers synthesized via batch FRP. This is confirmed by

$\Delta T_{\text{transition}}$ values reported in Table 2 being smaller than in the case of materials prepared via batch FRP due to the more homogeneous composition. This fact can also explain the shift of the T_{cp} between copolymers with similar final compositions but different synthesis processes. Indeed, in the case of batch samples, F is determined by NMR and represents the mean value of a broad composition distribution, as confirmed in Figure 5b,d. For example, at the beginning of the process, copolymers with a high content of EG₂MA and, as a consequence, higher T_{cp} are formed. However, as the reaction proceeds, polymeric chains richer in LMA are produced, which have higher solvophilicity and hence lower T_{cp} . On the other hand, in the case of copolymers produced with the power feed strategy, the polymeric chains all have the same composition and uniform thermoresponsive behavior.

Eventually, the semibatch power feed approach was confirmed to be a valid solution to synthesize thermoresponsive materials with well-defined composition and tunable thermoresponsive properties, combining the advantages of FRP with a precise control of the copolymer structure and behavior, usually achieved via CRP techniques.

3.4. Extension of the Study to EG_nMA–LMA Systems.

Once the advantages of the power feed for the system EG₂MA–LMA were demonstrated, the study was extended to systems with thermoresponsive monomers with longer poly(ethylene glycol) side chains, namely EG₄MA and EG₈MA. Indeed, increasing the length of the brush of the thermoresponsive unit allows to increase the T_{cp} of the copolymers for the same LMA content. In this way, it is possible to introduce a

