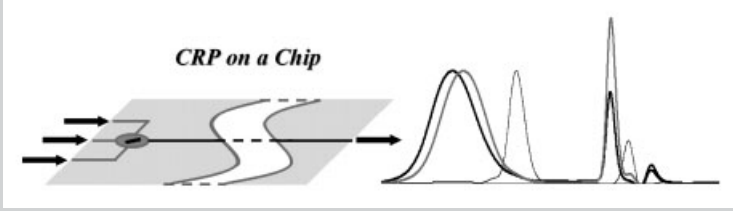
Summary: Block copolymers of poly(ethylene oxide-*block*-2-hydroxypropyl methacrylate) (PEO-*b*-PHPMA) with a range of molecular masses of the PHPMA block were obtained by controlled radical polymerization on a chip (CRP chip) using a PEO macroinitiator. A series of well-controlled polymerizations were carried out at different pumping rates or reaction times with a constant ratio of monomer to initiator. The stoichiometry of the reactants was also adjusted by varying relative flow rates to change the reactant concentrations.



A schematic of a CRP chip and SEC traces of the PEO-*b*-PHPMA produced from different pump rates with a 1:100 ratio of initiator to monomer. The dashed peaks are the macroinitiator, PEO-Br (left), and monomer, HPMA (right).

Block Copolymer PEO-*b*-PHPMA Synthesis Using Controlled Radical Polymerization on a Chip[a,b]

*Tao Wu, Ying Mei, Chang Xu, H. C. Michelle Byrd, Kathryn L. Beers**

Polymers Division, National Institute of Standards and Technology, 100 Bureau Dr., Gaithersburg, Maryland 20899, USA
Fax: (+1) 301-975-4924; E-mail: beers@nist.gov

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Introduction

The development of controlled/''living'' radical polymerization (CRP)[1,2] has greatly extended the ability to control polymer molecular masses and molecular mass distribution, and to obtain macromolecules with desired topology, composition, and functionalization. Among them, atom transfer radical polymerization (ATRP)[3–5] has been developed into one of the most versatile and robust synthetic tools. Its unique characteristics make the integration of the reaction within a microfluidic system appealing to produce small quantities of polymers for the high-throughput screening of new polymer syntheses and on-line correlation with property measurements.[6,7]

The integration of important chemical processes onto a microchip has attracted much attention from scientists and engineers[8,9] because of the potentially better control of reaction conditions, speed, smaller length scales, improved safety, and portability.[10] However, the application of microdevices to polymerization processes are still few[11,12] because of the aggressive solvents, temperatures, and pressures of macromolecular processing and purification. Manufacturing microfluidic devices from polymeric materials could provide the opportunity for carrying out microfluidic polymerization studies if they have good solvent resistance and are easily fabricated with a rapid prototyping technique[13,14] or other various techniques.[15–17] In recent work, we have demonstrated that a well-controlled polymerization of homopolymer could be obtained by controlled radical polymerization on a two-input chip (CRP chip).[18]

[a] Supporting information for this article is available at the bottom of the article's abstract page, which can be accessed from the journal's homepage at http://www.mrc-journal.de, or from the author.

[b] Contribution of the National Institute of Standards and Technology, not subject to copyright in the United States.

Here we report that two successful synthesis strategies could be applied with a three-input CRP chip. We demonstrate this simple yet powerful technique with the synthesis of block copolymers, poly(ethylene oxide-*block*-2-hydroxypropyl methacrylate) (PEO-*b*-PHPMA) with a range of molecular masses of the second block using a PEO macroinitiator as one of three input sources inside a microchannel. In one strategy, a series of well-controlled copolymerizations were carried out at different pumping rates or reaction times with a constant ratio of monomer to initiator. In the other strategy, the stoichiometry of the reactants was adjusted by varying the relative flow rate of each input to change the reactant concentrations for a series of polymerizations that had the same reaction time.

