

Communication

## Scale-up of the Reversible Addition-Fragmentation Chain Transfer (RAFT) Polymerization Using Continuous Flow Processing

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**Abstract:** A controlled radical polymerization process using the Reversible Addition-Fragmentation Chain Transfer (RAFT) approach was scaled up by a factor of 100 from a small laboratory scale of 5 mL to a preparative scale of 500 mL, using batch and continuous flow processing. The batch polymerizations were carried out in a series of different glass vessels, using either magnetic or overhead stirring, and different modes of heating: Microwave irradiation or conductive heating in an oil bath. The continuous process was conducted in a prototype tubular flow reactor, consisting of 6 mm ID stainless steel tubing, fitted with static mixers. Both reactor types were tested for polymerizations of the acid functional monomers acrylic acid and 2-acrylamido-2-methylpropane-1-sulfonic acid in water at 80 °C with reaction times of 30 to 40 min. By monitoring the temperature during the exothermic polymerization process, it was observed that the type and size of reactor had a significant influence on the temperature profile of the reaction.

**Keywords:** RAFT polymerization; continuous flow; scale-up

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## 1. Introduction

The Reversible Addition-Fragmentation Chain Transfer (RAFT) method is arguably the most convenient and versatile approach to controlled free radical polymerizations, as it is compatible with most monomers amenable to free radical polymerization [1–6]. With appropriate selection of reaction conditions the RAFT process takes on most of the characteristics of a living polymerization, and it allows the synthesis of polymers with narrow molecular weight distributions and well defined end groups, as well as complex polymer architectures, such as blocks, stars and others [2–6].

In recent years, microreactor technology has transformed the way chemical synthesis is conducted in research laboratories [7–20], replacing batch reactions classically carried out in laboratory glassware by continuous flow processes using tubular [21–24] or chip/plate based [25–27] reactor designs. A continuous flow reactor can offer a range of benefits over batch processing; as one example, flow reactors have better heat and mass transfer properties, leading to increased control over the process and often to improvements in product quality [7–9].

The advantageous heat transfer performance of micro-structured flow reactors for use in exothermic solution phase polymerization reactions was first described by Iwasaki *et al.* [28]. The authors described the free radical polymerization of five different monomers in a steel reactor system containing capillaries with 500  $\mu\text{m}$  inner diameter (ID). The results were compared to a macro-scale batch process resulting in an improved control over the molecular weight distribution of the polymer product in the microreactor, especially for the highly exothermic reactions of (meth)acrylate monomers. Later work by the same group demonstrated the numbering-up of this continuous flow microreactor system to the pilot plant scale for the use in free radical polymerization of methyl methacrylate [29]. Here, a stainless steel shell and tube microreactor was developed consisting of 94 microtubes (500  $\mu\text{m}$  ID) with a total volumetric hold up 9.6 mL. The shell was divided into two sections accounting for the different temperatures in the two stages of the process. Hot oil was introduced in the first section of the shell in order to carry out the polymerization at 100  $^{\circ}\text{C}$ , and coolant in the second for fast termination. The authors concluded that precise temperature control by effective heat transfer, which is an inherent advantage of microreactor systems, was responsible for the effective control of the molecular weight distribution of the polymer. Since then, several other research groups have investigated continuous flow polymerizations in micro- and meso-structured flow reactors [27,30–36]. Over the past three years, our group has undertaken extensive research in the area of continuous flow RAFT polymerizations, including post-polymerization steps such as RAFT end group removal or modification [37–42]. In this paper, we report the scale-up of exothermic RAFT polymerizations of acid functional monomers in water. The reactions were performed in a prototype tubular continuous flow reactor containing static mixer arrays and compared to batch reactions performed at different scales and in different reaction vessels.