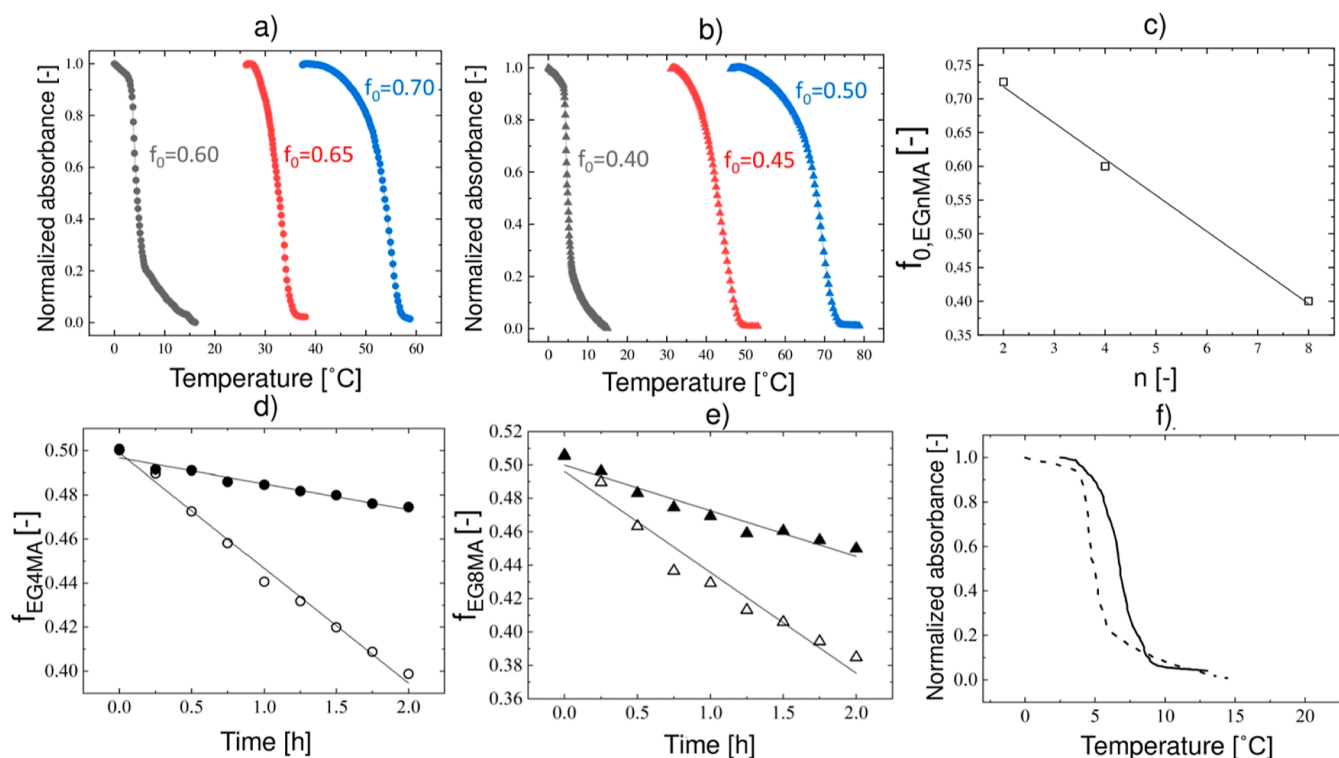


Figure 7. Normalized absorbance ($\lambda = 500$ nm) vs temperature for EG₄MA–LMA (a) and EG₈MA–LMA (b) copolymers with different f_0 values. The curves were used to determine the T_{cp} for each copolymer. (c) f_0 vs n for EG_nMA–LMA copolymers with comparable T_{cp} of 7 °C. Residual monomer mixture composition during time using EG₄MA (d) and EG₈MA (e) as thermoresponsive monomers for power feed (full symbol) and batch (empty symbol) processes. The reactions were performed with 15% w/w solid content and $f_0 = 0.5$. (c) Normalized absorbance ($\lambda = 500$ nm) vs temperature curves recorded for EG₈MA–LMA copolymers with comparable T_{cp} . The continuous line refers to the power feed synthesis while the dashed one refers to the batch case.

further degree of freedom to modulate the T_{cp} of the final material.

While this statement is true for polymers made via RAFT polymerization,⁵² it had to be verified in the case of materials made via FRP. Therefore, a library of copolymers was synthesized with LMA as the solvophilic monomer and EG₄MA or EG₈MA as the thermoresponsive unit, varying f_0 via batch FRP.

Interestingly, the change of the thermoresponsive unit led to overall conversions and MWDs similar to the case with EG₂MA, as verified via NMR and GPC (Tables S3 and S4).

The phase separation of the samples was then analyzed and is shown as normalized absorbance vs temperature in Figure 7a for EG₄MA–LMA and in Figure 7b for EG₈MA–LMA. These curves confirm the trend already highlighted for EG₂MA, i.e., an increase in the mole fraction of thermoresponsive monomer in the copolymer leads to a higher T_{cp} . Moreover, also in these cases, the copolymers have a wide temperature transition range since the batch FRP causes the formation of chains with a broad composition distribution. Finally, it can also be noticed that thermoresponsive units with longer side chains require less amount of solvophilic monomer in the copolymer to obtain materials with comparable T_{cp} (i.e., 7 °C, Figure 7c). This finding is of particular interest since it allows the synthesis of materials with a specific thermoresponsive behavior but different content in LMA.

After having confirmed the possibility of decoupling T_{cp} and LMA content in the copolymer by exploiting different EG_{*n*}MA, we wanted to apply to this EG_{*n*}MA–LMA system the power feed process, with the aim of a precise control over its thermoresponsive behavior.

First, we tracked the composition of the residual monomer mixture during the batch FRP of LMA and EG_{*n*}MA, with $n = 2, 4, \text{ and } 8$ at fixed $f_0 = 0.5$ and 15% w/w solid content. As can be seen from Figure S9, the difference between all of the tested EG_{*n*}MA is limited, which makes the prediction of the experimental data with the same set of reactivity ratios estimated for the system EG₂MA–LMA (i.e., $r_{EG_2MA} = 1.24$ and $r_{LMA} = 0.77$) quite accurate.

For this reason, we concluded that these reactivity ratios could also be exploited to design the power feed for EG₄MA and EG₈MA, expanding the versatility of the investigation reported herein.

Considering the same initial composition $f_0 = 0.5$, Figure 7d, e compares the mole fraction of, respectively, EG₄MA and EG₈MA in the residual monomer mixture during time for batch (empty symbols) and power feed (full symbols) processes.

We demonstrated that by directly applying the reactivity ratios determined for EG₂MA to the case of monomers with longer poly(ethylene glycol) side chains, the power feed process is able to significantly mitigate the depletion of these monomers in the mixture during time and hence ensure a more constant copolymer composition with respect to the batch FRP. The deviation from a constant monomer mixture composition is ascribed to a slight difference in the reactivity of the different monomers, which becomes more and more accentuated with increasing n .

Still, it is worth pointing out that the direct application of the same set of reactivity ratios allows both saving experimental labor and the possibility of obtaining polymeric chains with controllable thermoresponsive behavior. This is evident in

Figure 7f, showing that for the EG₈MA–LMA copolymers made with the power feed approach, a narrower phase separation (i.e., lower $\Delta T_{transition}$) can be obtained with respect to the corresponding copolymer made via batch polymerization (3.9 °C vs 5.6 °C).