Experimental Part[c]

Materials

The thiolene-based optical adhesive NOA 81 was purchased from Norland Products. Poly(ethylene oxide) methyl ether (PEO-OH) ($\overline{M}_n$ 2 000 $g \cdot mol^{-1}$), 2-bromoisobutyryl bromide, anhydrous triethylamine, dichloromethane, 2-hydroxypropyl methacrylate (HPMA), 2,2′-bipyridine (bpy), copper(I) chloride (CuCl), methyl 2-bromopropionate (MBP), and methanol (MeOH) were all purchased from Aldrich and used as received. Deionized water was obtained from a Millipore Rios 16 system.

Microchannel Device Fabrication

The device was prepared as described previously.[14,18] One CRP device was prepared with three inputs, one output, and one mixer with a magnetic stir bar (460 μm ID × 3 mm). Two additional devices with only one input and one output were also prepared following a similar procedure and were used to increase the length of microchannel reactor. The three devices were connected with short Teflon tubing (OD 1.588 mm and ID 0.794 mm). The microchannel had a height of 500 μm and width of 600 μm. The round mixer unit had a 5 mm diameter. The total volume of the CRP chip microchannel was 750 μL.

Macroinitiator Synthesis

Macroinitiators were prepared by reaction of the terminal hydroxy group of the PEO-OH with a two-fold molar excess of 2-bromoisobutyryl bromide and triethylamine in dichloromethane according to the literature.[19,20] Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) experiments verified that the hydroxy end group of PEO-OH was fully converted into the alkyl bromide ester, denoted here as PEO-Br (see Supporting information).

[c] Equipment and instruments or materials are identified in the paper in order to adequately specify the experimental details. Such identification does not imply recommendation by NIST, nor does it imply the materials are necessarily the best available for the purpose.

Block Copolymer Synthesis in Microchannel

Water, HPMA, and MeOH were first purged separately with argon for 1 h. The catalyst (bpy and CuCl) and PEO-Br were degassed in separate flasks by three cycles of vacuum with argon backfill. Three solutions were prepared as listed in Table 1. The solutions were then drawn into three 10 mL syringes and mounted to syringe pumps as inputs, as shown in Figure 1.

Two series of polymerizations were carried out as described below.

Method 1: Constant Initiator Concentration Polymerizations

The three input solution pumping rates were identical during the experiments, therefore, the molar ratio of monomer/initiator/CuCl/bpy was held constant at 100:1:1:2 in the final, mixed solution. With different overall input pumping rates (solution residence time inside microchannel), products of different polymerization time could be obtained.

Method 2: Different Initiator Concentration Polymerizations

The two input pumping rates of the solutions containing initiator (a) and catalyst (b) were kept identical during the experiments. By changing their pumping rate relative to that of solution (c) containing HPMA and solvent only, we obtained reaction mixtures with different concentrations of catalyst and initiator. A total flow rate of 450 $\mu L \cdot h^{-1}$ was maintained by adjusting the relative pumping rates, preserving the same residence time of the reaction solution inside the microchannel, or the same polymerization time of 100 min.

Constant stirring of a micro-stir bar embedded inside the microchannel ensures complete mixing after the three solutions converge at the beginning of the microchannel reactor. In order to obtain enough product for conventional analysis, we collected steady state samples at every pumping condition for extended times. The reaction solution ran directly into air-saturated ethanol to terminate the polymerization. At each fixed pumping condition, about 1 mL of polymer solution was collected for analysis purposes after reaching a steady state. An aliquot of the solution was reserved for nuclear magnetic resonance (NMR) spectroscopy analysis and the remaining material was filtered through alumina to remove the catalyst. The solvent was allowed to evaporate prior to dilution in tetrahydrofuran (THF) for analysis by size exclusion chromatography (SEC). The polymer products were characterized without further precipitation or purification in order to avoid any fractionation or other artificial modification of the resulting product. Conversions were determined from NMR spectra by comparing monomer vinyl proton signals at 5.5 and 6.0 ppm and methyl signals at 1.0 and 1.9 ppm from the reacted and unreacted methacrylate, respectively. The number-average relative molecular mass ($\overline{M}_{n,NMR}$) of the polymers was determined from conversion, rather than the relative signal intensities from the two block segments, because of overlap of the PEO block methylene signal at δ 3.5 with the solvent ethanol peak. The standard uncertainty for both SEC and NMR results is within 5%.

