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RAFT Polymerization in Supercritical Carbon Dioxide Based on an Induced Precipitation Approach: Synthesis of 2-Ethoxyethyl methacrylate/Acrylamide Block Copolymers

Gerard Hawkins,¹ Per B. Zetterlund,² Fawaz Aldabbagh¹

¹School of Chemistry, National University of Ireland Galway, University Road, Galway, Ireland

²Centre for Advanced Macromolecular Design (CAMD), School of Chemical Engineering, The University of New South Wales, Sydney, NSW 2052, Australia

Correspondence to: P. B. Zetterlund (E-mail: p.zetterlund@unsw.edu.au) or F. Aldabbagh (E-mail: fawaz.aldabbagh@nuigalway.ie)

Additional Supporting Information may be found in the online version of this article.

ABSTRACT

A new controlled/living heterogeneous polymerization technique using RAFT in benign supercritical CO₂ is described involving the formation of monomer-swollen seed particles by precipitation of MacroRAFT agent prior to polymerization. Controlled/living character of the induced precipitation is compared with the equivalent solution polymerization. The large scale synthesis of poly(2-ethoxyethyl methacrylate)-*b*-poly(acrylamides) useful for biomedical applications is made possible with the polymer isolated as powders at high conversions, thus circumventing the requirement for volatile organic solvents.

KEYWORDS: Green chemistry, dispersions, living polymerization, polyacrylamides, radical polymerization

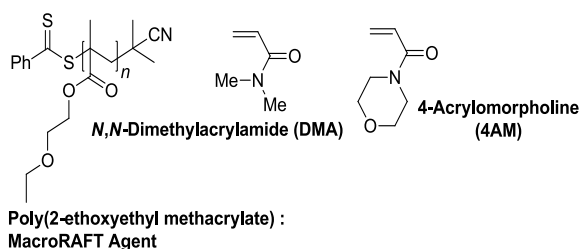
INTRODUCTION

Over the past decade, heterogeneous controlled/living radical polymerizations in benign supercritical carbon dioxide (scCO₂) have become commonplace, and have been the subject of recent reviews.¹⁻³ Nitroxide-mediated polymerization (NMP),^{1,2,4-7} atom transfer radical polymerization (ATRP),^{1,2,8,9} reversible addition-fragmentation chain transfer (RAFT),^{1,2,10-12} and iodine transfer polymerization (ITP)^{13,14} have all been reported in scCO₂. Most of these systems are classified as precipitation or dispersion polymerizations, where the monomer is initially soluble in the reaction medium, but the resultant polymer precipitates at a critical degree of polymerization (J_{crit}).⁴ The polymerization can then proceed to high conversion in a

controlled/living manner in the particle phase. An exception is the NMP of *N*-isopropylacrylamide (NIPAM), which proceeded in a controlled/living manner to high conversion as an inverse suspension polymerization.^{5,6} Howdle and co-workers have reported many different controlled/living dispersion RAFT polymerizations giving well-defined microparticles with high blocking efficiency achieved.^{1,2,10,12}

In this article we report a new controlled/living heterogeneous system, which is based upon induced precipitation of a macroRAFT agent occurring prior to polymerization on pressurization with CO₂, thus forming seed particles that are swollen with monomer. The use of CO₂ to induce particle formation in heterogeneous polymerization systems has

previously been reported for conventional (non-living) radical polymerization under non-supercritical conditions.^{15,16} The present RAFT seeded precipitation polymerization in $scCO_2$ uses poly(2-ethoxyethyl methacrylate) as the macroRAFT agent, which is employed to give block copolymers upon chain extension with acrylamides; *N,N*-dimethylacrylamide (DMA) and 4-acrylomorpholine (4AM) (Scheme 1).



SCHEME 1 Reactants used.

Potential applications for these poly(2-ethoxyethyl methacrylate) containing block copolymers are numerous due to the presence of both ether and ester groups imparting flexibility and hydrogen bonding, while also offering the possibility for biomedical applications due to their thermoresponsiveness.¹⁷ Controlled/living character for the heterogeneous polymerizations in $scCO_2$ is compared with the equivalent solution polymerizations in toluene.