## 2. Experimental Section

### 2.1. Materials and Analysis

The initiator 4,4'-azobis(4-cyanovaleric acid), supplied by Fluka (Buchs, Switzerland), was used without further treatment. The RAFT agent 2-(2-carboxyethylsulfanylthiocarbonylsulfanyl)propionic

acid was synthesized in our group, using the experimental protocol described by Wang *et al.* [43]. The monomers acrylic acid (AAc) and 2-acrylamido-2-methylpropane-1-sulfonic acid (AMPS) were pre-treated using polymer resin (for removal of hydroquinone and monomethyl ether hydroquinone, Sigma Aldrich, St. Louis, MO, USA, Cat. No: 31,133-2) in order to remove the radical inhibitor. The solvent diethyl ether was obtained from Merck KGaA and was used without further purification. Reaction conversions were calculated from  $^1\text{H-NMR}$  spectra. In some cases the conversion was calculated using 1,3,5-trioxane as an internal standard, a method successfully applied and described in previous work [37–39]. Average molecular weight of the polymer,  $M_n$  and its dispersity,  $D$ , were measured using size exclusion chromatography (SEC). An aqueous SEC system was used, the different components were: a Waters E2695 separation module running at a flow rate of 1 mL/min, two PL aquagel-OH 8  $\mu\text{m}$  mixed columns ( $300 \times 7.5$  mm) and a PL aquagel-OH 8 mm guard column ( $50 \times 7.5$  mm), water as the eluent (containing 0.2 M  $\text{NaNO}_3$ , 0.01 M  $\text{NaH}_2\text{PO}_4$ , pH adjusted to 8.2) and a differential refractive index detector calibrated with linear poly(ethylene oxide) standards ( $M_p = 6 \times 10^2$  to  $435 \times 10^3$   $\text{g}\cdot\text{mol}^{-1}$ ).

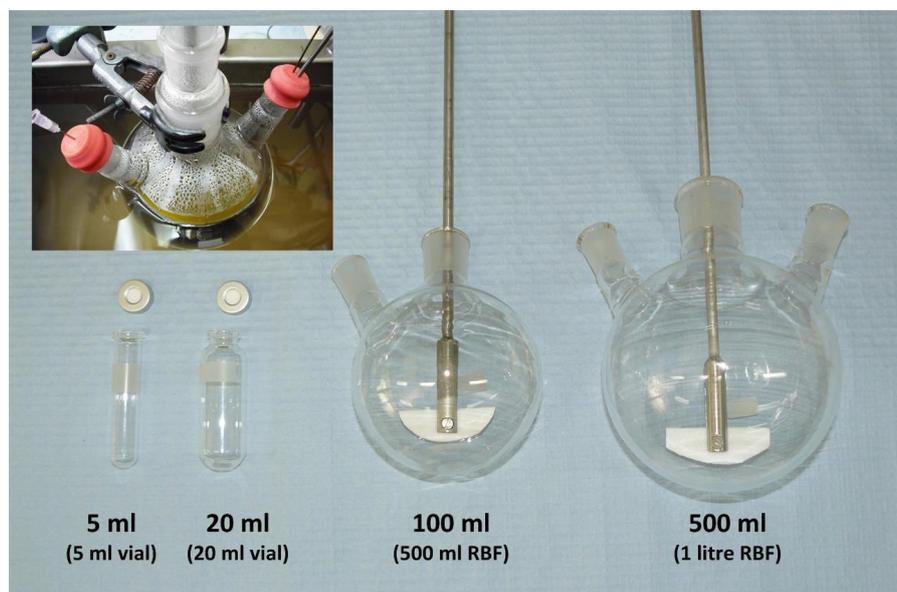
### 2.2. RAFT Polymer Synthesis in Batch Using a Microwave Reactor—Scale: Up to 20 mL

