Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering. This journal is © The Royal Society of Chemistry 2022

Supporting information (SI) for:

Continuous synthesis of block copolymer nanoparticles via telescoped RAFT solution and dispersion polymerisation in a miniature CSTR cascade

Peter M. Pittaway, Ghadir Ghasemi, Stephen T. Knox, Olivier J. Cayre, Nikil Kapur and Nicholas J. Warren

Heat transfer performance

Fluid temperature was measured in each of the 5 reactors using a set of custom K-type thermocouples (Thermosense) for a range of flow rates. This was initially done using water for a heating block set temperature of 90.5 °C to target a fluid temperature of 80 °C at the flow rates of interest (Fig. S1). At higher flow rates, the temperature deviates significantly from this target and is very different across the 5 reactors. At 0.17 mL/min (~50-minute residence time) the fluid temperature is uniform across the 5 reactors, with the temperature reaching 76 °C in the first reactor (for the first 5 minutes of reaction time). At 0.35 mL/min (~25-minute residence time) the temperature is less uniform and overall lower across the 5 reactors. For each experiment, the set temperature was adjusted prior to feeding the reaction mixture to reach the reaction temperature no later than the third reactor.



Fig. S1 Measured temperature of water in the CSTR cascade at various flow rates for a heating block set temperature of 90.5 °C.

Fig. S2 shows a typical temperature profile over the CSTR cascade during polymerisation. The exotherm results in large temperature variations between reactors, making precise control of the reaction temperature challenging over the length of the CSTR cascade. However, the large surfacearea to volume ratio of the miniature cascade means that the exotherm is quickly dissipated, with most of the heat removed before the next reactor.



Fig. S2 (Left) Measured fluid temperature of the reacting material during the RAFT polymerisation of DMAm for a heating block set temperature of 92 °C. (Right) Molecular weight distributions of PDMAm prepared at each residence time.

Residence time distributions

Residence time distributions (RTDs) were evaluated using the UV absorption at 517 nm of a 10 μ L solution of Eosin Y tracer injected via a sample loop at the inlet to the reactor. The RTD was measured for 1, 2, 3, and 5 reactors in the cascade at 0.35 mL/min and compared to theoretical distributions based on the tanks-in-series model (Fig. S3). In each run, the concentration of Eosin Y was adjusted to maintain peak absorbance below 1. Absorbance was measured for at least 5 reactor volumes and a further 3 reactor volumes of water were used to remove residual tracer before the next experiment. The RTD of the telescoped system comprising a tube, pre-mixer, and 5 CSTRs is shown in Fig. S4.



Fig. S3 Measured (red lines) versus theoretical tanks-in-series (black lines) RTDs for the miniature CSTR cascade. Traces were measured in water with 10 μ L of an Eosin Y solution injected at the inlet for a flow rate of 0.35 mL/min. Traces are normalised to the mean residence time.



Fig. S4 Measured RTD of the telescoped tube-CSTR reactor configuration (black line). The RTD of the tube and pre-mixer (blue line) was also measured separately. Traces were measured in water with 10 μ L of an Eosin Y solution injected at the inlet for a flow rate of 0.35 mL/min. Traces are normalised to the mean residence time.

Mixtures of glycerol and water were prepared with various weight fractions of glycerol to evaluate the mixing performance of the CSTR cascade for polymers at increased viscosities. An MCR 301 rheometer (Anton Paar) was used to measure the viscosity of aqueous PDMA samples with increasing chain length. Glycerol was added to water incrementally and the viscosity measured until a representative mixture was identified for each polymer sample (Fig. S5).



Fig. S5 Viscosity of 30 wt% polymer solutions of PDMA compared to glycerol/water mixtures used for representative RTD studies.

Fig. S6 illustrates the difficulty in obtaining steady-state operation when only three CSTRs are used.



Fig. S6 Molecular weight distributions obtained at different time points for the aqueous solution RAFT polymerisation of DMAm at 80 °C in a cascade of three CSTRs. Average residence time of 25 minutes, [CTA] : [initiator] = 10 : 1.

Intensity-averaged particle size distributions

Intensity averaged data is shown in Fig. S7 for the equivalent number averaged distributions presented in the main article.