EXPERIMENTAL

Materials

2-Ethoxyethyl methacrylate (>98%, TCI), *N,N*-dimethylacrylamide (DMA, >99%, TCI), and 4-acrylomorpholine (4-AM, >98%, TCI) were distilled under reduced pressure before use. 2,2'-Azobisisobutyronitrile (AIBN, DuPont Chemical Solution Enterprise) was recrystallized twice from methanol before use. 2-Cyano-2-propyl benzodithioate (>97%, Aldrich), petroleum ether (40-60 °C, Aldrich), *N,N*-dimethylformamide (DMF, 99.9%, Aldrich), tetrahydrofuran (THF, 99.9%, Aldrich), diethyl ether (>98%, Aldrich), toluene (99%, Aldrich),

$CDCl_3$ (99.8 atom %, Aldrich) and LiBr (99%, Aldrich) were used as received.

Preparation of MacroRAFT Agent

Poly(2-ethoxyethyl methacrylate) (MacroRAFT agent, $M_n = 9,000$, $M_w/M_n = 1.10$) was prepared by bulk polymerization of 2-ethoxyethyl methacrylate (10.4 mL, 63.2 mmol) at 60 °C for 10 hours using AIBN (41.5 mg, 0.253 mmol) and 2-cyano-2-propyl benzodithioate (0.28 g, 1.26 mmol) as initiator and RAFT agent respectively. The polymer was isolated by solubilising the resultant mixture using a minimum of THF with precipitation from an excess of petroleum ether. The polymer was dried under vacuum to give MacroRAFT agent (8.98 g, 87%).

Measurements for Polymerizations

M_n and polydispersity (M_w/M_n) were measured using a gel permeation chromatography (GPC) system consisting of a Viscotek DM 400 data manager, a Viscotek VE 3580 refractive index detector, and two Viscotek Viscogel GMH_{HR}-M columns. Measurements were carried out at 60 °C at a flow rate of 1.0 mL min⁻¹ using HPLC-grade DMF containing 0.01 M LiBr as the eluent. The columns were calibrated using twelve poly(styrene) standards ($M_n = 580$ -6,035,000 g mol⁻¹). M_n is given in g mol⁻¹ throughout. All GPC corresponds to polymer before purification, unless otherwise stated. The use of poly(styrene) standards inevitably leads to error, however control/living character can be assessed based on the shapes of molecular weight distributions (MWDs) and trends in M_n and M_w/M_n versus conversion.

¹H NMR spectra were recorded using a Joel GXFT 400 MHz instrument equipped with a DEC AXP 300 computer workstation. ¹H NMR spectra were obtained in $CDCl_3$ and used for conversion measurements from polymerization mixtures prior to precipitation. Conversions for the polymerizations of DMA were obtained by comparing the integrals of the copolymer peak at 2.7-3.2 ppm (CH₃, 6H) with the monomer vinyl peak at ~5.65 ppm with deduction of the

monomer contribution from the copolymer peak. Conversions for the polymerizations of 4AM were obtained by comparing the integrals of the copolymer peak at 3.1-3.9 ppm (CH₂, 8H) with the monomer vinyl peak at ~5.69 ppm with deduction of the monomer and macroRAFT contributions from the copolymer peak. For polymerization of 4AM to ≥70% conversion in supercritical carbon dioxide (scCO₂), conversion was also measured by gravimetry with measurements found to be in close agreement (within 1%) to that obtained from ¹H NMR.

The theoretical number-average molecular weights ($M_{n,th}$) were calculated according to:

$$M_{n,th} = \frac{\alpha[M]_0 MW_{mon}}{[MacroRAFT]_0} + MW_{MacroRAFT} \quad (1)$$

Where α is the fractional monomer conversion, $[M]_0$ is the initial monomer concentration, $[MacroRAFT]_0$ is the initial MacroRAFT concentration, MW_{mon} is the molecular weight of the monomer, and $MW_{MacroRAFT}$ is the molecular weight of the MacroRAFT determined by GPC.

Equipment

Polymerizations in scCO₂ were conducted in a 25 mL stainless steel Parr reactor with maximum operating pressure and temperature of 40 MPa and 130 °C respectively or 100 mL stainless steel Thar reactor with a maximum operating pressure and temperature of 41.4 MPa and 125 °C respectively. The pressure was produced by a Thar P-50 series high pressure pump to within ±0.2 MPa and the temperature was monitored by a Thar CN6 controller to within ±0.1 °C. The reactors are connected to a Thar automated back pressure regulator (ABPR, a computer-controlled needle valve) for controlled venting. For the 25 mL reactor stirring was achieved using a magnetic stirring bar and the 100 mL reactor is equipped with Magdrive maintaining stirring at ~1200 rpm.