Small, discovery scale RAFT polymerization experiments in batch were conducted on a laboratory microwave (MW) reactor (Biotage Initiator; Biotage AB, Uppsala, Sweden) [44]. The following procedure is typical. A starting material solution of 3.60 g (50 mmol) monomer (AAc), 14.0 mg initiator (0.05 mmol), 63.6 mg RAFT agent (0.25 mmol), in 16.6 mL of deionised water, was premixed and deoxygenated for 20 min using nitrogen purging. The polymerization was carried out at 80 °C with a reaction time of 40 min. This reactor uses magnetic stirring to agitate the solution during reaction. At the end of the heating cycle, the glass vial was cooled down by blowing a stream of cold air or nitrogen around it. The product was a yellow viscous polymer solution, from which conversion was determined by  $^1\text{H-NMR}$ . For a 20 mL reaction a small aliquot of the polymer solution was purified by precipitation, for 3 and 5 mL reactions the entire product solution was purified: Following solvent removal and re-dissolving in DCM, the product, polyacrylic acid (pAAc), was precipitated in  $\text{Et}_2\text{O}$ , resulting in a yellow polymer powder, after filtration and drying.

### 2.3. RAFT Polymer Synthesis in Batch Using an Oil Bath—Scale: Up to 500 mL

Scale-up RAFT polymerization experiments of AAc in batch were performed using an oil bath. The following procedure is typical. Two starting material solution were prepared: the first one consisted of 90.1 g (1.25 mol) monomer (AAc) and 1590 mg RAFT agent (6.25 mmol) in 380 mL of deionised water; the second contained 350 mg initiator (1.25 mmol) in 34.3 mL of deionised water. Both solutions were deoxygenated separately for 40 min using nitrogen purging. The polymerization was conducted in a 1 L, 3-neck round bottom flask (RBF) at 80 °C with a reaction time of 40 min. The reaction vessel was heated by an oil bath and the reaction mixture was stirred using an overhead stirrer (IKA, Eurostar power control-visc; IKA-Werke GmbH & Co. KG, Staufen, Germany) with a PTFE blade type impeller. During the reaction, the stirrer speed was set to 200 rpm. The photograph in Figure 1 gives a comparison between the four different batch glass vessels used.

**Figure 1.** Photo of batch glass reaction vessels for 5 mL, 20 mL, 100 mL and 500 mL reaction scale; the insert on the top left shows an image taken during the 500 mL reaction.

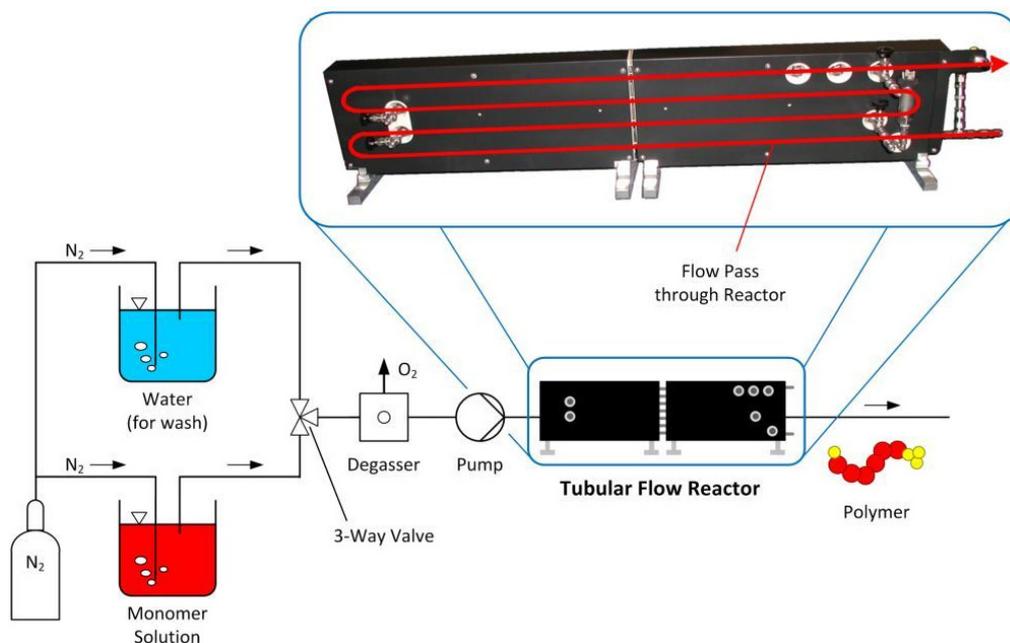


A yellow viscous polymer solution was obtained after reaction, from which conversion was determined by  $^1\text{H-NMR}$ . A small aliquot of the polymer solution was purified by precipitation; following solvent removal and re-dissolving in DCM, the pAAc product was precipitated in  $\text{Et}_2\text{O}$ , resulting in a yellow polymer powder, after filtration and drying.