Table 1. Solution composition of input sources for PEO-*b*-PHPMA synthesis in a CRP chip.

Solution	Composition		
a	PEO-Br (2.384 g)	HPMA (5 mL)	water/MeOH (50/50)[a] (5 mL)
b	CuCl (0.110 g) + bpy (0.346 g)	HPMA (5 mL)	water/MeOH (50/50)[a] (5 mL)
c		HPMA (5 mL)	water/MeOH (50/50)[a] (5 mL)

[a] Volume fraction.

Batch Block Copolymer Synthesis

To enable comparison with the microchannel polymerization, the block copolymerization of PEO-*b*-HPMA was also performed in a flask reactor. As described earlier, water, HPMA, and MeOH were first purged with argon. Catalyst (bpy, 0.2309 g and CuCl, 0.0732 g) and PEO-Br (1.589 g) in separate flasks were degassed by three cycles of vacuum with argon backfill. Water (2 mL) and MeOH (2 mL) were added into the PEO-Br flask, and HPMA (10 mL), water (3 mL), and MeOH (3 mL) were separately added into the catalyst flask. After both solutions became homogeneous, the PEO-Br solution was quickly withdrawn and added into the catalyst solution to start the reaction. The molar ratio of monomer/initiator/CuCl/bpy in the final solution was 100:1:1:2. During the polymerization, 2 mL of the solution was taken at different times and diluted into 5 mL air-saturated ethanol to terminate the reaction. For comparison with the microchannel reaction, samples for NMR and SEC analysis were prepared following the same procedure as described above. The reaction conversion and relative molecular mass were determined using NMR results. SEC was used to determine the polydispersity of the polymer products.

Characterization

^{1}H NMR spectra were recorded on a JEOL 270 MHz spectrometer with a relaxation delay of 20 s and 32 scans of 16 384 data points and a spectroscopic width of 15 ppm. SEC were obtained using a system from Waters Technologies (Milford, MA) equipped with a 1515 isocratic HPLC pump with online degassing, 717 Plus autosampler, 2414 refractive index detector, a guard column, and two mixed bed columns (Waters HR4 and HR4E) with 5 μm particle size. The HR4 is specified for the molar mass separation range of 5 000 to 600 000 $g \cdot mol^{-1}$ and the HRE4 a 50 to 100 000 $g \cdot mol^{-1}$ range. The separation was performed in THF at a 1 $mL \cdot min^{-1}$ nominal flow rate at 30 °C with a sample concentration of 5 $mg \cdot mL^{-1}$ and injection volume of 20 μL. The columns were calibrated by a series of narrow polydispersity polystyrene standards.

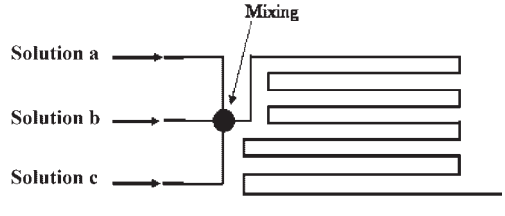

Figure 1. Schematic of the mask used to fabricate the chip for microchannel block copolymerization (the three solution compositions are shown in Table 1. The channel cross-section dimension is 500 μm deep and 600 μm wide).

Results and Discussion

Method 1: Constant Initiator Concentration Polymerizations

A series of microchannel copolymerizations were performed by changing the three solution pumping rates identically. SEC data for PEO-*b*-PHPMA is shown in Figure 2. As the reaction progresses, the macroinitiator peak disappears, which suggests quantitative initiation of the macroinitiator. The polymer peak shifts to shorter elution times as the pumping rate decreases and reaction time increases, corresponding with the expected decrease in the monomer peak because of the higher monomer conversion. All polymer products show symmetric monomodal traces and relatively low polydispersities, 1.17 to 1.24 (Table 2).