Polymerizations in Supercritical Carbon Dioxide (scCO₂)

The above MacroRAFT agent (5.67 g, 0.63 mmol) and AIBN (20.7 mg, 0.126 mmol) were dissolved in DMA (12.5 g, 0.126 mol) in the 25 mL stainless steel reactor. Alternatively, the above MacroRAFT agent (4.700 g, 0.52 mmol) and AIBN (17.2 mg, 0.104 mmol) were dissolved in 4AM (15.25 g, 0.108 mol) in the 25 mL stainless steel reactor. The reaction mixture was purged for 20 minutes by passing gaseous CO₂ through the mixture to remove oxygen. Liquid CO₂ (~5 MPa) was added and the reactor immersed in an oil bath. The temperature was raised to the reaction temperature of 65 °C followed by the pressure to the reaction pressure of 30 MPa by further addition of CO₂. The reaction was quenched by submersion of the reactor into an ice-water bath. When at approximately room temperature, the CO₂ was vented slowly from the reactor into a conical flask to prevent loss of the polymer. The polymers were isolated by dissolving the reaction mixture in THF and precipitating by dropwise addition into cold petroleum ether (DMA) or diethyl ether (4AM). The polymerizations of 4AM taken to ≥70% conversion were purified using scCO₂. The light pink powder obtained after venting of CO₂ (was not precipitated using organic solvent), and was purified by washing three times with scCO₂ at 50 °C and 30 MPa. The polymer was filtered and dried under vacuum for 24 h at room temperature.

Solution Polymerizations

The above MacroRAFT (0.450 g, 0.050 mmol) and AIBN (1.65 mg, 0.01 mmol) were dissolved in DMA (1.00 g, 10 mmol) and toluene (1 mL) added. For 4AM, the MacroRAFT (0.302 g, 0.0335 mmol) and AIBN (1.16 mg, 0.007 mmol) were dissolved in 4AM (1.00 g, 7.08 mmol) and toluene (0.63 mL) added. Polymerization reaction mixtures were added to Pyrex ampoules and subjected to several freeze-degas-thaw cycles to remove oxygen before

sealing under vacuum. The ampoules were heated at 65 °C in an aluminum heating block for various times. Polymerizations were stopped by placing ampoules in an ice-water bath.

RESULTS AND DISCUSSION

Induced Precipitation Polymerization in scCO₂

Polymerizations were conducted in a 100 mL stainless steel reactor equipped with two 180° sapphire windows,⁴ which allowed for the observation of the solubility of the poly(2-ethoxyethyl methacrylate) (macroRAFT agent) in scCO₂ at 65 °C and 30 MPa. Under these conditions, the macroRAFT agent (~19 g; $M_n = 9000$ g/mol, $M_w/M_n = 1.10$) was found to be insoluble in scCO₂, forming a whitish emulsion. For polymerizations, a similar quantity of macroRAFT was first dissolved in the acrylamide monomer, which is miscible with scCO₂.⁶ Upon

introduction of CO₂ at 5 MPa and 24 °C, a phase separation is induced, which is observed as a whitish emulsion indicating the presence of particles (a dispersed phase) prior to polymerization. The dispersion persisted under scCO₂ conditions (30 MPa/65 °C) used for polymerization of the monomers DMA and 4AM with 2,2'-azoisobutyronitrile (AIBN) as initiator.

RAFT Polymerizations in scCO₂

Reasonably narrow MWDs ($M_w/M_n < 1.38$) shifting to higher MWs with conversion for the RAFT of DMA (Figure 1) and 4AM (Figure 2) at $[\text{Monomer}]_0/[\text{MacroRAFT}]_0 = 200$ and 400 are indicative of good controlled/living character. MWs increased approximately linearly with conversion and were mostly close to the theoretical number average molecular weight ($M_{n,\text{th}}$) lines, although some discrepancy is expected because the M_n values are based on polystyrene standards (Figures 3 and 4).