4. CONCLUSIONS

The batch FRP of EG₂MA and LMA in a non-polar medium (Dectol) has been studied as an example of a system displaying an UCST that can be controlled by adjusting the composition of the copolymer. In our previous works, we demonstrated that strict control over the copolymer composition and in turn on its T_{cp} in Dectol could be obtained via RAFT polymerization, which however is affected by high costs of the chain transfer agent and low polymerization rates.^{17,20,25} On the other hand, the batch FRP, despite being more industrially appealing, causes a significant compositional drift that is reflected in a broad phase separation.

After having determined the reactivity ratios for the two monomers, we demonstrated in this work that the limited interchain compositional drift ensured by the power feed process allows obtaining well-defined thermoresponsive properties and sharp phase separations even via FRP.

Moreover, it was verified that the thermoresponsive behavior could be tuned not only by changing the composition of the copolymer but also by employing thermoresponsive monomers with variable lengths of the poly(ethylene glycol) side chain. This finding is pretty interesting since it introduces a further degree of freedom, which is useful to decouple the T_{cp} and the LMA content in the copolymer, providing a way for a more precise design of the materials for specific applications.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsapm.3c02254>.

NMR spectra of the monomers, GPC and NMR characterizations of the EG_{*n*}MA–LMA copolymers made via batch and semibatch polymerization, average size and polydispersity of the copolymers synthesized, pictures of the samples at temperatures below and above the T_{cp} , feeding strategy for the semibatch case, and data of interest for the batch syntheses (Mn, Mw, f_0 , etc.) (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Mattia Sponchioni – Department of Chemistry, Materials and Chemical Engineering “Giulio Natta”, Politecnico di Milano, Milano 20131, Italy; orcid.org/0000-0002-8130-6495; Email: mattia.sponchioni@polimi.it

Authors

Gianmaria Gardoni – Department of Chemistry, Materials and Chemical Engineering “Giulio Natta”, Politecnico di Milano, Milano 20131, Italy

Riccardo Menegon – Department of Chemistry, Materials and Chemical Engineering “Giulio Natta”, Politecnico di Milano, Milano 20131, Italy

Davide Moscatelli – Department of Chemistry, Materials and Chemical Engineering “Giulio Natta”, Politecnico di Milano, Milano 20131, Italy; orcid.org/0000-0003-2759-9781

Complete contact information is available at:
<https://pubs.acs.org/10.1021/acsapm.3c02254>

Author Contributions

G.G.: investigation, data curation, writing—original draft; R.M.: validation; M.S.: conceptualization, supervision, writing—review and editing; D.M.: funding acquisition, writing—review and editing. All authors have read and given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