Because the three syringe barrels were being discharged into the channel at the same rate, the total solution flow rate is three times larger than the pump rate. Using the channel

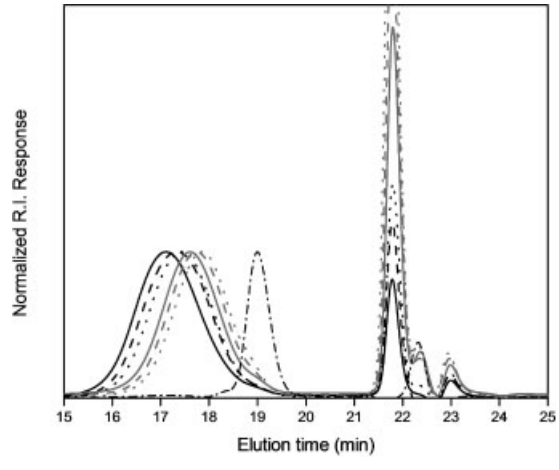

Figure 2. SEC traces of PEO-*b*-PHPMA produced in a CRP chip from different pump rates with a 1:100 ratio of initiator to monomer. Traces are normalized to the polymer peaks for clarity. Copolymer peaks from left to right correspond to single pump rates of 80, 150, 240, 350, 500, and 750 $\mu L \cdot h^{-1}$. The peak at 19 min is the macroinitiator, PEO-Br, and just below 22 min is the monomer, HPMA.

Table 2. Results for PEO-*b*-PHPMA synthesis on a chip with different pumping rates and reaction times.[a)]

Pump rate	Total flow rate	Reaction Time	Conv.	$\bar{M}_{n,NMR}$	$\bar{M}_{n,GPC}$	PDI ($\bar{M}_w/\bar{M}_n$)	HPMA block mass fraction
$\mu L \cdot h^{-1}$	$\mu L \cdot h^{-1}$	min		$g \cdot mol^{-1}$	$g \cdot mol^{-1}$		
80	240	188	0.69	12 100	10 200	1.24	0.83
110	330	136	0.65	11 500	9 400	1.24	0.82
150	450	100	0.64	11 400	9 100	1.22	0.82
190	570	79	0.59	10 600	8 900	1.24	0.80
240	720	63	0.56	10 200	8 600	1.22	0.79
350	1 050	45	0.49	9 200	7 000	1.19	0.77
500	1 500	31	0.41	8 000	6 500	1.19	0.74
600	1 800	26	0.37	7 500	6 500	1.17	0.72
750	2 250	21	0.30	6 500	6 100	1.17	0.68
1 000	3 000	16	0.27	6 100	5 600	1.18	0.65

[a)] PEO-Br had a $\bar{M}_n$ value of 2 150 and 2 904, determined by MALDI-MS and GPC, respectively, and a PDI of 1.02.

volume (750 μL) and the pump speed, reaction times were calculated based on the residence time in the channel (Table 1). As the pumping rate increased, the residence time of the solution inside the microchannel, or polymerization time, decreased along with the length and weight fraction of the HPMA block. Hence, with the CRP chip we simply control the copolymerization time by adjusting the pumping rate. Using rational design, a certain length of HPMA block or mass fraction of HPMA in PEO-*b*-PHPMA is produced by setting the three pumps at certain rates.

In principle, with this method polymer products at different pumping rates are the same as the polymers produced at different reaction times with a traditional batch reaction, since both reactions start with constant reactant concentrations. For comparison, we performed a batch polymerization of PEO-*b*-PHPMA with the molar ratio of monomer/PEO-Br/CuCl/bpy in solution as 100:1:1:2, which is the same as the final mixed solution in the microchannel polymerization. A series of samples were taken out at 10, 20, 30, 40, 60, 90, 150, and 210 min. More information on the reactions carried out in a flask can be found in the Supporting information.

