Electronic Supplementary Material (ESI) for Chemical Science.

Supporting information

From monomer to micelle: A facile approach in the multi-step synthesis of block copolymers via inline purification

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Contents

Materials

Chemicals

The monomers methyl methacrylate (MMA, 99% Merck), butyl acrylate (BA, 99% Merck) and poly(ethylene glycol) methyl ether acrylate (PEGMEA, M_n 480, Sigma-Aldrich) were deinhibited over a column of activated basic alumina before use. 2-(Dodecylthiocarbonothioylthio)propionic acid (DOPAT) was synthesized according to the literature.[1] The reagents and chemicals used to synthesize DOPAT were purchased from Sigma Aldrich or VWR. 4-Cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl]pentanoic acid (CDP-TTC, 97% Boron Molecular) was used as received. 1,1'-azobis(isobutyronitrile) (AIBN, 98% Sigma-Aldrich) was recrystallized twice from methanol before use. Dimethyl sulfoxide (DMSO, Merck) and 2-butanol (Sigma-Aldrich) were used as received.

Reactor Setup

A Gastight syringe (100MR-LL-GT 10ML, SGE) and syringe pumps (Fusion 100, Chemyx) were used to feed the reactor mixture to the flow reactor. PFA tubing (1/16" x 0.5 mm ID) was used for all flow segments of the setup. A peristaltic pump (SF-10, Vapourtec) is placed in the dialysis loop and regulates the flow during the dialysis. The solvent flow into the dialysis block was controlled by an HPLC pump (Knauer Azura P 2.1S). A 6-port switch valve (VICI VALCO EUDA-C6W) managed the switch from polymerization to purification and vice versa.

	IDEX XP-230	Flangeless Fitting Natural, PEEK, 1/4- 28 Flat-Bottom, for 1/16" OD
	IDEX F-120	One-Piece Fingertight 10-32 Coned, for 1/16" OD Natural
	IDEX P-628	Luer Adapter Female Luer x Female 1/4-28 Flat Bottom, TefzelTM (ETFE) Natural
	IDEX P-702	Union Assembly PEEK .020 thru-hole, for 1/16" OD"

	IDEX P-512	Y Assembly PEEK 1/4-28 .020in
	IDEX U-466	High Pressure Mixing Tee UHMWPE Frit 10um
	CV-3340	Check Valve Inline Non-Metallic 10-32

Table S1: Overview of flow parts used in the setup

Characterization

Inline NMR reaction monitoring was accomplished by recording ^1H spectra (acquisition bandwidth 5 kHz: 83 ppm; 90 pulse width: 7 microseconds; dwell time: 200 microseconds; time: 6.554 seconds; repetition time: 60 seconds) using a low field benchtop 60 MHz NMR (Magritek, Spinsolve 1.19.0). A Powershim (40 min) was performed before the dialysis. The reaction monitor protocol (RMX) was used for data acquisition. All spectra were auto-phased in the Spinsolve software before analysis.

PSS SECcurity2 GPC systems operated by PSS WinGPC software, equipped with an SDV 5.0 µm guard column (50 x 8 mm), followed by three SDV analytical 5.0 µm columns with varying porosity (1000 Å, 100000 Å, and 1000000 Å) (50 x 8 mm) and a differential refractive index three detectors using THF as the eluent at 40 ˚C with a flow rate of 1 $mL\cdot min^{-1}$. The GPC system was calibrated using linear narrow polystyrene standards from PSS Laboratories ranging from 682 to 2.52×10^6 $g.mol^{-1}$ PS ($K = 14.1 \times 10^{-5}$ $dL\cdot g^{-1}$and $\alpha = 0.70$). Molar masses of the PMMA samples were determined by universal calibration using Mark-Houwink-Sakurada (MHS) parameters for PMMA reported literature values ($K = 12.9 \times 10^{-5}$ $dL\cdot g^{-1}$ and $\alpha = 0.68$).

DLS was used to measure the hydrodynamic diameter. The particle size of the micelles was analyzed by DLS using the Litesizer™ 500 under the following conditions (Sidescatter at wavelength 658 nm, particle absorption coefficient 0.01, particle refractive index 1.5850, water refractive index 1.33). To measure the particle size, a volume of 2 ml of the block copolymer solution in deionized water (DI H2O) was placed in a polystyrene cuvette and measured at 25°C.

Electrospray ionization mass spectrometry (ESI-MS): ESI-MS Analysis was carried out at the Monash Analytical Platform, Australia (School of Chemistry, Monash University). From each sample 1 mg was dissolved in 1 mL THF (THF, HPLC grade). The THF solution was diluted (±100 times) by adding 1 drop to a 1 mL mixture of THF:methanol (MeOH) (THF:MeOH = 3:2 v/v). This mixture was infused via a Kd Scientific infusion pump at a static flow rate of 300 mL/h into the MS. The MS setup was as follows: Agilent 6220 time-of-flight mass spectrometry (Q-TOF MS) system (Santa Clara, CA, USA). The MS was operated in positive mode using the following conditions: nebulizer pressure 35 psi, gas flowrate 8 L·min-1, gas temperature 300 °C, vaporizer temperature 250 °C, capillary voltage 250 V, fragmentor 150 V and skimmer 65 V. Instrument was operated in the extended dynamic range mode with data collected in m/z range 200–3000. Spectra were recorded over a 1-minute time period with 1 scan/s and subsequently averaged out before analysis. Spectra were analysed with Agilent Masshunter Qualitative Analysis B.07.00.

Dialysis block design

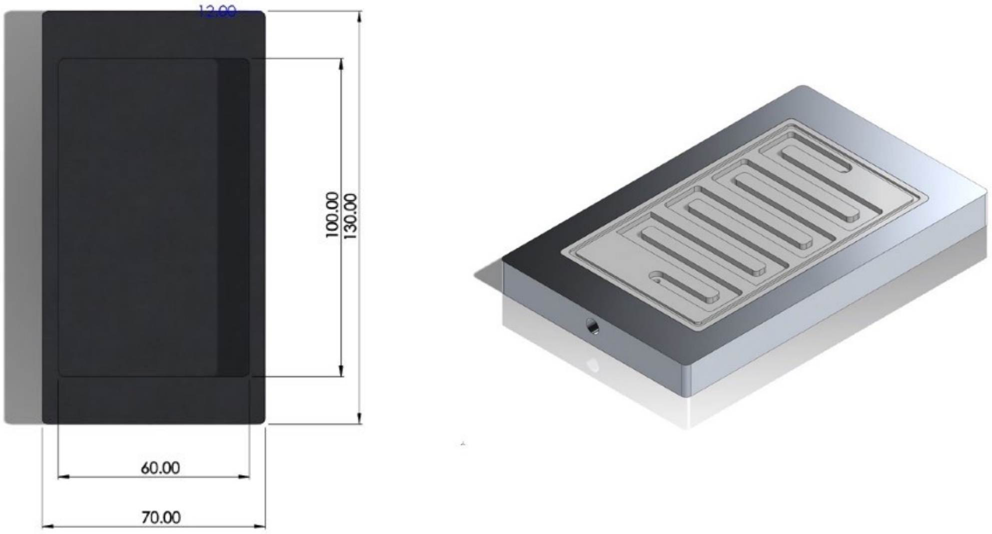


Figure S1: Schematic representation of the dialysis block.