#### 2.4. RAFT Polymer Synthesis in Continuous Flow—Scale: 500 mL

Scale-up RAFT polymerization experiments in continuous flow were performed using a prototype tubular flow reactor from Cambridge Reactor Design Ltd., (Cambridge Reactor Design Ltd., Cottenham, UK) [45], the Salamander Flow Reactor. The reactor chamber is a 4 m long stainless steel tube (8 mm OD, 6 mm ID), which is arranged in a serpentine fashion and housed in a metal heating block. The heating is provided by a series of electrical cartridge heaters which are controlled with custom built software coded in LabVIEW (National Instruments Co., Austin, TX, USA) via a graphical user interface (GUI). Temperature and pressure measurements are automatically recorded and plotted on the GUI. The reactor temperature can be set between room temperature and  $150\text{ }^\circ\text{C}$  on the GUI, while pressure is manually adjusted by an inline backpressure regulator, situated at the outlet of the reactor. The maximum operation pressure of the reactor is 20 bar. In order to enhance mixing of the reagent solution inside the reactor, the straight sections of the pipe were fitted with static mixer units, which in turn reduced the total reactor volume to 108 mL. The flow through the reactor was provided with a Gilson 305 dual piston pump, which can operate at flow rates between  $0.5\text{ mL/min}$  and  $50\text{ mL/min}$ . Deoxygenation of the stock solutions was provided by nitrogen purging and an inline degasser (Uniflows Degasys DG-1310, Uniflows Co. Ltd., Tokyo, Japan), situated before the pump. Figure 2 shows a flow diagram of the continuous flow polymerization process, with a photograph of the tubular flow reactor on the top right, highlighting the flow path through it in red.

**Figure 2.** Flow diagram of the continuous Reversible Addition-Fragmentation Chain Transfer (RAFT) polymerization of water-soluble monomers; the magnified photograph on the top right shows the tubular flow reactor, highlighting the flow path through it in red.

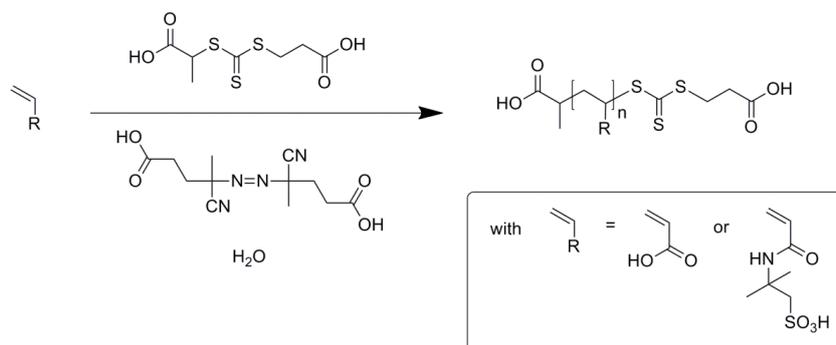


The following procedure is typical. A starting material solution of 90.1 g (1.25 mol) monomer (AAc), 350 mg initiator (1.25 mmol), 1590 mg RAFT agent (6.25 mmol), in 414 mL of deionised water, was premixed and deoxygenated for 40 min using nitrogen purging. The washing solvent (water) was also deoxygenated using nitrogen. After the reactor was flushed with deoxygenated water and brought up to the reaction temperature of 80 °C, the 3-way valve was switched and the monomer solution was pumped into the reactor as a continuous stream (see Figure 1). Polymerization was conducted at a flow rate of 2.7 mL/min resulting in a reaction time of 40 min. At the end of the reaction, deoxygenated water was used to flush the reactor. In order to obtain concentration and conversion profiles over the entire duration of the reaction, small samples of the product solution were collected at predetermined time intervals at the outlet of the reactor and analyzed by  $^1\text{H-NMR}$ . The yellow viscous solution, obtained at the outlet of the reactor was collected in several fractions. A small aliquot of the main fraction of the polymer solution (processed under steady state conditions) was purified by precipitation. Following solvent removal and re-dissolving in DCM, the pAAc product was precipitated in  $\text{Et}_2\text{O}$ , resulting in a yellow polymer powder, after filtration and drying.