For comparison, we plotted the $\ln([M]_0/[M])$, where $[M]_0$ and [M] are the initial and time-dependent monomer concentrations, respectively, and polydispersity of polymer products versus time for the ATRP of PEO-*b*-PHPMA in the microchannel and batch reactor in Figure 3. From the kinetic data of $\ln([M]_0/[M])$ versus time, we found that the reaction proceeded with a similar trend by both methods. Both polymerizations show a fast (apparent) initial rate, followed by slowing of the reaction. Interestingly, the block copolymerization in the batch reactor has a slightly faster initial rate, exhibiting higher conversions at shorter reaction times than that in the microchannel reaction with short residence time. At longer reaction times, the reaction rate for the batch reactor decelerates more quickly and reaches lower conversion than that of the microchannel reaction. The polydispersities of polymers produced from the two reactors were similar. As the conversion increases, the relative molecular mass distribution broadens to around 1.25. Therefore, we believe that the ATRP of HPMA from a macroinitiator, PEO-Br, inside a microchannel is as well controlled as that by traditional ATRP in a flask reactor, if not better. The polymerization on a chip shows a more stable apparent rate and preliminary results suggest that reactions will reach higher conversion. This may be the result of diffusion-limited reaction kinetics in the chip, however, more experiments are necessary to establish this.

Method 2: Different Initiator Concentration Polymerizations

A series of polymerizations with different initiator concentrations but constant reaction time were performed by keeping the total flow rate fixed at 450 $\mu L \cdot h^{-1}$, as shown in Table 3. Since the total microchannel volume is 750 μL, the residence time inside the microchannel or polymerization time is 100 min. The monomer conversion varies from 0.47 to 0.81. For the same reaction time, polymerization with a lower initiator concentration or higher ratio of monomer to initiator has a lower conversion. Still, the molecular mass of

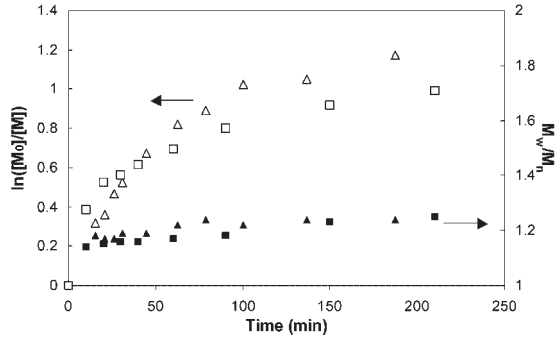

Figure 3. Comparison of kinetic data $\ln([M]_0/[M])$ (open symbols) and polydispersity (solid symbols) of PEO-*b*-PHPMA synthesis in a CRP chip (triangles) and in a flask (squares). The molar ratio of monomer/initiator/CuCl/bpy in the initial reaction solution was 100:1:1:2.

Table 3. CRP chip synthesis of PEO-*b*-PHPMA with different initiator concentrations at a total pumping rate of 450 $\mu L \cdot h^{-1}$ or 100 min reaction time.

Solution a	Solution b	Solution c	[M]/[I][a)]	Conversion (NMR)	$\bar{M}_{n,NMR}$	$\bar{M}_{n,GPC}$	PDI ($\bar{M}_w/\bar{M}_n$)	HPMA block mass fraction
$\mu L \cdot h^{-1}$	$\mu L \cdot h^{-1}$	$\mu L \cdot h^{-1}$			$g \cdot mol^{-1}$	$g \cdot mol^{-1}$		
190	190	70	39	0.76	6 500	6 900	1.27	0.68
170	170	110	44	0.81	7 300	7 700	1.2	0.71
150	150	150	50	0.74	7 400	8 000	1.24	0.72
130	130	190	58	0.72	8 100	8 100	1.26	0.74
110	110	230	68	0.70	9 000	8 100	1.31	0.77
90	90	270	83	0.67	10 200	9 400	1.22	0.79
70	70	310	107	0.55	10 600	9 000	1.29	0.80
60	60	330	131	0.51	11 700	9 400	1.22	0.82
50	50	350	150	0.47	12 200	9 700	1.26	0.83

[a)][M] monomer concentration; [I] initiator concentration.

the polymer product increases as the initiator concentration decreases.