Flat-bottom connectors can be connected to the inlet and outlet of the dialysis block. The channels are very shallow, 1mm in depth. This enhances the contact area between the polymer mixture and the solvent and, therefore, the rate of dialysis. The zig-zag structure enhances the turbulence in the reaction solution. This is important to promote the contact area even further. The monomer that crosses over the membrane will leave a void. Mixing the polymer mixture is essential to fill this void with more monomers close to the membrane to promote dialysis.

Reactor Setup

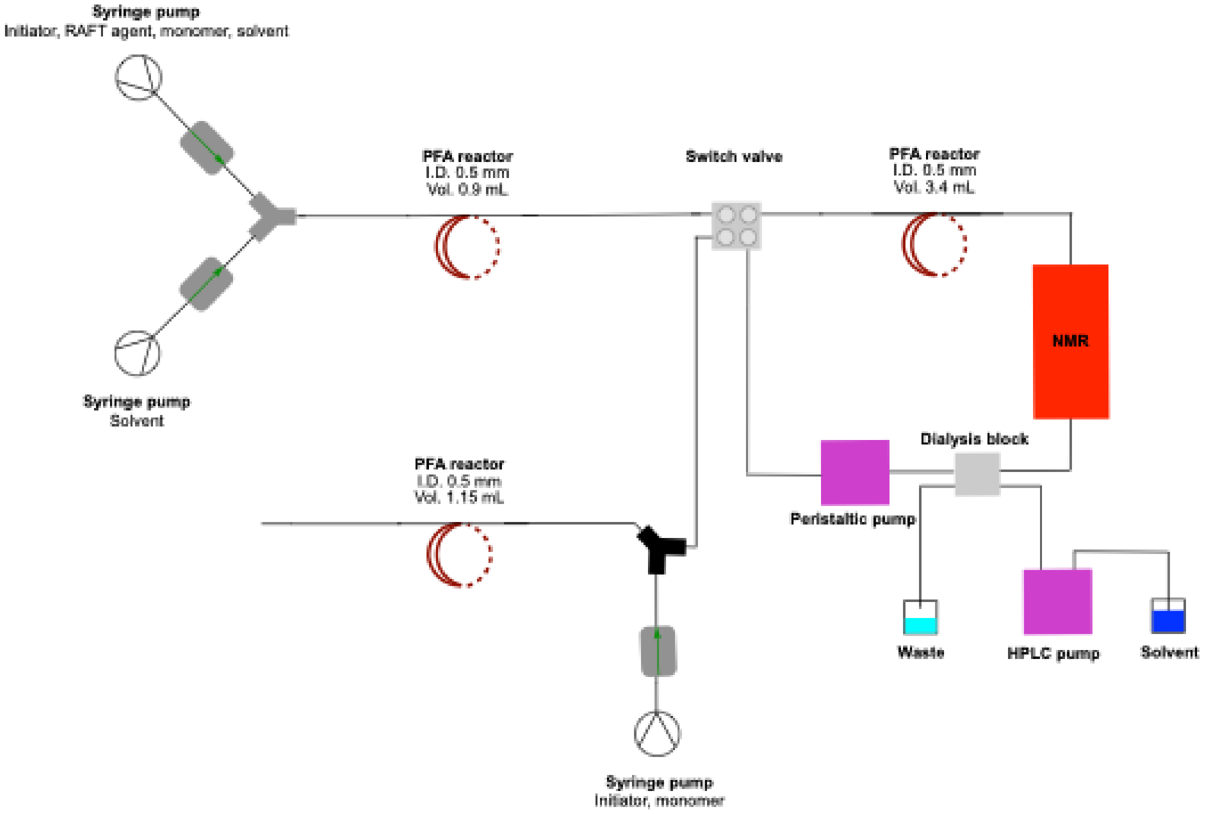


Figure S2: Dialysis platform. The NMR is connected to a PC for data acquisition and analysis via RMX.

Reaction solutions were transferred to a 10 mL gastight syringe and placed in the holder of the syringe pump. The syringe pump delivered the reagent solution to the flow reactor ($V_{reactor}$ = 0.9 mL), which was placed in an isothermal oil bath (90°C). This reactor was illuminated with blue light (450 nm) for MMA. The outlet of the reactor was connected to a switch valve. (Figure S3) The stream out of the first reactor was sent to the dialysis loop, containing the inline NMR, dialysis block and peristaltic pump. The switch valve is activated when the loop is filled, and the dialysis loop runs independently with the peristaltic pump. After the dialysis is completed, the switch valve switches back, and the purified macroRAFT can be used in the second reactor. Fresh initiator and monomer are also added via another syringe pump.

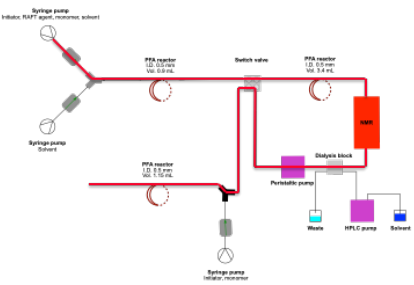
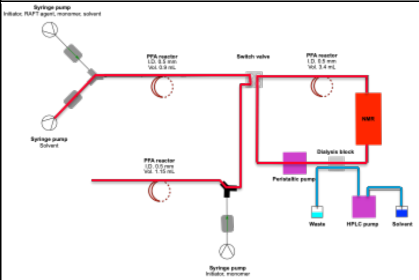
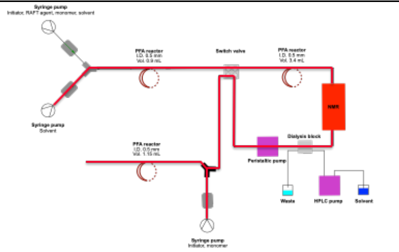
	Step 1	First, homopolymers are made via RAFT polymerization. After that, the dialysis loop is filled with the reaction mixture. The dialysis loop is overfilled, and waste is sent to reactor two, which is cleaned in step 2. **Pumps activated:** Syringe pump 1, peristaltic pump **Switch valve:** A **NMR:** off
	Step 2	A dialysis loop is created. HPLC pump provides fresh solvent to the dialysis block. A syringe pump with solvent cleans the reactors. **Pumps activated:** Syringe pump 2, peristaltic pump, HPLC pump **Switch valve:** B **NMR:** on
	Step 3	MacroRAFT purification is carried out. The reaction mixture is sent to the second reactor for block copolymerization. **Pumps activated:** Syringe pump 2-3, peristaltic pump **Switch valve:** A **NMR:** off