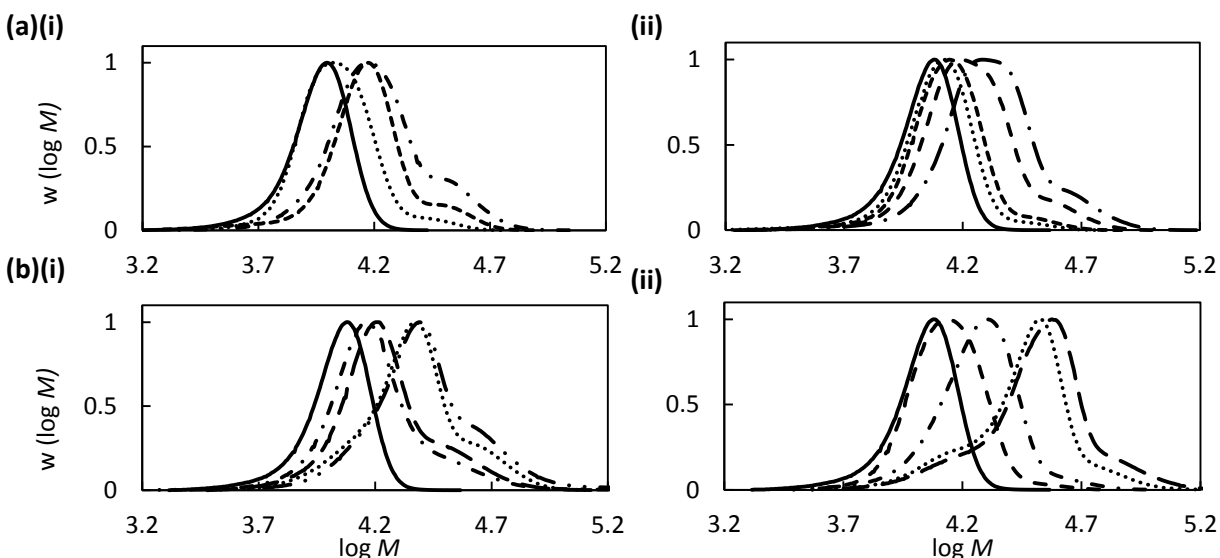


FIGURE 1 MWDs for polymerization mixtures of the RAFT of DMA at 65 °C using poly(2-ethoxyethyl methacrylate) macroRAFT (continuous line), where $[\text{MacroRAFT}]_0/[\text{AIBN}]_0 = 5$; **(a)** $[\text{DMA}]_0/[\text{MacroRAFT}]_0 = 200$ **(i)** in scCO₂ at 8, 26 and 41% conversion and **(ii)** in solution (toluene) at 15, 28, 34 and 47% conversion, and **(b)** $[\text{DMA}]_0/[\text{MacroRAFT}]_0 = 400$ **(i)** in scCO₂ at 14, 21, 41 and 54% conversion and **(ii)** in solution (toluene) at 15, 26, 37 and 48% conversion.