REFERENCES

- (1) Roy, D.; Brooks, W. L. A.; Sumerlin, B. S. New Directions in Thermo-responsive Polymers. *Chem. Soc. Rev.* **2013**, *42* (17), 7214–7243.
- (2) Kim, Y. J.; Matsunaga, Y. T. Thermo-Responsive Polymers and Their Application as Smart Biomaterials. *J. Mater. Chem. B* **2017**, *5* (23), 4307–4321.
- (3) Manfredini, N.; Gardoni, G.; Sponchioni, M.; Moscatelli, D. Thermo-Responsive Polymers as Surface Active Compounds: A Review. *Eur. Polym. J.* **2023**, *198*, 112421.
- (4) Sponchioni, M.; Capasso Palmiero, U.; Moscatelli, D. Thermo-Responsive Polymers: Applications of Smart Materials in Drug Delivery and Tissue Engineering. *Mater. Sci. Eng., C* **2019**, *102* (April), 589–605.
- (5) Lai, H.; Chen, G.; Wu, P.; Li, Z. Thermoresponsive Behavior of an LCST-Type Polymer Based on a Pyrrolidone Structure in Aqueous Solution. *Soft Matter* **2012**, *8* (9), 2662–2670.
- (6) Chen, G. T.; Wang, C. H.; Zhang, J. G.; Wang, Y.; Zhang, R.; Du, F. S.; Yan, N.; Kou, Y.; Li, Z. C. Toward Functionalization of Thermoresponsive Poly (N-Vinyl-2-Pyrrolidone). *Macromolecules* **2010**, *43* (23), 9972–9981.
- (7) Huang, Y. S.; Ejeta, D. D.; Kuo, S. W.; Nakamura, Y.; Huang, C. F. Combinations (ϵ) among Controlled/Living Polymerizations and Utilizations of Efficient Chemical Reactions for the Synthesis of Novel Polymeric Materials. *Polym. Chem.* **2023**, *14*, 4783–4803.
- (8) Huang, Y. S.; Chen, J. K.; Kuo, S. W.; Hsieh, Y. A.; Yamamoto, S.; Nakanishi, J.; Huang, C. F. Synthesis of Poly(N-Vinylpyrrolidone)-Based Polymer Bottlebrushes by ATRPA and RAFT Polymerization: Toward Drug Delivery Application. *Polymers (Basel)* **2019**, *11* (6), 1079.
- (9) Gibson, R. R.; Fernyhough, A.; Musa, O. M.; Armes, S. P. Synthesis of Well-Defined Diblock Copolymer Nano-Objects by RAFT Non-Aqueous Emulsion Polymerization of: N -(2-Acryloyloxy)Ethyl Pyrrolidone in Non-Polar Media. *Polym. Chem.* **2021**, *12* (26), 3762–3774.
- (10) Derry, M. J.; Mykhaylyk, O. O.; Armes, S. P. Shear-Induced Alignment of Block Copolymer Worms in Mineral Oil. *Soft Matter* **2021**, *17* (39), 8867–8876.
- (11) Thompson, K. L.; Fielding, L. A.; Mykhaylyk, O. O.; Lane, J. A.; Derry, M. J.; Armes, S. P. Vermicious Thermo-Responsive Pickering Emulsifiers. *Chem. Sci.* **2015**, *6* (7), 4207–4214.
- (12) Paquin, F.; Rivnay, J.; Salleo, A.; Stingelin, N.; Silva-Acuña, C. Multi-phase microstructures drive exciton dissociation in neat semicrystalline polymeric semiconductors. *J. Mater. Chem. C* **2015**, *3*, 10715–10722.
- (13) Li, L.; Xu, J.; Lyu, X.; Liu, Z.; Song, Z.; Wei, J. Novel Polymer-Based Thermoresponsive Photonic Crystal Sensors with Broad Wavelength Shifts. *Chem. Commun.* **2022**, *58* (72), 10032–10035.
- (14) Ward, M. A.; Georgiou, T. K. Thermoresponsive Polymers for Biomedical Applications. *Polymers (Basel)* **2011**, *3* (3), 1215–1242.
- (15) Vanparijs, N.; Nuhn, L.; De Geest, B. G. Transiently Thermoresponsive Polymers and Their Applications in Biomedicine. *Chem. Soc. Rev.* **2017**, *46* (4), 1193–1239.
- (16) Doberenz, F.; Zeng, K.; Willems, C.; Zhang, K.; Groth, T. Thermoresponsive Polymers and Their Biomedical Application in Tissue Engineering-A Review. *J. Mater. Chem. B* **2020**, *8* (4), 607–628.
- (17) Manfredini, N.; Tomasoni, M.; Sponchioni, M.; Moscatelli, D. Influence of the Polymer Microstructure over the Phase Separation of Thermo-Responsive Nanoparticles. *Polymers (Basel)* **2021**, *13* (7), 1032.
- (18) Sponchioni, M.; Morosi, L.; Lupi, M.; Capasso Palmiero, U. Poly(HPMA)-Based Copolymers with Biodegradable Side Chains Able to Self Assemble into Nanoparticles. *RSC Adv.* **2017**, *7* (80), 50981–50992.