### 3. Results and Discussion

The herein presented solution phase RAFT polymerizations of the acid functional monomers AAc and AMPS follow the general reaction pathway shown in Scheme 1. A series of different reactors in batch and continuous mode using different heating mechanisms were compared as well as different reaction scales ranging from 3 mL to 500 mL. The reaction conditions, temperature and time, as well as the composition of the monomer stock solution were kept constant for all experiments, so performance of the reactors could be compared directly. Experimental conditions and results are listed in Table 1.

**Scheme 1.** RAFT polymerization of water-soluble monomers acrylic acid (AAc) and 2-acrylamido-2-methylpropane-1-sulfonic acid (AMPS).



**Table 1.** Experimental conditions and results for RAFT polymerizations in batch and continuous flow.

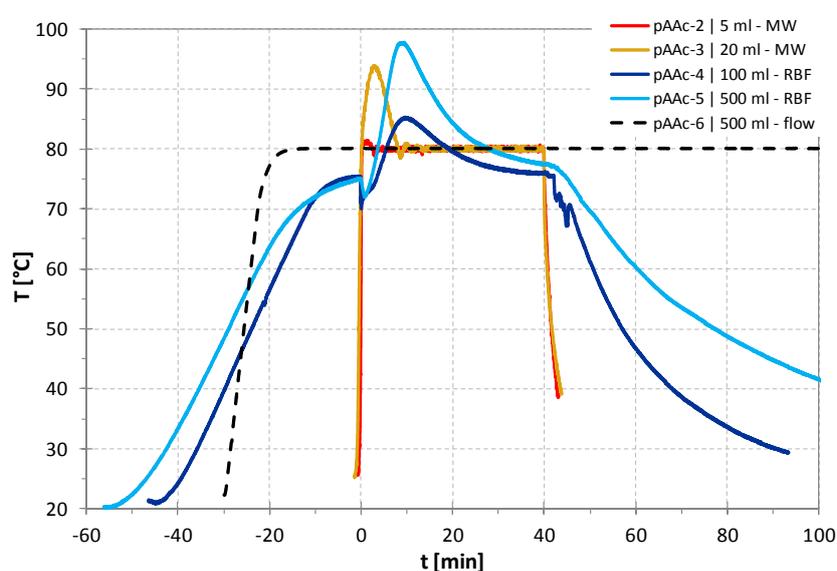
Polymer	Process	Scale (mL)	Monomer wt-% <sup>c</sup>	T (°C)	t (min)	Conversion (%)	M <sub>n</sub> (g/mol)	Đ
pAAc-1	batch <sup>a</sup>	3	17.7	80	30	95.4	22,700 <sup>f</sup>	1.35 <sup>f</sup>
pAAc-2	batch <sup>a</sup>	5	17.7	80	40	95.5	20,200	1.37
pAAc-3	batch <sup>a</sup>	20	17.7	80	40	96.7	27,000	1.45
pAAc-4	batch <sup>b</sup>	100	17.7	80	40 <sup>d</sup>	94.2 <sup>d</sup>	24,900	1.36
pAAc-5	batch <sup>b</sup>	500	17.7	80	40 <sup>e</sup>	97.4 <sup>e</sup>	21,600	1.45
pAAc-6	cont.	500	17.7	80	40	94.7	23,200	1.53
pAMPS-1	batch <sup>a</sup>	5	30.0	80	30	96.3	32,200 <sup>f</sup>	1.44 <sup>f</sup>
pAMPS-2	cont.	500	30.0	80	40	92.6	31,500	1.50