Fig. S7 Intensity-averaged particle size distributions of PDMAm₄₀-*b*-PDAAm_m copolymers prepared using different manufacturing methods (A – batch-batch, B – batch-CSTR cascade, C – tube-CSTR cascade)

Statistical/gradient PDMAm-b-PDAAm copolymers

During the telescoped synthesis experiments to prepare PDMAm₄₀-*b*-PDAAm_m copolymers, the weight fraction of macro-CTA was reduced in the first stage of the process to control the molar flow of CTA to the CSTR cascade. In doing so, unconverted DMA reached the first stage of the cascade and resulted in the formation of polymer microgels, with large >1 μ m size particles revealed by DLS (Fig. S8). At 17.2 %w/w, nanoparticle formation does occur, indicating that this concentration was sufficient to achieve high enough DMA conversion for the formation of PDMAm_m-*b*-PDAAm_n block copolymers. At 9.6 %w/w there was still some nanoparticle formation however the formation of larger structures begins to be more prevalent until at 5.1 %w/w there is no nanoparticle formation, and the product is likely to be a statistical copolymer of PDMAm_m-*b*-PDAAm_n. Final conversions of each copolymer as determined by ¹H NMR were greater than 96 %.



Fig. S8 Particle size distributions by DLS on unfiltered samples of PDMAm-PDAAm copolymer prepared in a telescoped tube-CSTR cascade (25 min, 80 °C, 50 min, 70 °C). Different macro-CTA solution concentrations were used in the first stage to target different copolymer block lengths. [CTA] : [initiator] = 10 : 1.

Conversion of PDMA₄₀ macro-CTA prepared during telescoped reactions

During telescoped synthesis of the 4 block copolymers, samples of PDMAm₄₀ macro-CTA were collected from the outlet of the tubular reactor at the end of the reaction and the conversion measured using ¹H NMR. Table S1 shows the measured conversion of each sample.

Table S1 Conversions of PDMAm₄₀ macro-CTA samples collected from the outlet of the 1 mL tubular reactor (80 °C, 40 min) as determined by ¹H NMR during telescoped synthesis of PDMAm₄₀-b-PDAAm_m copolymers. Different concentrations were used to target different molar flow rates of macro-CTA to the CSTR cascade (8.1 %w/w for PDMAm₄₀-b-PDAAm₄₀₀, 27.6 %w/w for PDMAm₄₀-b-PDAAm₁₀₀).

Concentration (% w/w)	Conversion (%)		
8.1	97		
10.6	92		
15.3	98		
27.6	98		

Equipment details

CSTR cascade

The CSTR cascade used (Fig. S9) is commercially available (Asynt), comprising five ~2 mL reactors each containing a cross-shaped PTFE stirrer bar constructed from polyether ether ketone (PEEK). Reactors are connected with standard 1/4-28 fittings. A toughened glass window allows for direct observation of the reacting material. The five reactors are mounted on an aluminium heating block containing a pair of temperature controlled cartridge heaters. Below the heating block is a custom magnetic stirrer device, with individual motors used to mix each reactor. K-type thermocouples are inserted into each reactor through one of the spare 1/4-28 ports, and the remaining spare port is blanked off.



Fig. S9 (Left) Full CSTR cascade assembly with 5 reactors mounted on a heating block with the magnetic stirrer device underneath. (Right) One reactor disassembled.

Custom stirrer device

To make the reactor accessible to a broad range of users, it is designed to be heated and stirred using common hot-plate stirrer devices. The relative position of the five stirrer bars to the magnet of the hot-plate stirrer makes the mixing non-uniform, with the stirrer bars not spinning on a fixed axis but instead bouncing around randomly. This increases the likelihood of stirrers becoming jammed by polymer hardening in dead-zones and makes the flow patterns more difficult to predict. A custom stirring device was constructed comprising five pairs of neodymium magnets, each glued to a 5 V DC computer fan, and contained between a pair of laser-cut polyacrylic plates with a power socket and on/off switch (Fig. S10). The device bolts directly beneath the aluminium heating block with each fan aligned below one cell of the CSTR cascade. Using this device, each stirrer spins uniformly on a fixed axis, as a more traditional agitator would operate.



Fig. S10 (Left) a single stirrer unit comprising a 40x40 mm 5 V DC computer fan, 10 pence coin and two 10 mm neodymium magnets. (Right) full assembly with 5 stirrer units connected in parallel with a socket and on/off switch between two polyacrylic plates.