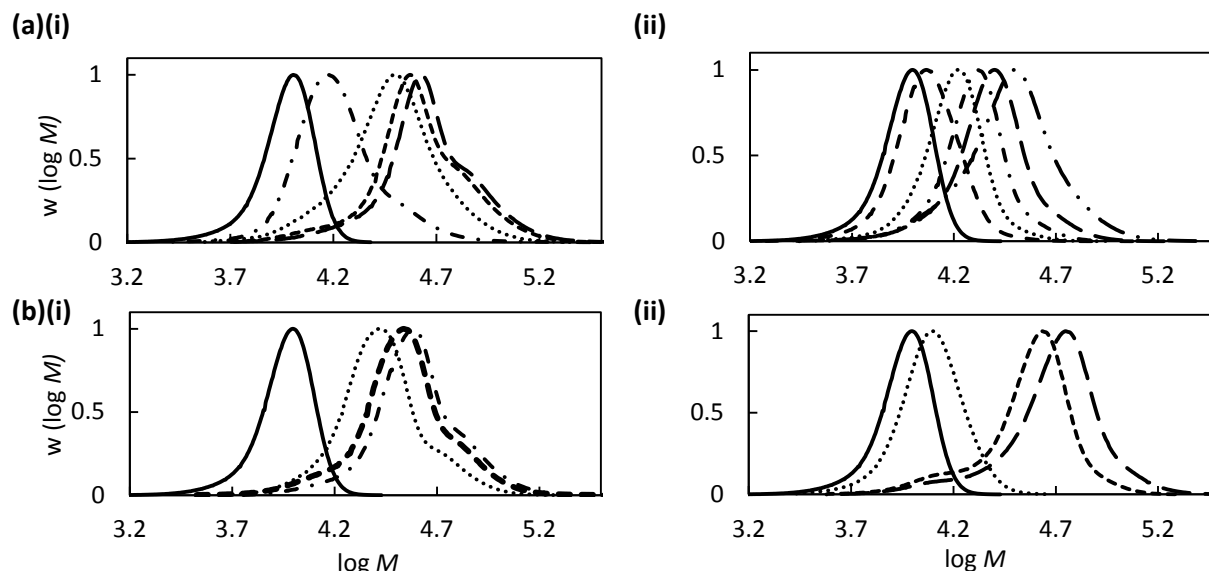


FIGURE 2 MWDs for polymerization mixtures of 4AM at 65 °C using poly(2-ethoxyethyl methacrylate) macroRAFT (continuous line), where $[\text{MacroRAFT}]_0/[\text{AIBN}]_0 = 5$; **(a)** $[\text{4AM}]_0/[\text{MacroRAFT}]_0 = 200$ **(i)** in scCO_2 at 21, 45, 70 and 87% conversion and **(ii)** in solution (toluene) at 11, 26, 31, 49 and 62% conversion, and **(b)** $[\text{4AM}]_0/[\text{MacroRAFT}]_0 = 400$ **(i)** in scCO_2 at 27, 35 and 64% conversion and **(ii)** in solution (toluene) at 10, 36 and 43% conversion.

It is noted that for DMA, M_n values tended to deviate to less than $M_{n,\text{th}}$ to a greater extent than for the RAFT of 4AM in scCO_2 reflecting a greater loss in control in comparison to 4AM. Overall, the fact that reasonable controlled/living character is observed indicates minimal macroRAFT partitioning into the continuous phase. Generally, decreasing the $[\text{MacroRAFT}]_0$ concentration by a factor of two (from $[\text{Monomer}]_0/[\text{MacroRAFT}]_0 = 200$ to 400) resulted in almost doubling of M_n .

Comparisons with Solution RAFT Polymerizations

The heterogeneous polymerizations described above were compared with homogeneous systems at the same temperature carried out in solutions of toluene, where the concentrations of AIBN, macroRAFT and monomer were the same as in the scCO_2 -reactor (based on the entire reactor volume) (Figure 3 and 4).

The polymerizations were significantly faster in solution than in scCO_2 (Figure 5) - polymerizations were about 4.5 and 1.5-2 times

faster in solution for DMA and 4AM, respectively. RAFT polymerization of hydrophobic monomers such as styrene in aqueous miniemulsions (*i.e.* another type of dispersed system) is typically markedly faster than the corresponding homogeneous system as a result of compartmentalization effects (segregation) on bimolecular termination.^{19,20} However in the present system, the particle size is significantly larger than in miniemulsions (~ 100 nm), and moreover, the monomer solubility in scCO_2 is much higher than that of hydrophobic monomers in water. As a consequence of the latter, significant monomer partitioning to the continuous phase would occur in the scCO_2 system, resulting in less monomer being available at the main locus of polymerization (the particles) and hence a reduction in polymerization rate. Overall, the influence of system heterogeneity on polymerization rate is complex, including also possible effects of initiator partitioning and the termination rate coefficient (k_t) being different in the two systems. A decrease in polymerization rate at the onset of

heterogeneity has previously been observed in RAFT dispersion polymerization in non-CO₂ systems (although the opposite may also occur depending on the particular system).^{21,22}