<sup>a</sup> reaction performed in a batch microwave reactor (see section 2.2); <sup>b</sup> reaction performed in batch in a round bottom flask using an oil bath (see section 2.3); <sup>c</sup> for all reactions the ratio of monomer to RAFT agent to initiator was 200:1:0.2; <sup>d</sup> an <sup>1</sup>H-NMR sample of this reaction was taken at 20 min reaction time, resulting in a conversion of 86.1%; <sup>e</sup> an <sup>1</sup>H-NMR sample of this reaction was taken at 20 min reaction time, resulting in a conversion of 95.5%; <sup>f</sup> SEC samples of pAAc-1 and pAMPS-1 were taken from the dried product after precipitation, all other SEC samples were taken from the crude product solution.

When comparing the batch polymerizations of AAc, pAAc-1 to pAAc-5, with the continuous flow experiment, pAAc-6, it can be observed that the polymerization in all these cases was near complete, with conversions varying between 94% and 97%. For the two experiments conducted in the round bottom flask, pAAc-4 and pAAc-5, an <sup>1</sup>H-NMR sample was also taken at 20 min, revealing that the 500 mL reaction had progressed already significantly further than the 100 mL reaction: the conversion in the 100 mL reaction at 20 min was 86.1%, in the 500 mL reaction it was 95.5%. The reason for faster reaction on the larger scale is due to the exothermic chain reaction of the radical polymerization (see for example Saldivar-Guerra and Vivaldo-Lima [46]) and the fact that the bigger round bottom flask was not as efficient in cooling this excess heat as the smaller system was. This development becomes very apparent when looking at the temperature curves, taken for reactions pAAc-2 to pAAc-5, which are plotted in Figure 3. Here the temperatures for the three different reactor types are shown: (1) batch microwave reactor (5 mL and 20 mL scale), using microwave irradiation to heat, and a nitrogen stream to cool down the vial after reaction; (2) batch round bottom flask reactor (100 mL

and 500 mL scale), using an oil bath to heat up the vessel and regulate the temperature; the reaction was cooled by lifting the flask out of the reactor (no active cooling mechanism); (3) the continuous flow reactor (500 mL scale), using electrical cartridge heaters, embedded within a metal heating block alongside the reactor tubing. These three reactor types resulted in fundamentally different temperature profiles for the RAFT polymerization process. It also needs to be noted that the temperature measurements in these three cases were taken at different points in the system. While for the round bottom flask reactions, the temperature of the reaction solution was measured directly using a thermocouple submersed in it, the microwave reactor measures the temperature of the glass vial via an infrared sensor [44], and the continuous flow reactor measures the temperature of the metal heating mantel via a set of thermocouples [45]. Therefore, the latter two temperature profiles are only an approximation of the bulk fluid temperature during polymerization.

**Figure 3.** Temperature profiles of RAFT polymerizations of AAc in various batch reactors (MW = Biotage microwave reactor, RBF = round bottom flask) and in the continuous flow reactor; for the MW reactions  $t = 0$  corresponds to the point where the temperature of the solution reaches  $\sim 80$  °C; for the RBF reactions  $t = 0$  corresponds to the addition of initiator to the previously heated up monomer solution; for the continuous flow reaction  $t = 0$  corresponds to the change-over from pumping solvent to pumping monomer solution into the reactor (see also text below).



As Figure 3 shows, the temperature in the microwave reactor rises rapidly in the matter of a few seconds at the start of the heating cycle from room temperature to the set value of 80 °C. The temperature stays very close to this value for the entire 40 min in the case of the 5 mL reaction (**pAAc-2**). In the case of the 20 mL reaction (**pAAc-3**), the microwave reactor is not capable of compensating for the exothermic process; hence the temperature rises to 94 °C over the first 5 min before stabilizing at 80 °C for the remaining reaction time. The cooling profile for both reactions is similarly rapid and takes less than 2 min. This shows very clearly the effect of reaction scale on the temperature performance of a batch reactor. A similar observation can be made when comparing the 100 mL and 500 mL reactions in the round bottom flask (**pAAc-4** and **pAAc-5**). Firstly, it can be