Selected SEC data for this series of polymers are shown in Figure 4, which were normalized with the polymer peaks. The polymer elution time shifts to shorter time or high relative molecular mass as the ratio of monomer to initiator increases. Different from previous traditional studies, the monomer peak increases or conversion decreases as the polymer peak shifts to higher relative molecular mass. Again, we can calculate the mass fraction of the HPMA block in the copolymers, which were synthesized with polymerization method 2. As listed in Table 3, the HPMA block mass fraction was a function of initial ratio of monomer to initiator. It shows that for identical polymerization times the copolymer has a higher weight fraction of HPMA or longer HPMA block with the larger ratio of initial monomer to initiator. Therefore, with the CRP chip, we have a second easy method for rational design and tunabiltiy in the composition or architecture of block copolymers.

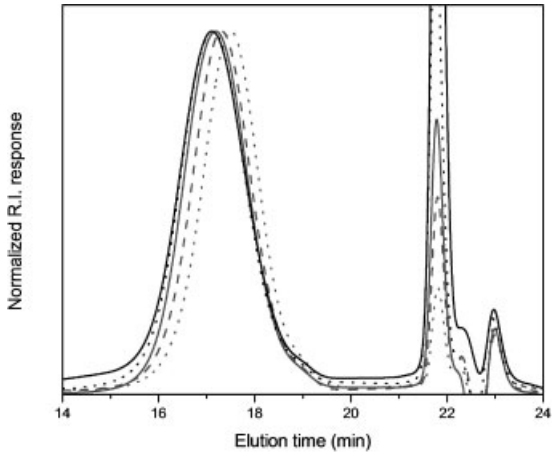

Figure 4. SEC traces of PEO-*b*-PHPMA produced from different initiator/catalyst concentration with the same polymerization time (100 min). Traces are normalized to the polymer peaks for clarity. Different lines represent copolymers synthesized with different monomer-to-initiator ratios. [Solid black line is 150:1, black dotted line is 107:1, gray solid line is 83:1, gray dashed line is 58:1, gray dotted line is 44:1] (the sequence of monomer peaks is also from top to bottom).

Conclusion

We demonstrate two strategies for the block copolymer synthesis of PEO-*b*-PHPMA using a three-input CRP chip. One method kept the three solution pumping rates equal during the experiments, so the reagent concentrations were held constant in the final mixed solution. Polymerizations with different reaction time were achieved by changing the three pumping rates together. The mass fraction of HPMA block in the obtained copolymer changed with the total flow rate or polymerization time. The second method kept the pumping rates of solutions containing macroinitiator and catalyst equal during the polymerization. By changing their pumping rate relative to the pumping rate of the solution containing monomer and solvent only, a series of polymerizations with varying stoichiometry were obtained, where initiator and catalyst concentration remain equal but vary relative to monomer concentration. The resulting copolymer had a higher weight fraction of HPMA or longer HPMA block with lower initiator concentration when the polymerization time was held constant. All SEC traces of polymer products showed symmetric traces with low polydispersities, which suggested a low rate of irreversible termination during the microchannel polymerization. The disappearance of the macroinitiator peak in the SEC traces of block copolymers also suggests that there was quantitative initiation during the polymerization. Traditional batch polymerization of PEO-*b*-PHPMA under the same conditions was compared with the microchannel polymerization. The kinetic behavior of ATRP and the polydisperisities of polymer products from the two different reaction methods were similar to each other. Results demonstrate that the CRP chip is an easy and convenient tool for block copolymer library synthesis.

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