Table S2: Different steps in the dialysis setup

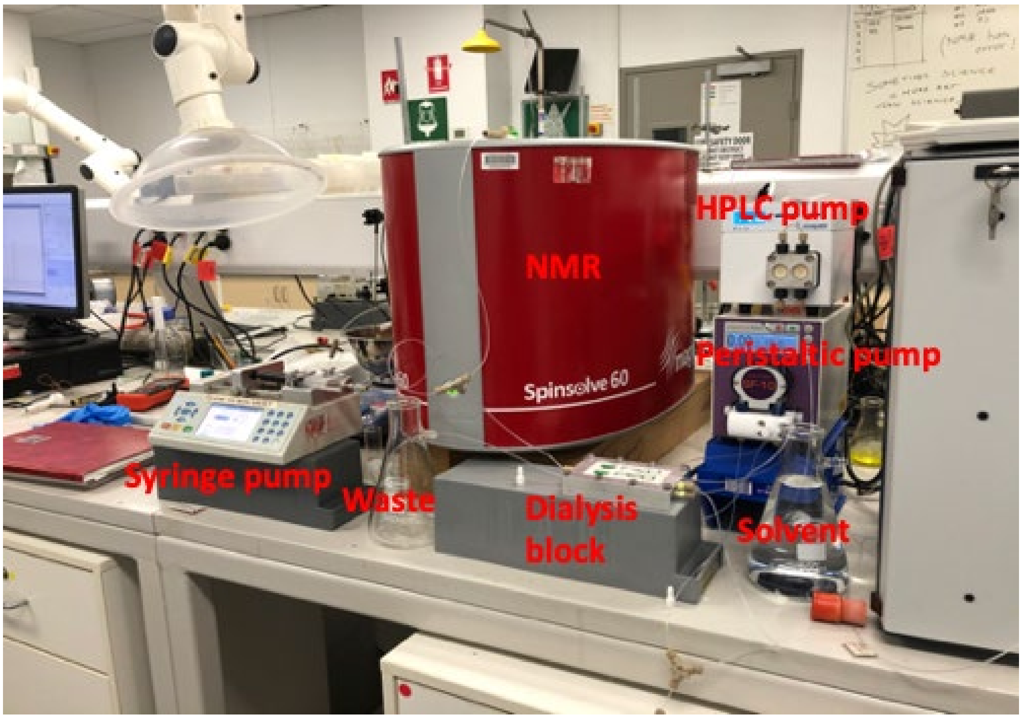


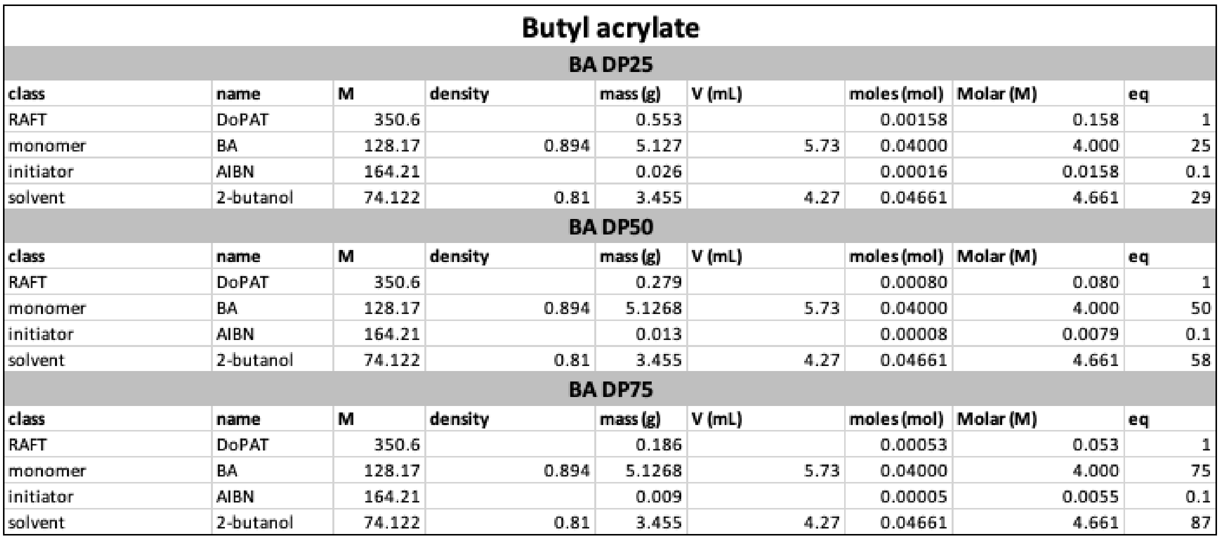
Figure S3: Dialysis platform in the lab

Polymerization procedures

Butyl acrylate (first block)

Experimental procedure.

In a typical procedure, the RAFT-agent DOPAT (0.5 mmol, 1 eq.), the thermal initiator AIBN (0.05 mmol, 0.1 eq), butyl acrylate (40 mmol, 50 eq.) and the solvent 2-butanol (4.27 mL) were added in a glass vial. The different ratios [monomer]:[DOPAT] (DP) were 25, 50 and 75, and the concentration of AIBN was set to 0.1 eq. (See Table S3). The glass vial was sealed with a rubber septum, and the solution was purged with nitrogen (argon) for 20 minutes. Next, the reaction solution was transferred to a 10 mL gastight syringe, prepurged with argon (3x), and placed in the holder of the syringe pump. The flow reactor was manually flushed with 2-butanol before each new reaction. All reactions were performed at 90 ^{0}C.