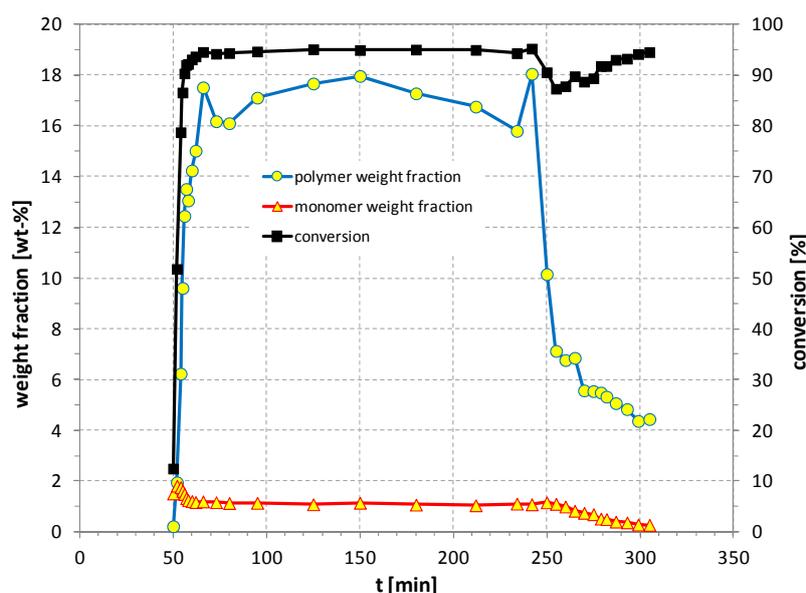
observed that the transient regimes before the start and after the end of the reaction are many times longer than in the microwave reactor, taking up to 60 min and longer to heat up the reaction mixture or cool it down again. Other than in the microwave and continuous flow reactions, where a stock solution containing all components including the initiator was heated up, for the experiments in the round bottom flask a solution containing only the monomer and RAFT agent were heated up first to near reaction temperature and by adding degassed initiator solution, the reaction was started. This was necessary because of the long heating up time, during which initiation would otherwise already have occurred. Because the initiator solution was injected into the vessel at room temperature, the temperature traces show a small drop at  $t = 0$ , but rise very quickly afterwards to 85 °C (100 mL reaction, **pAAc-4**) or 98 °C (500 mL reaction, **pAAc-5**). Similar to the microwave reactor experiments, the trend for these two reactions is non-ambiguous: the larger the reaction scale, the higher the maximum temperature, because the reactor set-up is less efficient in compensating for the exothermic process. For comparison, the temperature trace recorded by the thermocouples of the continuous flow reactor is plotted for reaction **pAAc-6**. As in the case of the 5 mL microwave batch reaction, the continuous flow reactor does not show a measurable deviation from the set temperature value of 80 °C over the entire reaction time, despite the fact that 100 times the amount of material were processed. This demonstrates the efficiency of the continuous flow reactor for the scale-up of exothermic reactions, especially in comparison to batch reactors.

The SEC results show similar performance between comparable batch and continuous flow experiments. All polyacrylic acids had an average molecular weight around 23,000 g/mol, with the only major deviation being **pAAc-3** with 27,000 g/mol. The continuous flow experiment resulted in similar, but slightly higher  $\bar{D}$  than the corresponding large scale batch experiment, which was not expected given the difference in temperature profile between batch and flow. One possible explanation could be that  $\bar{D}$  was higher because of axial dispersion inside the tubular reactor, leading to a residence time distribution (RTD) profile which deviates significantly from plug flow behavior. Preliminary RTD experiments, currently ongoing, suggest that axial dispersion might have an impact on  $\bar{D}$ . The lowest  $\bar{D}$  in all experiments was 1.35 and was observed in the small scale microwave experiment, using 3 mL of reagent solution. The higher  $\bar{D}$  values of **pAAc-3** and **pAAc-5** also confirm the results from the temperature measurements, as it was these two experiments that showed the highest temperature spike. It is believed that during this overheating period large amounts of radicals are formed by the thermal initiator, which leads to a loss of control of the polymerization process in comparison to a reaction that is kept at a constant temperature of 80 °C.