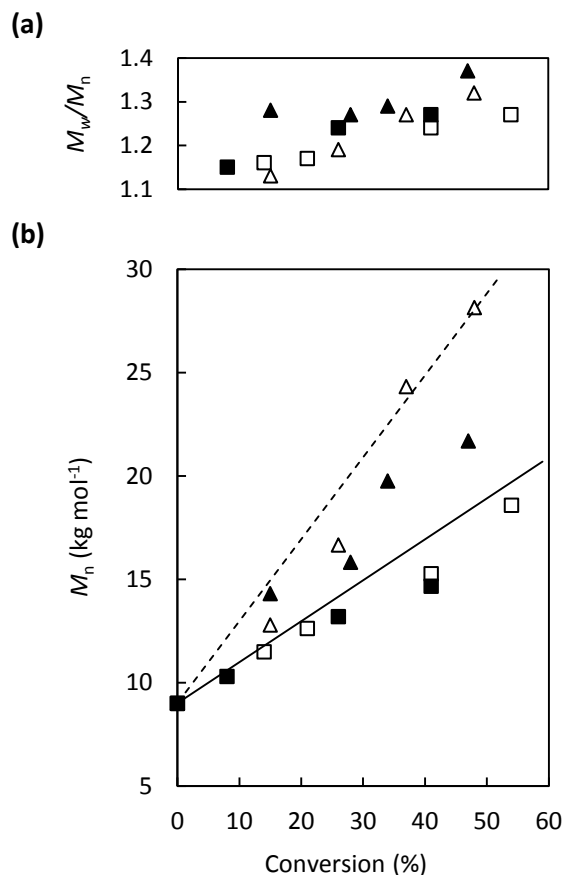


FIGURE 3 (a) M_w/M_n and (b) M_n versus conversion for polymerizations of DMA at 65 °C using poly(2-ethoxyethyl methacrylate) macroRAFT, where $[\text{MacroRAFT}]_0/[\text{AIBN}]_0 = 5$. Closed symbols are in scCO_2 and open symbols are in solution (toluene). Squares and triangles are $[\text{DMA}]_0/[\text{MacroRAFT}]_0 = 200$ and 400 with $M_{n,\text{th}}$ line full and dashed respectively.

The longer polymerization times in scCO_2 led to higher dispersities in comparison to the solution polymerizations due to the cumulative number of radicals generated from AIBN decomposition increasing with time (assuming no other radical side reactions, the number of termination events corresponds to half the number of radicals generated by AIBN). This is manifested as an increasing low MW tail with conversion as

well as¹⁸ prominent high MW shoulders at the highest conversions due to termination by coupling. In addition, it is possible that the heterogeneity of the system results in some broadening of the MWD due to different particles having different $[\text{monomer}]/[\text{RAFT}]$ ratios.

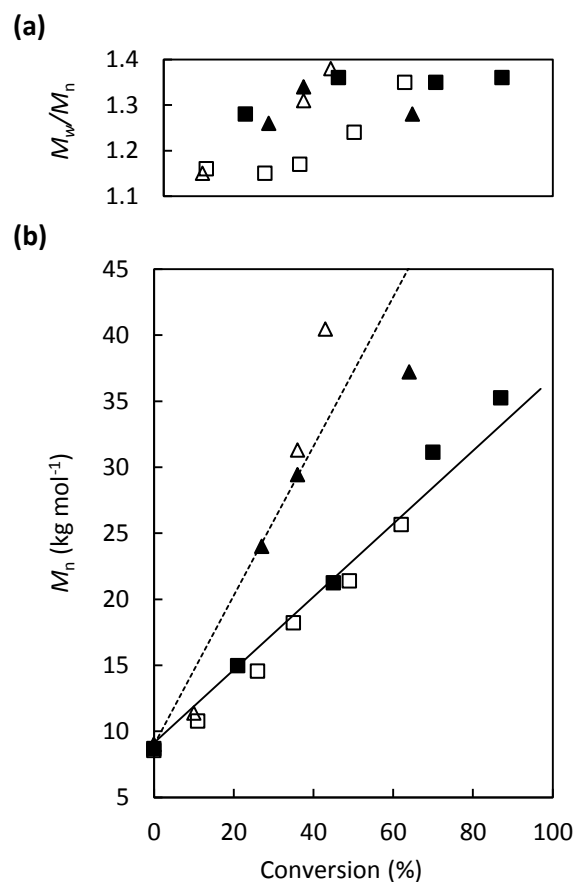


FIGURE 4 (a) M_w/M_n and (b) M_n versus conversion for polymerizations of 4AM at 65 °C using poly(2-ethoxyethyl methacrylate) macroRAFT, where $[\text{MacroRAFT}]_0/[\text{AIBN}]_0 = 5$. Closed symbols are in scCO_2 and open symbols are in solution (toluene). Squares and triangles are $[\text{4AM}]_0/[\text{MacroRAFT}]_0 = 200$ and 400 with $M_{n,\text{th}}$ line full and dashed respectively.