Butyl acrylate

BA DP25

class	name	M	density	mass (g)	V (mL)	moles (mol)	Molar (M)	eq
RAFT	DoPAT	350.6		0.553		0.00158	0.158	1
monomer	BA	128.17	0.894	5.127	5.73	0.04000	4.000	25
initiator	AIBN	164.21		0.026		0.00016	0.0158	0.1
solvent	2-butanol	74.122	0.81	3.455	4.27	0.04661	4.661	29

BA DP50

class	name	M	density	mass (g)	V (mL)	moles (mol)	Molar (M)	eq
RAFT	DoPAT	350.6		0.279		0.00080	0.080	1
monomer	BA	128.17	0.894	5.1268	5.73	0.04000	4.000	50
initiator	AIBN	164.21		0.013		0.00008	0.0079	0.1
solvent	2-butanol	74.122	0.81	3.455	4.27	0.04661	4.661	58

BA DP75

class	name	M	density	mass (g)	V (mL)	moles (mol)	Molar (M)	eq
RAFT	DoPAT	350.6		0.186		0.00053	0.053	1
monomer	BA	128.17	0.894	5.1268	5.73	0.04000	4.000	75
initiator	AIBN	164.21		0.009		0.00005	0.0055	0.1
solvent	2-butanol	74.122	0.81	3.455	4.27	0.04661	4.661	87

Table S3: Reaction solutions for the first block with butyl acrylate

Methyl methacrylate (first block)

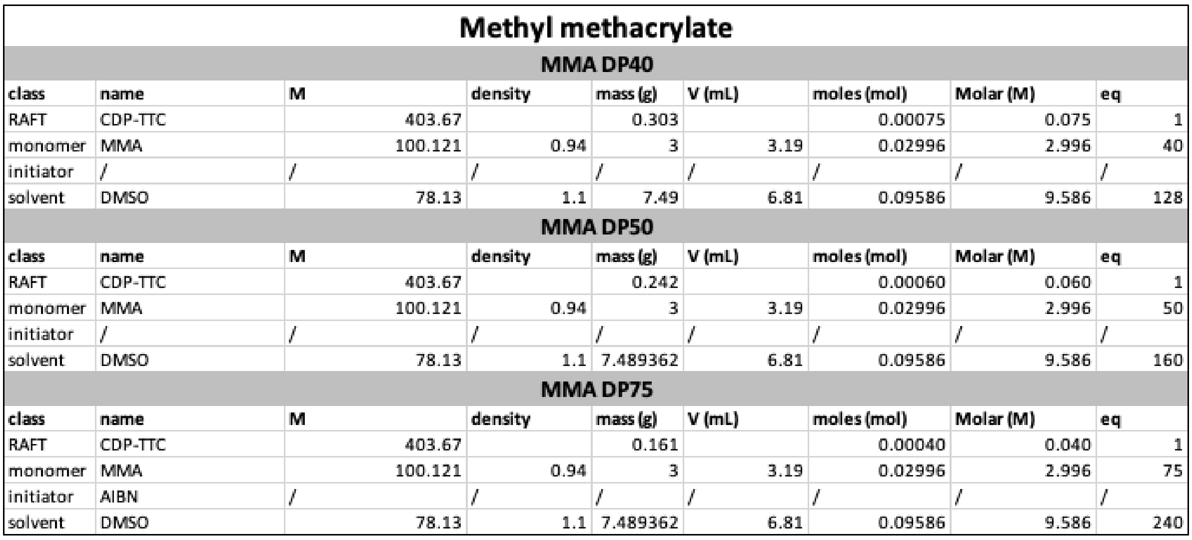
The tubular reactor setup

The reactor consists of PFA tubing (1/16'' OD, 0.75 mm ID) wrapped around a glass framework and placed in an oil bath heated up to 90 ^{0}C on an IKA stirrer hot plate. The blue light LEDs connected with the programmable variable DC power supply unit are placed inside the glass framework. The intensity of blue light is measured using an optical power meter. (Model-

S401C, Pmax- 1W, Wave- 0.19-20 µm, ThorLabs). Reactor volumes could easily be adapted by varying the length of the reactor tubing. Reaction solutions are pumped into the reactor via a Fusion 100 classic syringe pump, using 10 mL SGE gastight syringes flushed with N2. In a typical procedure, the monomer, photo-iniferter-agent, and solvent were added to a glass vial. The glass vial was sealed with a rubber septum, and the solution was purged with nitrogen (N2) for 5 minutes. Next, the reaction solution was transferred to a 10 mL gastight syringe (Trajan Scientific), preflushed with N2, and placed in the holder of the syringe pumps. For the photothermal iniferter polymerization, no need for any thermal initiator like AIBN. A 0.9 mL tubular reactor is employed for the polymerization at a temperature of 90 °C under illumination with blue light (450 nm).

Experimental procedure.

The monomer MMA (3 M, 30 mmol, 3 g, 40 equiv.) and the photoRAFT agent CDP-TTC (0.75 mmol, 0.303 g, 1 equiv.) were dissolved in DMSO and passed N2 for 5 min. The solution was then transferred to a gastight syringe and placed in the syringe pump holder. The photo flow reactor has a volume of 0.9ml and is kept at 90 °C under illumination with blue light (450 nm), controlled by the variable power supply unit. In photopolymerization, only the initiation step is photoinduced, and chain growth is still thermally initiated.



Methyl methacrylate

MMA DP40

class	name	M	density	mass (g)	V (mL)	moles (mol)	Molar (M)	eq
RAFT	CDP-TTC	403.67		0.303		0.00075	0.075	1
monomer	MMA	100.121	0.94	3	3.19	0.02996	2.996	40
initiator	/	/	/	/	/	/	/	/
solvent	DMSO	78.13	1.1	7.49	6.81	0.09586	9.586	128

MMA DP50

class	name	M	density	mass (g)	V (mL)	moles (mol)	Molar (M)	eq
RAFT	CDP-TTC	403.67		0.242		0.00060	0.060	1
monomer	MMA	100.121	0.94	3	3.19	0.02996	2.996	50
initiator	/	/	/	/	/	/	/	/
solvent	DMSO	78.13	1.1	7.489362	6.81	0.09586	9.586	160

MMA DP75

class	name	M	density	mass (g)	V (mL)	moles (mol)	Molar (M)	eq
RAFT	CDP-TTC	403.67		0.161		0.00040	0.040	1
monomer	MMA	100.121	0.94	3	3.19	0.02996	2.996	75
initiator	AIBN	/	/	/	/	/	/	/
solvent	DMSO	78.13	1.1	7.489362	6.81	0.09586	9.586	240

Table S4: Reaction solutions for the first block with methyl methacrylate

Poly(ethylene glycol) methyl ether acrylate (second block)

The first step of doing a reaction is transforming the conventional mol/l that can be used in flasks or syringes to mol/min. The macroRAFT in the dialysis loop will be mixed with fresh monomer and initiator. Firstly, the residence time of the second reactor is determined. A residence time of 30 minutes was chosen. Because the reactor is 1.15 mL in volume, the total flow rate, consisting of the macroRAFT flow rate and the monomer flow rate, will be 0.038 mL/min. A calculation has to be made of how much every stream has to contribute to the total flow rate. In table S5 it is showed how the calculations are made. The ratio of the two flow rates is compared. The flow rate of the RAFT agent is kept at ratio 1, and the flow rate of the monomer is compared with the flow rate of the RAFT agent. Depending on the ratio, the calculation is as follows:

$$Flowrate_{RAFT} = \left(Flowrate_{Total}/(Ratio_{RAFT} + Ratio_{Monomer})\right) \cdot Ratio_{RAFT}$$

$$Flowrate_{Monomer} = \left(Flowrate_{Total}/(Ratio_{RAFT} + Ratio_{Monomer})\right) \cdot Ratio_{Monomer}$$