In order to quantify the consistency of the product solution exiting the continuous flow reactor, a set of  $^1\text{H-NMR}$  samples were taken at the reactor outlet, over the entire duration of the experiment. Weight fractions of monomer and polymer as well as reaction conversions were calculated from these samples: the resulting profiles are plotted in Figure 4. Both the monomer and polymer weight fraction profiles rise sharply at early times and have a tail at long times, which can also be called a “wash out curve”. It can further be observed that the monomer profile rises faster than the polymer profile and has a small peak around 50 min, while at the end of the profile the opposite is the case; the monomer profile drops faster than the polymer profile. This suggests that the monomer flows through the reactor faster than the polymer. It is believed that this is due to a stronger physical interaction of the polymer with the tubing wall and the static mixer inserts, which could potentially be a result of the difference in

surface charge density between polymer and monomer. This effect is reflected even more in the conversion profile, which is derived from the same set of  $^1\text{H-NMR}$  data as the monomer and polymer weight fraction values. At the beginning the conversion rises steeply before stabilizing around 95% at steady state conditions, and then drops off lightly after 240 min. The conversion past this time is still relatively high, meaning that significantly more polymer was being washed out of the reactor than monomer, but the total concentration of both was low. This means that the conversion data past 240 min cannot be regarded as such, and its relatively high values are more likely to be an artifact of the polymer retention phenomena within the tubular reactor, as described above. In a similar way than the pAAc process the polymerization of AMPS was also successfully scaled up from 5 mL in the microwave to 500 mL in the continuous flow reactor, with only small differences in conversion,  $M_n$  and  $\bar{D}$  (see Table 1). Here the average molecular weight was around 32,000 g/mol and  $\bar{D}$  was around 1.5. In general, it was feasible to produce pAAc and pAMPS continuously in the flow reactor, with a similarly good quality than in the batch experiments.

**Figure 4.** Polymer and monomer weight fraction profiles (to be read on the left y-axis) and conversion profile (to be read on the right y-axis) for the 500 mL RAFT polymerization of AAc in the continuous flow reactor, pAAc-6.



With the current reactor configuration, it was not possible to measure the temperature of the bulk fluid inside the flow reactor. In future work we are planning to reconfigure our equipment, so that the bulk fluid temperature can be measured at various points along the length of the tubular reactor. We are also planning further investigations looking at the residence time performance and fluid characteristics of the reactor, which might resolve the question why the flow reactor produced polymers with higher  $\bar{D}$  than the corresponding batch experiments.

#### 4. Conclusions

We have successfully demonstrated the scale-up of aqueous RAFT polymerizations in a continuous flow reactor, using the monomers AAc and AMPS. The reactions were carried out on a 500 mL scale

at 80 °C and concentration profiles at the outlet of the reactor were taken over time. The reactor produced high conversions in excess of 90% and the recorded temperature was stable at 80 °C throughout the entire duration of the experiments. In comparison, a series of batch reactions were conducted at different scales, ranging from 3 to 500 mL and in different reactor vessels; temperature profiles were taken during the course of the reactions. A strong dependence of temperature with scale was observed for these experiments, with the larger scales resulting in a higher temperature rise at the start of the reaction (up to 98 °C), as well as a longer overheating period. During this overheating period more radicals are formed by the thermal initiator than in a system which is kept constant at 80 °C, resulting in a loss of control over the polymerization process. The SEC data confirmed these findings. The polymerization process is also simplified in the continuous flow reactor, where the premixed stock solution can be pumped into the reactor directly. In comparison, processing the same amount of material in a round bottom flask, requires a long heating up period first, where the monomer and solvent are brought up to temperature over one hour (which is 1.5 times longer than the reaction time), before the reaction is started by adding the initiator.

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### Conflicts of Interest

The authors declare no conflict of interest.

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