- (19) Capasso Palmiero, U.; Sponchioni, M.; Manfredini, N.; Maraldi, M.; Moscatelli, D. Strategies to Combine ROP with ATRP or RAFT Polymerization for the Synthesis of Biodegradable Polymeric Nanoparticles for Biomedical Applications. *Polym. Chem.* **2018**, *9* (30), 4084–4099.
- (20) Gardoni, G.; Manfredini, N.; Monzani, M.; Sponchioni, M.; Moscatelli, D. Thermoresponsive Modular Nano-Objects Via RAFT Dispersion Polymerization in a Non-Polar Solvent. *ACS Appl. Polym. Mater.* **2023**, *5* (1), 494–503.
- (21) Fielding, L. A.; Lane, J. A.; Derry, M. J.; Mykhaylyk, O. O.; Armes, S. P. Thermo-Responsive Diblock Copolymer Worm Gels in Non-Polar Solvents. *J. Am. Chem. Soc.* **2014**, *136* (15), 5790–5798.
- (22) Derry, M. J.; Mykhaylyk, O. O.; Armes, S. P. A Vesicle-to-Worm Transition Provides a New High-Temperature Oil Thickening Mechanism. *Angew. Chem., Int. Ed.* **2017**, *56* (7), 1746–1750.
- (23) Hunter, S. J.; Armes, S. P. Pickering Emulsifiers Based on Block Copolymer Nanoparticles Prepared by Polymerization-Induced Self-Assembly. *Langmuir* **2020**, *36* (51), 15463–15484.
- (24) Gibson, R. R.; Fernyhough, A.; Musa, O. M.; Armes, S. P. RAFT Dispersion Polymerization of: N, N -Dimethylacrylamide in a Series of n -Alkanes Using a Thermoresponsive Poly(Tert -Octyl Acrylamide) Steric Stabilizer. *Polym. Chem.* **2021**, *12* (14), 2165–2174.
- (25) Gardoni, G.; Manfredini, N.; Bagnato, G.; Sponchioni, M.; Moscatelli, D. Role of the Polymer Microstructure in Controlling Colloidal and Thermo-Responsive Properties of Nano-Objects Prepared Via RAFT Polymerization in a Non-Polar Medium. *Langmuir* **2023**, *39* (29), 10133–10144.
- (26) György, C.; Armes, S. P. Recent Advances in Polymerization-Induced Self-Assembly (PISA) Syntheses in Non-Polar Media. *Angew. Chem., Int. Ed.* **2023**, *62* (42), No. e202308372.
- (27) Kwan, S.; Marić, M. Thermoresponsive Polymers with Tunable Cloud Point Temperatures Grafted from Chitosan via Nitroxide Mediated Polymerization. *Polymer (Guildf)* **2016**, *86*, 69–82.
- (28) Sponchioni, M.; Capasso Palmiero, U.; Manfredini, N.; Moscatelli, D. RAFT Copolymerization of Oppositely Charged Monomers and Its Use to Tailor the Composition of Nonfouling Polyampholytes with an UCST Behaviour. *React. Chem. Eng.* **2019**, *4* (2), 436–446.
- (29) Penfold, N. J. W.; Yeow, J.; Boyer, C.; Armes, S. P. Emerging Trends in Polymerization-Induced Self-Assembly. *ACS Macro Lett.* **2019**, *8* (8), 1029–1054.
- (30) Ramírez-Jiménez, A.; Montoya-Villegas, K. A.; Licea-Claverie, A.; González-Ayón, M. A. Tunable Thermo-Responsive Copolymers from DEGMA and OEGMA Synthesized by RAFT Polymerization and the Effect of the Concentration and Saline Phosphate Buffer on Its Phase Transition. *Polymers (Basel)* **2019**, *11* (10), 1657.
- (31) Semsarilar, M.; Abetz, V. Polymerizations by RAFT: Developments of the Technique and Its Application in the Synthesis of Tailored (Co)Polymers. *Macromol. Chem. Phys.* **2021**, *222* (1), 2000311.
- (32) Perrier, S. 50th Anniversary Perspective: RAFT Polymerization - A User Guide. *Macromolecules* **2017**, *50* (19), 7433–7447.
- (33) Iqbal, S.; Ahmad, S. Recent Development in Hybrid Conducting Polymers: Synthesis, Applications and Future Prospects. *J. Ind. Eng. Chem.* **2018**, *60* (June 2018), 53–84.
- (34) Distler, D.; Neto, W. S.; Machado, F. Emulsion Polymerization. *Reference Module in Materials Science and Materials Engineering*; Elsevier, 2017; pp 1–14.