Custom back-pressure regulator

Back-pressure regulators are frequently used with flow reactors to maintain a precise and repeatable pressure in the reactor, eliminate the risk of material evaporating, and to help pumps deliver more precise flow rates. Often, back-pressure is created using a narrow spring-loaded channel through which the product of the reactor flows. In the case of particle synthesis this can often lead to blockages and subsequent over pressurisation resulting in failure of the reactor or fittings upstream. To overcome this, a 1 L glass bottle rated to 1.5 bar (Duran) was fitted with a 3-port solvent delivery cap. One port was used for compressed air, another for the process outlet, and the third containing a blanking nut for manual depressurisation when required (Fig. S11). Importantly, the compressed air is regulated to <1.5 bar with a self-relieving regulator so that the pressure does not increase as the bottle is filled.



Fig. S11 Custom back-pressure regulator comprising a pressure-rated (1.5 bar) bottle (Duran) with a 3-port GL-45 cap. One port is the reactor outlet, another is the air inlet regulated upstream to <1.5 bar, and the third is blanked.

Components of the telescoped platform

Fig. S12 gives an overview of the components used to perform the continuous-flow and telescoped reactions.



Fig. S12 Reactor platform for the copolymerisation of DMAm and DAAm via telescoped solution and dispersion polymerisation. A gas-tight syringe pump delivers DMAm solution to a tubular reactor heated by a temperature controlled oil bath to prepare the macro-CTA, which is mixed inline with the DAAm solution and fed to the CSTR cascade.

Material balance equations for telescoped copolymer synthesis

The following material balances were used to define the solution concentrations required to target different copolymers, where equations S1 and S2 define the concentrations (% w/w) of each monomer flask. Table S2 summarises the final parameters used in each telescoped reaction.

$$w_A = \left(\frac{\tau_1 V_2}{\tau_2 V_1}\right) \left(\frac{w_F M_{CTA}}{(DP)M_M + M_{CTA} + \left(\frac{M_I}{R}\right)}\right)$$
(S1)

$$w_B = \left(\frac{(DP)w_1 M_M w_F}{w_1 \left((DP)M_M + M_{CTA} + \left(\frac{M_I}{R}\right)\right) - M_{CTA} w_F}\right) + \left(\frac{w_1 M_I w_F}{w_1 R \left((DP)M_M + M_{CTA} + \left(\frac{M_I}{R}\right)\right) - M_{CTA} w_F R}\right)$$
(S2)

Subscripts 1 and 2 refer to the first and second stage of the telescoped system, where the first stage is the PDMAm macro-CTA synthesis in a tubular reactor, and the second is the PDMAm-*b*-PDAAm copolymer synthesis in the 5-stage miniature CSTR cascade. Subscripts A and B refer to flask A (DMAm solution) and flask B (DAAm solution). Subscript F refers to the final product.

w = total concentration (% w/w).

 τ = reactor residence time

V = reactor volume

DP = target degree of polymerisation of the PDAAm block

 M_{CTA} = molecular weight of the PDMAm macro-CTA at full conversion

 M_M = molecular weight of monomer DAAm

 M_I = molecular weight of the ACVA initiator

R = molar ratio of CTA to initiator

Table S2 Reaction parameters for telescoped RAFT synthesis of PDMAm₄₀-b-PDAAm_m copolymers ina tubular-mini-CSTR cascade system. Target product concentration is 20% w/w, [CTA] : [initiator] =10 : 1. Tubular reactor temperature = 80 °C, CSTR cascade target fluid temperature = 70 °C.

Targeted polymer	$ au_1$ (min)	$ au_2$ (min)	V_1 (mL)	V ₂ (mL)	<i>w_A</i> (% w/w)	<i>w_B</i> (% w/w)
PDMAm ₄₀ -b-PDAAm ₄₀₀	40	50.8	1	8.64	8.1	22.0
PDMAm ₄₀ -b-PDAAm ₃₀₀	40	50.8	1	8.64	10.6	21.6
PDMAm ₄₀ -b-PDAAm ₂₀₀	40	50.8	1	8.64	15.3	20.8
PDMAm ₄₀ -b-PDAAm ₁₀₀	40	50.8	1	8.64	27.5	18.7