Example (Ratio RAFT1:Monomer0.5):

$$Flowrate_{RAFT} = \left((0.038\ mL/min)/(1 + 0.5)\right) \cdot 1 = 0.0256\, mL/min$$

$$Flowrate_{Monomer} = \left((0.038\ mL/\mathrm{min})\ /(1 + 0.5)\right) \cdot 0.5 = 0.0128\, mL/min$$

Depending on the concentration used in the preparation of the reaction solvents, the conversion of mL/min to mol/min. For the molarity of the first block, there is looked at the molarity of the RAFT agent. In this example, BA with a DP of 50 was used, which means that DOPAT has a molarity of 0.08 mol/L (0.00008 mol/mL). For the PEGMEA, a reaction mixture molarity of 2 mol/L (0.002 mol/mL) was chosen. This gives the following calculations:

$$Mol/min_{RAFT} = Flowrate_{RAFT} \cdot Molarity_{RAFT}$$

$$Mol/min_{Monomer} = Flowrate_{Monomer} \cdot Molarity_{Monomer}$$

Example (Ratio RAFT1:Monomer0.5):

$$Mol/min_{RAFT} = (0.0256\ mL/\text{min}) \cdot (0.00008\ mol/mL) = 2.044 \cdot 10^{-6}\ mol/min$$
$$Mol/min_{Monomer} = (0.0128\ mL/\text{min}) \cdot (0.002\ mol/mL) = 2.56 \cdot 10^{-5}\ mol/min$$

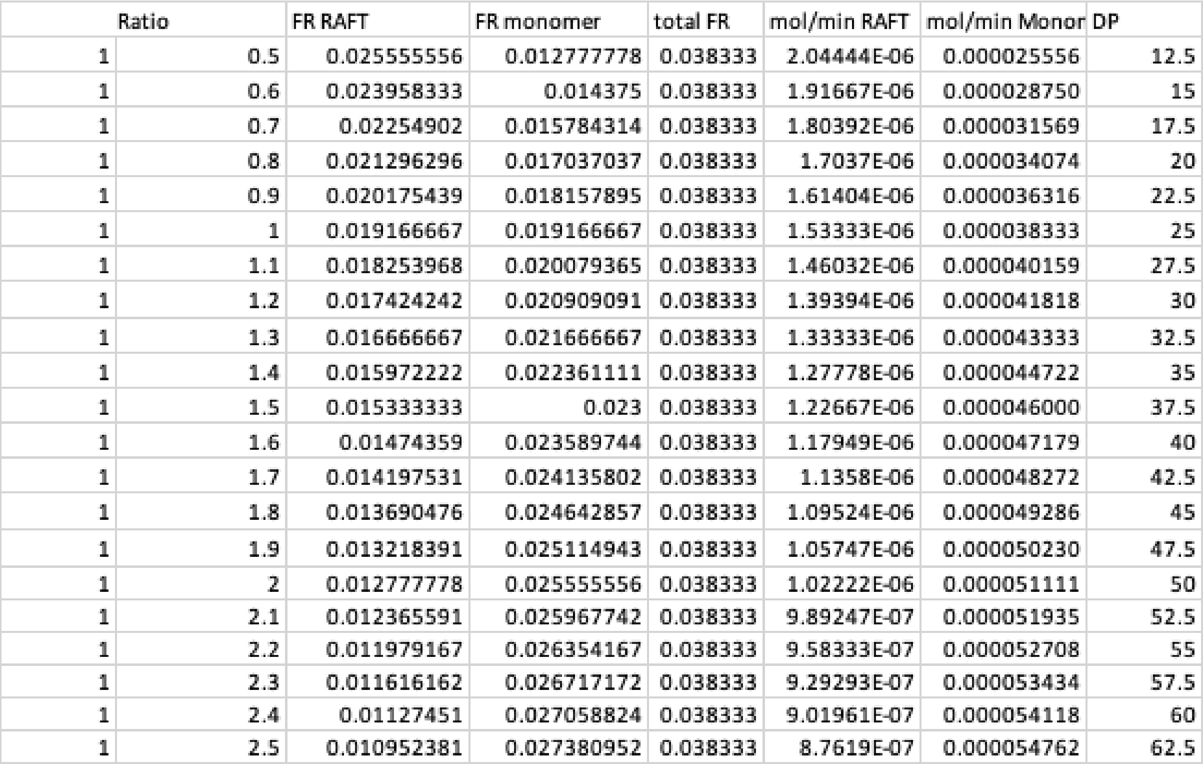
The degree of polymerization (DP) can be determined for the different flow rate ratios. The mol/min of the two streams can be compared, and the DP can be found in this scenario via the following calculations:

$$DP_{Ratio\ x} = (Mol/min_{Monomer}) \ / \ (Mol/min_{RAFT})$$

Example (Ratio RAFT1:Monomer0.5):

$$DP_{0.5} = (2.56 \cdot \ 10^{-5}\ mol/\text{min}) \ / \ (2.044 \cdot \ 10^{-6}\ mol/\text{min}) = 12.5$$

This calculation can be performed for all the different ratios possible. These relationships between the ratio of the flow rates and the DP can be plotted, and a simple linear regression can be made. This relationship will be used to choose future DPs.



Ratio		FR RAFT	FR monomer	total FR	mol/min RAFT	mol/min Monor	DP
1	0.5	0.025555556	0.012777778	0.038333	2.04444E-06	0.000025556	12.5
1	0.6	0.023958333	0.014375	0.038333	1.91667E-06	0.000028750	15
1	0.7	0.02254902	0.015784314	0.038333	1.80392E-06	0.000031569	17.5
1	0.8	0.021296296	0.017037037	0.038333	1.7037E-06	0.000034074	20
1	0.9	0.020175439	0.018157895	0.038333	1.61404E-06	0.000036316	22.5
1	1	0.019166667	0.019166667	0.038333	1.53333E-06	0.000038333	25
1	1.1	0.018253968	0.020079365	0.038333	1.46032E-06	0.000040159	27.5
1	1.2	0.017424242	0.020909091	0.038333	1.39394E-06	0.000041818	30
1	1.3	0.016666667	0.021666667	0.038333	1.33333E-06	0.000043333	32.5
1	1.4	0.015972222	0.022361111	0.038333	1.27778E-06	0.000044722	35
1	1.5	0.015333333	0.023	0.038333	1.22667E-06	0.000046000	37.5
1	1.6	0.01474359	0.023589744	0.038333	1.17949E-06	0.000047179	40
1	1.7	0.014197531	0.024135802	0.038333	1.1358E-06	0.000048272	42.5
1	1.8	0.013690476	0.024642857	0.038333	1.09524E-06	0.000049286	45
1	1.9	0.013218391	0.025114943	0.038333	1.05747E-06	0.000050230	47.5
1	2	0.012777778	0.025555556	0.038333	1.02222E-06	0.000051111	50
1	2.1	0.012365591	0.025967742	0.038333	9.89247E-07	0.000051935	52.5
1	2.2	0.011979167	0.026354167	0.038333	9.58333E-07	0.000052708	55
1	2.3	0.011616162	0.026717172	0.038333	9.29293E-07	0.000053434	57.5
1	2.4	0.01127451	0.027058824	0.038333	9.01961E-07	0.000054118	60
1	2.5	0.010952381	0.027380952	0.038333	8.7619E-07	0.000054762	62.5