- (35) Barsbay, M.; Güven, O. Nanostructuring of Polymers by Controlling of Ionizing Radiation-Induced Free Radical Polymerization, Copolymerization, Grafting and Crosslinking by RAFT Mechanism. *Radiat. Phys. Chem.* **2020**, *169*, 107816.
- (36) Sponchioni, M.; Ferrari, R.; Morosi, L.; Moscatelli, D. Influence of the Polymer Structure over Self-Assembly and Thermo-Responsive Properties: The Case of PEG-b-PCL Grafted Copolymers via a Combination of RAFT and ROP. *J. Polym. Sci., Part A: Polym. Chem.* **2016**, *54* (18), 2919–2931.
- (37) Rusli, W.; Benjamin Tan, S. W.; Parthiban, A.; van Herk, A. M. Free Radical Solution Copolymerization of Monomers of Dissimilar Reactivity - Influencing Chemical Composition Distribution and Properties of Copolymers of Methyl Methacrylate and N-Vinyl Imidazole by Varying Monomer Feeding Profiles. *Polymer (Guildf)* **2022**, *247* (March), 124774.
- (38) Siqueira, J. S.; Florenzano, F. H.; Reed, W. F. Kinetic Analysis of Continuous Reaction Data for RAFT and Free Radical Copolymerization with Acrylic and Styrenic Monomers. *Polymer (Guildf)* **2021**, *226* (January), 123798.
- (39) Popescu, D.; Hoogenboom, R.; Keul, H.; Moeller, M. Thermoresponsive Polyacrylates Obtained via a Cascade of Enzymatic Transacylation and FRP or NMP. *Polym. Chem.* **2010**, *1* (6), 878–890.
- (40) Marsili, L.; Dal Bo, M.; Eisele, G.; Donati, I.; Berti, F.; Toffoli, G. Characterization of Thermoresponsive Poly-n-Vinylcaprolactam Polymers for Biological Applications. *Polymers (Basel)* **2021**, *13* (16), 2639.
- (41) Bergueiro, J.; Calderón, M. Thermoresponsive Nanodevices in Biomedical Applications. *Macromol. Biosci.* **2015**, *15* (2), 183–199.
- (42) Pernia Leal, M.; Torti, A.; Riedinger, A.; La Fleur, R.; Petti, D.; Cingolani, R.; Bertacco, R.; Pellegrino, T. Controlled Release of Doxorubicin Loaded within Magnetic Thermo-Responsive Nanocarriers under Magnetic and Thermal Actuation in a Microfluidic Channel. *ACS Nano* **2012**, *6* (12), 10535–10545.
- (43) Boulding, N. A.; Millican, J. M.; Hutchings, L. R. Understanding Copolymerisation Kinetics for the Design of Functional Copolymers: Via Free Radical Polymerisation. *Polym. Chem.* **2019**, *10* (41), 5665–5675.
- (44) Fierens, S. K.; Van Steenberge, P. H. M.; Reyniers, M. F.; D'Hooge, D. R.; Marin, G. B. Analytical and Advanced Kinetic Models for Characterization of Chain-Growth Copolymerization: The State-of-the-Art. *React. Chem. Eng.* **2018**, *3* (2), 128–145.
- (45) D'Hooge, D. R.; Van Steenberge, P. H. M.; Derboven, P.; Reyniers, M. F.; Marin, G. B. Model-Based Design of the Polymer Microstructure: Bridging the Gap between Polymer Chemistry and Engineering. *Polym. Chem.* **2015**, *6* (40), 7081–7096.
- (46) Wang, W.; Hutchinson, R. A. Recent Advances in the Study of High-Temperature Free Radical Acrylic Solution Copolymerization. *Macromol. React. Eng.* **2008**, *2* (3), 199–214.
- (47) Nasresfahani, A.; Schiavi, D.; Grady, M. C.; Hutchinson, R. A. An Automated Recipe Generator for Semi-Batch Solution Radical Copolymerization via Comprehensive Stochastic Modeling and Derivative-Free Algorithms. *Chem. Eng. J.* **2021**, *417* (November 2020), 127920.
- (48) Schultz, E. S.; Sheibat-Othman, N.; Mitsos, A.; Mhamdi, A. Model-Based Optimization of Semibatch Emulsion Polymerization of Styrene. *Ind. Eng. Chem. Res.* **2020**, *59* (37), 16368–16379.
- (49) Hungenberg, K. D.; Jahns, E. Trends in Emulsion Polymerization Processes from an Industrial Perspective. *Adv. Polym. Sci.* **2017**, *280*, 195–214.
- (50) Lovell, P. A.; Schork, F. J. Fundamentals of Emulsion Polymerization. *Biomacromolecules* **2020**, *21* (11), 4396–4441.
- (51) Wenzel, F.; Hamzehlou, S.; Pardo, L.; Aguirre, M.; Leiza, J. R. Kinetics of Radical Ring Opening Polymerization of the Cyclic Ketene Acetal 2-Methylene-1,3-Dioxepane with Vinyl Monomers. *Ind. Eng. Chem. Res.* **2021**, *60* (29), 10479–10488.
- (52) Becer, R.; Hahn, S.; Fijten, M. W. M.; Thijs, H. M. L.; Hoogenboom, R.; Schubert, U. S. Libraries of Methacrylic Acid and Oligo(Ethylene Glycol) Methacrylate Copolymers with LCST Behavior. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46* (21), 7138–7147.