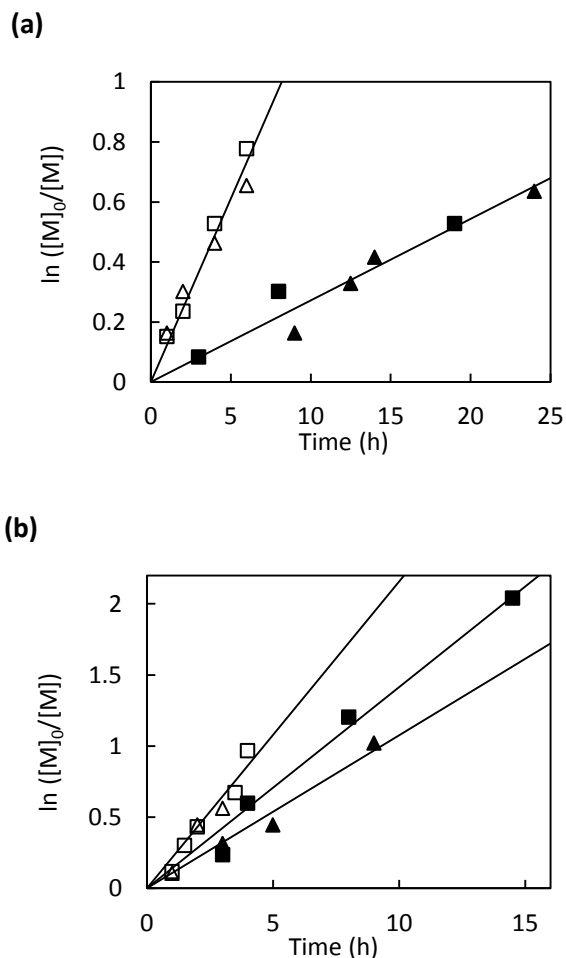


FIGURE 5 First order plots for polymerizations at 65 °C using poly(2-ethoxyethyl methacrylate) macroRAFT, where $[\text{MacroRAFT}]_0/[\text{AIBN}]_0 = 5$ in scCO_2 are closed symbols and in solution (toluene) are open symbols with squares and triangles are $[\text{Monomer}]_0/[\text{MacroRAFT}]_0 = 200$ and 400, respectively; **(a)** DMA and **(b)** 4AM. Lines are of best fit.

High Conversion RAFT Polymerizations in scCO_2

Given that polymerizations in scCO_2 of 4AM were 4-5 times faster than DMA, and that it took ~24 h to reach intermediate conversions with DMA, it was decided to only take polymerizations of 4AM to high conversion. The products of the RAFT polymerizations of 4AM taken to $\geq 70\%$ conversion in scCO_2 were isolated as powders upon venting of the CO_2 (Figure 6). The powders were repeatedly

washed with scCO_2 at 50 °C and 30 MPa in order to remove all traces of monomer (see Figure 7 for NMR of purified polymer). Thus the technique is suitable for large-scale synthesis of block copolymers without the requirement for toxic and hazardous volatile organic solvents. The SEM image of a sample of the powder reveals the formation of large irregularly shaped particles, which are similar to those obtained from precipitation NMP of styrene,²³ and inverse suspension polymerization NMP of *N*-isopropylacrylamide in scCO_2 ,⁵ although there are less prominent cavities from the expulsion of CO_2 present.

The MWDs for the RAFT polymerization of 4AM in scCO_2 at 70 and 87% conversions were somewhat broad (Figure 2; $M_w/M_n \sim 1.35$), but controlled/living character is evident and M_n remains close to theoretical values (Figure 4).

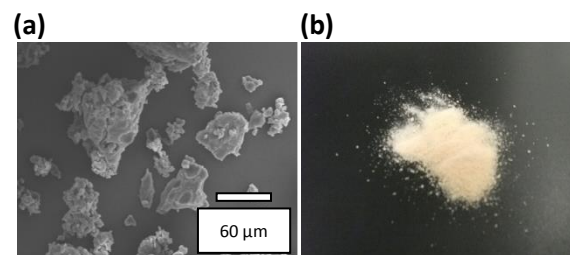


FIGURE 6 **(a)** SEM image and **(b)** optical image of poly(2-ethoxyethyl methacrylate)-*b*-poly(4AM) powder obtained at 70% conversion from the RAFT polymerization of 4AM in supercritical CO_2 .