Table S5: Relationships ratio flowrates with DP for the second block. (BA DP50 first block)

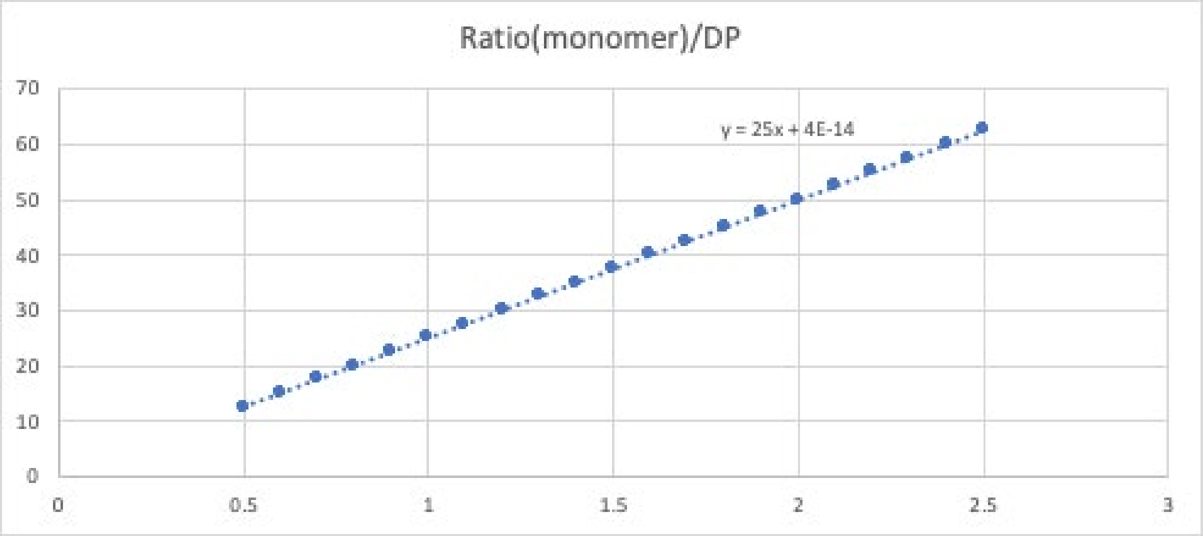


Figure S6: Relationships ratio flowrates with DP (BA DP50 first block)

Now we target specific flow rates for specific DP of the second block. The block copolymer (BA50-PEGMEA45) will be taken as an example. The relationship between the DP of the second block and the ratio for BA DP50 as the first block can be seen in figure S5. The calculation is as follows:

$$DP \;=\; 25 \;\cdot Ratio_{Monomer} + 4 \cdot 10^{-14}$$

Example (BA50-PEGMEA45):

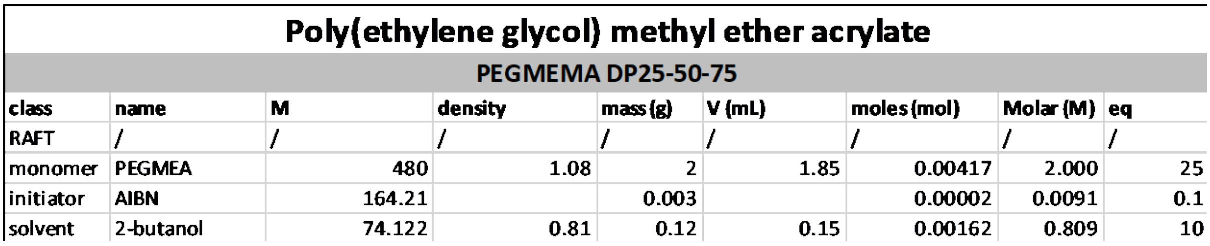
$$Ratio_{monomer} \;= (DP - 4 \cdot 10^{-14})/25 = (45 - 4 \cdot 10^{-14})/25 \;=\; 1.8$$

With this ratio, we can find the flow rates we have to put on the peristaltic pump (RAFT flow rate) and the syringe pump (monomer flow rate). The calculation for DP45 for the second:

$$Flowrate_{RAFT} \;= \big(Flowrate_{Total}/(Ratio_{RAFT} + Ratio_{Monomer})\big) \cdot Ratio_{RAFT}$$
$$Flowrate_{Monomer} \;= \big(Flowrate_{Total}/(Ratio_{RAFT} + Ratio_{Monomer})\big) \cdot Ratio_{Monomer}$$

Example (BA50-PEGMEA45):

$$Flowrate_{RAFT} \;= \big((0.038 \; mL/min)/(1 + 1.8)\big) \cdot 1 = 0.0137 \, mL/min$$
$$Flowrate_{Monomer} \;= \big((0.038 \; mL/\mathrm{min}) \,/(1 + 1.8)\big) \cdot 1.8 = 0.0246 \, mL/min$$



Poly(ethylene glycol) methyl ether acrylate

PEGMEMA DP25-50-75

class	name	M	density	mass (g)	V (mL)	moles (mol)	Molar (M)	eq
RAFT	/	/	/	/	/	/	/	/
monomer	PEGMEA	480	1.08	2	1.85	0.00417	2.000	25
initiator	AIBN	164.21		0.003		0.00002	0.0091	0.1
solvent	2-butanol	74.122	0.81	0.12	0.15	0.00162	0.809	10

Table S6: Reaction solutions for the second block with PEGMEA

Block copolymer analysis

Name	**Conversion NMR (%)**	***Mn*** **NMR (g/mol)**	***Mn*** **GPC (g/mol)**	**Dispersity GPC**	**DLS Intensity (nm)**	**DLS Volume (nm)**	**DLS Number (nm)**
BA 60	87	6890	4100	1.177	/	/	/
BA 80	82	9066	5300	1.18	/	/	/
BA 100	90	11240	7160	1.13	/	/	/
BA60 – PEGMA25	16	8800	7660	1.482	34	18	24
BA60 – PEGMA45	17	10560	9570	1.559	70	6	64
BA60 – PEGMA65	16	11880	13230	1.638	134	14	15
BA80 – PEGMA25	30	12670	8280	1.471	49	27	34
BA80 – PEGMA45	30	15550	12000	1.553	78	22	32
BA80 – PEGMA65	33	19360	13740	1.564	144	15	17
BA100 – PEGMA25	45	16650	8200	1.499	90	50	64
BA100 – PEGMA45	73	27000	10970	1.575	154	64	64
BA100 – PEGMA65	73	34330	12200	1.653	188	14	15

Table S7: NMR and SEC results for BA block copolymers

Name	**Conversion NMR (%)**	***Mn*** **NMR (g/mol)**	***Mn*** **GPC (g/mol)**	**Dispersity GPC**	**DLS Intensity (nm)**
MMA 25	89	2580	2660	1.162	/
MMA 50	90	4860	3920	1.162	/
MMA 75	88	6607	5750	1.032	/
MMA25 – PEGMA25	78	11940	9750	1.268	26
MMA25 – PEGMA45	71	17900	14000	1.451	23
MMA25 – PEGMA65	65	22860	18560	1.759	25
MMA50 – PEGMA25	82	14700	11090	1.601	24
MMA50 – PEGMA45	78	21700	16000	1.742	36
MMA50 – PEGMA65	90	32940	21730	1.792	28
MMA75 – PEGMA25	88	16160	17870	1.624	42
MMA75 – PEGMA45	72	21150	28530	1.787	37
MMA75 – PEGMA65	91	34000	33040	2.008	36

Table S8: NMR and SEC results for MMA block copolymers

End-group analysis

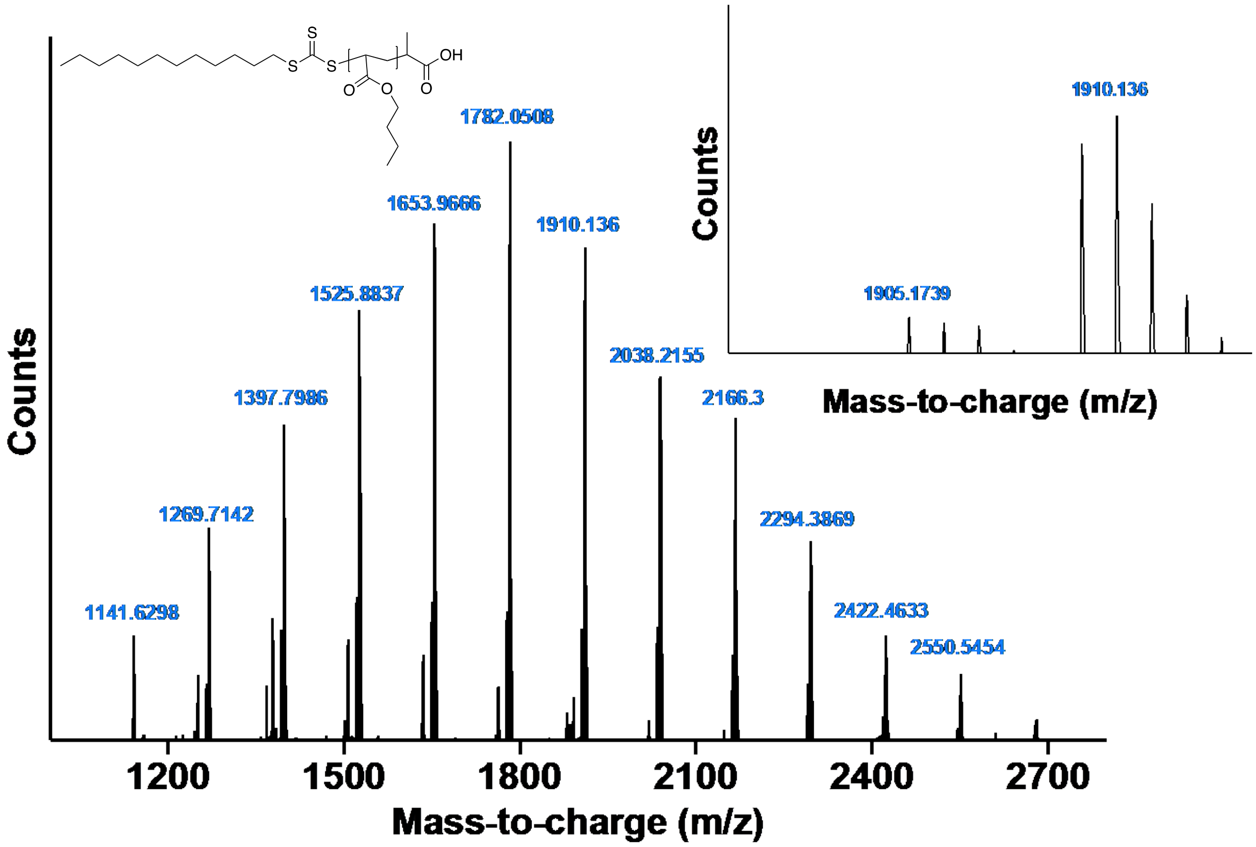


Figure S4: Example ESI spectra of poly(butyl acrylate) with a targeted molecular weight of 2000 g/mol. Structure of the RAFT polymer is shown in the insert. The expansion of one repeat unit shows a major and a minor distribution. The major districbution is assigned to the expected RAFT polymer, while the small sub distribution stems from AIBN-initiated trithiocarbonate-capped pBA (see Table S9).

End-group analysis was performed via Electrospray Ionization (ESI). The same procedure was followed as previously described for the homopolymerization of butyl acrylate. The targeted degree of polymerization was 13. The dialysis block could not be used due to the pore size of 3.5 kDa. To mimic the setup, the polymer mixture was pumped in the dialysis loop, and the dialysis block was replaced by a union (IDEX-P-702). After 3 hours, the polymer was dried under a gentle nitrogen flow. The results can be found in table S8. All the expected peaks can be found, which confirms the presence of the end group on the polymers.