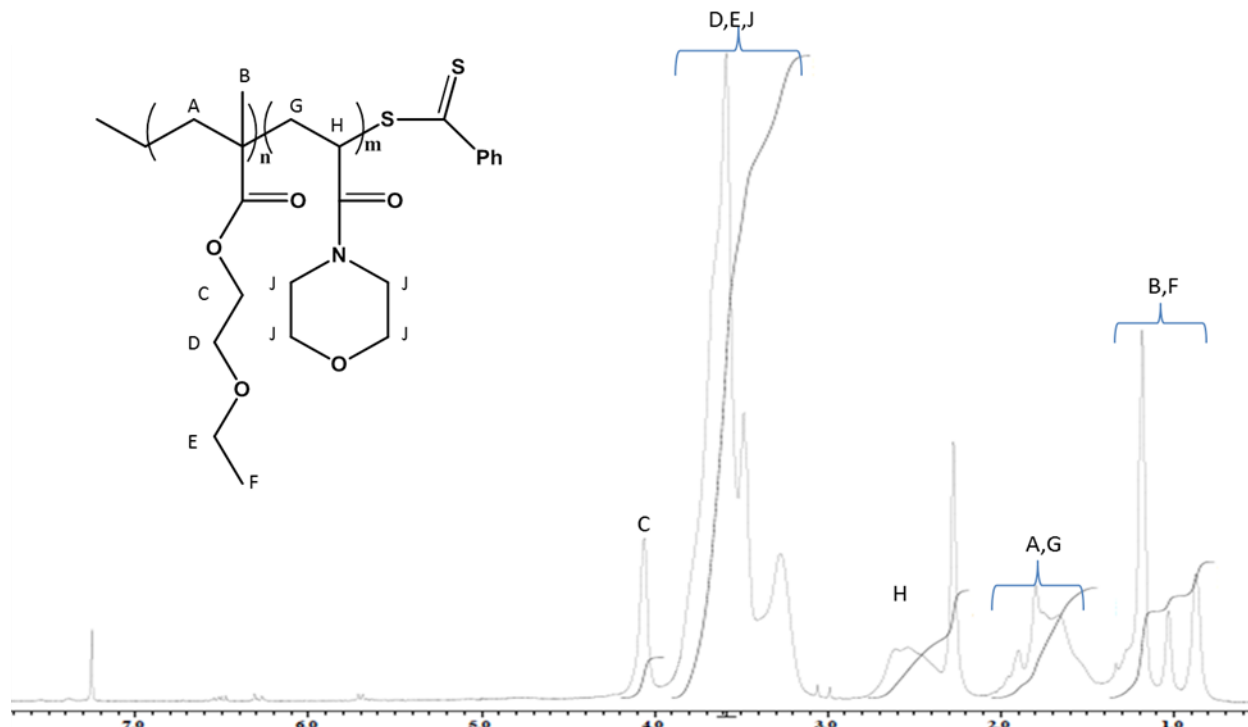


FIGURE 7 ^1H NMR (in CDCl_3) of poly(2-ethoxyethyl methacrylate)-*b*-poly(4AM) (polymer purity ~98%) purified by washing three times with scCO_2 . ^1H NMR spectra of the macroRAFT and poly(2-ethoxyethyl methacrylate)-*b*-poly(DMA) are provided in the Supporting Information.

CONCLUSIONS

Poly(2-ethoxyethyl methacrylate)-*b*-poly(acrylamide) polymers with important biotechnology applications are prepared using a new controlled/living heterogeneous polymerization technique in scCO_2 . This involves forming seed particles swollen with monomer by precipitation of the macroRAFT agent by the introduction of CO_2 . Despite the precipitation of the macroRAFT prior to polymerization, controlled/living character comparable to the equivalent solution system is achieved. The block copolymers of 4AM were isolated as powders at high conversions without the requirement for volatile organic solvents.

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GRAPHICAL ABSTRACT

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A new controlled/living heterogeneous polymerization technique in benign supercritical CO₂ is described involving the formation of monomer-swollen seed particles by precipitation of MacroRAFT agent prior to polymerization. The technique offers the large scale synthesis of poly(2-ethoxyethyl methacrylate)-*b*-poly(acrylamides) useful for biomedical applications, which can be isolated as powders at high conversion circumventing the requirement for volatile organic solvents.