Chemical Species	**Theoretical Mass (Da)**	**Exact Mass (Da)**	**Δ (m/z)**
DOPAT-BA-DP6, Na^+	1141.6324	1141.6298	0.0026
DOPAT-BA-DP7, Na^+	1269.7161	1269.7142	0.0019
DOPAT-BA-DP8, Na^+	1397.7999	1397.7986	0.0013
DOPAT-BA-DP9, Na^+	1525.8836	1525.8837	0.0001
DOPAT-BA-DP10, Na^+	1653.9673	1653.9666	0.0007
DOPAT-BA-DP11, Na^+	1782.051	1782.0508	0.0002
DOPAT-BA-DP12, Na^+	1910.1347	1910.136	0.0013
DOPAT-BA-DP13, Na^+	2038.2184	2038.2155	0.0029
DOPAT-BA-DP14, Na^+	2166.3021	2166.3	0.0021
DOPAT-BA-DP12, AIBN-initiated, Na^+	1905.156	1905.1739	0.022

Table S9: Theoretical and exact mass of different DPs of the ideal pBA RAFT polymer as shown in Figure S4. The last entry shows that the small subdistribution seen is attributable to AIBN-initiated RAFT polymer

Dialysis setup- kinetics

The dialysis rate depends on the concentration gradient over the membrane and the design of the dialysis setup used. Every design has a specific dialysis coefficient. This indicates the rate of the dialysis in the system. The dialysis coefficient of the system is obtained experimentally. A flow rate of 0.2 ml/min was used during the dialysis procedure. The residence time is 900 seconds, knowing that the volume of the one complete flow channel in the block is 3 mL. Every time the polymer mixture completed a loop, the clearance of the monomer could be calculated via inline NMR and end-group analysis. This gave the following results:

	BA60		**BA80**		**BA100**	
#Loops	**Clearance (%)**	***Difference (%)***	**Clearance (%)**	**Difference (%)**	**Clearance (%)**	**Difference (%)**
1	38		37		35	
2	62	24	60	23	57	22
3	77	15	76	16	73	16
4	85	8	86	10	84	11
5	91	6	91	5	91	7
6	95	4	95	4	95	4
	MMA45		**MMA50**		**MMA75**	
#Loops	**Clearance (%)**	***Difference (%)***	**Clearance (%)**	**Difference (%)**	**Clearance (%)**	**Difference (%)**
1	36		38		39	
2	59	23	59	21	63	24
3	74	15	73	14	78	15
4	85	11	83	10	88	10
5	91	6	90	7	93	5
6	95	4	94	4	96	3

Table S10: Clearance values of monomers BA and MMA obtained via inline NMR.

In the calculation for the dialysis coefficient, BA60 is used as an example. The clearance after one loop for the BA polymer is 38%. This conversion of the homopolymer was 87%. In a reaction that started with 4M monomer, only 0.52M monomer is left in the polymer mixture at the beginning of the dialysis. After one loop, 38% of 0.52M or 0.1976M monomer is cleared out of the solution. Now we have all the data to fill in the following equation:

$$\frac{dc_I}{dt} = -kc_I$$

$$\frac{-\ 0.1976\ M}{900\ s} = -k \cdot 0.52M$$

$$k = \frac{0.1976\ M}{900\ s\ \cdot 0.52M} = 4.22 \cdot 10^{-4}\ s^{-1}$$

Now that we have obtained the k value for the dialysis of this reaction, the rest of the NMR clearance values are checked against this k value. This is done to prove that dialysis solely depends on the polymer mixture's concentration and that the dialysis is always in its optimal range. An example is given for loop 2 for the BA60 polymer. After loop 1, a concentration of 0.3224M (0.52M-0.1976M) monomer is observed. After loop 2, the system obtained a total clearance of 62%. This means that 24% or 0.1248 M monomer is cleared. This is the experimental data. Now we can test this experimental data with the obtained k value.

$$\frac{dc_I}{dt} = -kc_I$$

$$\frac{dc_I}{900\ s} = -4.22 \cdot 10^{-4}\ s^{-1}\ \cdot 0.3224M$$

$$dc_I = -4.22 \cdot 10^{-4}\ s^{-1}\ \cdot 0.3224M \cdot 900\ s = 0.122\ M$$

If we calculate the clearance after the second loop theoretically, a clearance of 0.122 M is found) For NMR, we expect an error margin of 5% so that this value can be equalled to the value of 0.1248 M obtained via experimental work. This confirms that this setup only depends on the initial monomer concentration and that the concentration gradient is always optimal. The total clearance, calculated theoretically, of the setup is 62%. ((0.1976+0.122)/0.52). This is close to the 62% clearance of the NMR calculation. After every loop, the same calculation is done. All the calculations for BA60 can be found in table S11. The data from the other polymer systems can be found in figure S4.

#Loops	Clearance (%)	Difference (%)	Theoretical (%)
1	38		38
2	62	24	62
3	77	15	76
4	85	8	85
5	91	6	91
6	95	4	94

Table S11: Clearance in BA60 system obtained via inline NMR and calculations based on Eq. 3.

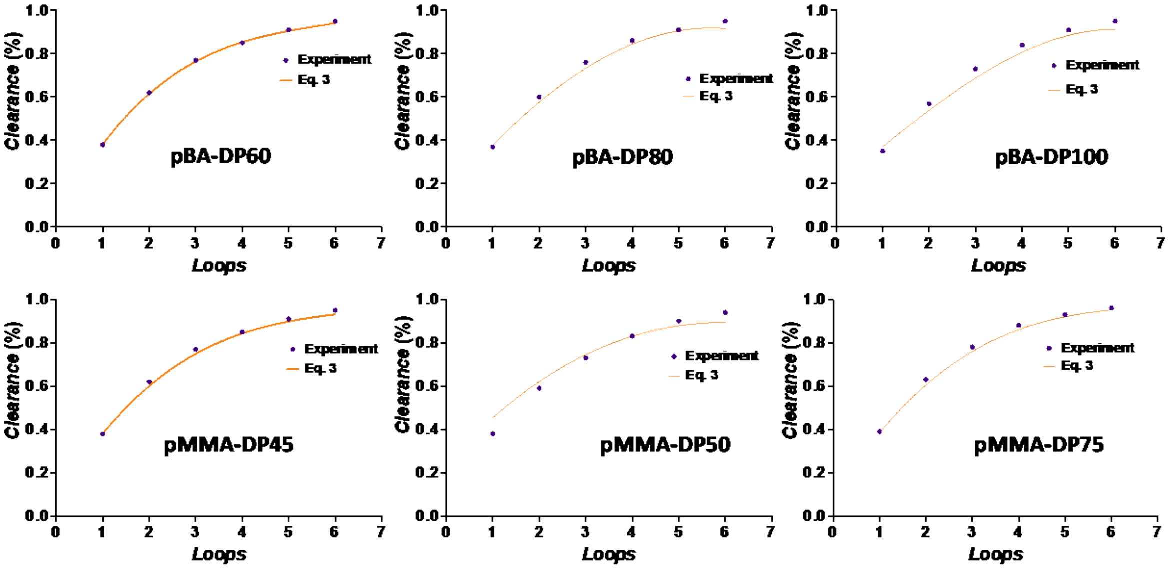


Figure S4: Comparison of theoretical and experimental clearance data of all the polymer systems.

References

1. Ferguson, C.J., et al., *Ab Initio Emulsion Polymerization by RAFT-Controlled Self-Assembly.* Macromolecules, 2005. **38**(6): p. 2191-2204.