Dambarudhar Parida, Christophe A. Serra*, Florence Bally, Dhiraj K. Garg and Yannick Hoarau

Intensifying the ATRP synthesis of statistical copolymers by continuous micromixing flow techniques[1]

Abstract: The impact of micromixers on copolymers' characteristics in a continuous-flow microprocess was studied. A stainless steel coiled tube was used as the microreactor. Several micromixers with different working principles, like bilamination, multilamination and impact jet, were used to mix the reactants' streams before entering the reactor. (Co)polymers of 2-dimethyl amino ethyl methacrylate (DMAEMA) and benzyl methacrylate (BzMA) were synthesized by the atom transfer radical polymerization (ATRP) technique, with two different compositions of BzMA (20% and 40%). A faster polymerization rate was observed in case of microprocess, as compared to batch process, highlighting the inherent intensification nature of microfluidic-assisted processes. Despite equal conversion for the three micromixers, a remarkable difference in molecular weight was observed. The highest molecular weights with lowest polydispersity indices (PDIs) were obtained when the multilamination micromixer was used, while the bilamination gave polymers with high PDIs and low molecular weights. Diffusion constraints arising from the increase in viscosity was clearly visible for highest residence times in the microreactor, resulting in a deviation of molecular weight from the theoretical value.

Keywords: ATRP; continuous-flow; copolymer; micromixing.

*Corresponding author: Christophe A. Serra, Ecole de Chimie Polymères et Matériaux (ECPM), Laboratoire d'Ingénierie des Polymères pour les Hautes Technologies (LIPHT) – EAc(CNRS) 4379, Groupe d'Intensification et d'Intrapolation des Procédés Polymères (G2IP), F-67087 Strasbourg, France, e-mail: ca.serra@unistra.fr
Dambarudhar Parida and Florence Bally: Ecole de Chimie Polymères et Matériaux (ECPM), Laboratoire d'Ingénierie des Polymères pour les Hautes Technologies (LIPHT) – EAc(CNRS) 4379, Groupe d'Intensification et d'Intrapolation des Procédés Polymères (G2IP), F-67087 Strasbourg, France
Dhiraj K. Garg and Yannick Hoarau: Institut de Mécanique des Fluides et des Solides (IMFS) – CNRS, F-67000 Strasbourg, France

1 Introduction

Functional polymers have interesting properties and find numerous applications in different fields. Linear polymers find applications, like dispersants and surfactants [1, 2], and complex counter parts like branched and crosslinked, find uses, e.g., in drug delivery, enzyme support and biomolecule transport [3–5]. Controlled radical polymerization techniques are widely used to synthesize architecture-controlled polymers. However, their properties strongly rely on the control of the polymerization reaction to get targeted composition and architecture. The benefits of controlled radical polymerization are not fully exploited in present conventional reactors, because of a large mixing time and broad temperature profile. In order to maximize the benefits of controlled radical polymerization, microreaction technology is considered as an alternative.

Efficient heat and mass transfers give microreaction technology an edge over conventional processes, and opened a new dimension in the field of fine chemical synthesis, pharmaceuticals and polymer chemistry. Efficient heat and mass transfers allow controlled handling of exothermic and endothermic reactions. However, polymer synthesis in microfluidic devices is still in its infancy and faces some challenges, like continuously changing reaction conditions with time and a high viscosity, which limit the equal flow distribution inside the microreactor [6]. This inhomogeneity can significantly neutralize the benefits of a microreactor. In spite of these challenging conditions, research is still going on to exploit the benefits of microsystems [7–9]. It is observed that microsystems have a pronounced impact on polymerization processes and polymer characteristics [10–12]. Different polymerization techniques have been recently investigated in microreactors, including controlled radical polymerizations to synthesize polymers starting from the simplest architecture as linear, to complex architectures such as hyper branched [13–18].

In chemical reactions, mixing of reactants is an important step and is usually achieved by diffusion in

microreactors. However, fast reactions require fast mixing to operate at their kinetic limit, instead of being diffusion-controlled. This led to the development of micromixers having mixing capabilities ranging from seconds to milliseconds [19]. Faster mixing leads to reduced reaction times, and thereby cleaner chemistry, since unwanted side reactions and terminations are suppressed. A variety of micromixers working on different principles are available [19–21]. Being an integral part of a microreaction setup, they can have a significant impact on reaction and polymer properties. To the best of our knowledge, the synthesis of statistical (co)polymers and the impact of different micromixers on polymerization have not been reported in the literature, especially polymerization reactions considered as "slow", like atom transfer radical polymerization (ATRP), in comparison with free radical or ionic polymerization reactions. In an attempt to fill this space, we investigated the effect of different micromixers, namely a T-Junction, an interdigital multilamination (HPIMM) and an impact jet (KM) micromixers, on the ATRP synthesis and properties of copolymers. 2-(Dimethylamino) ethyl methacrylate (DMAEMA) and benzyl methacrylate (BzMA) were used in this study. DMAEMA and its (co)polymers are well known for thermal and pH response behavior [22–25] while BzMA can undergo hydrogenolysis after polymerization to give desired acidic residue [26]. The functional behavior of these polymers makes them suitable for different biomedical applications, like drug/gene transfer or protein transport [27–29].

2 Materials and methods

2.1 Materials

2-(dimethylamino)ethyl methacrylate (Sigma Aldrich, Germany), benzyl methacrylate, copper (I) bromide (CuBr), 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA) (97%) all purchased from Sigma Aldrich (USA), isopropanol (Sigma Aldrich, France) were used as received. Ethyl 2-bromoisobutyrate (EBIB 98%) (Sigma Aldrich, USA) was distilled and stored in argon before use.

2.2 Instrumentation

Polymerization was performed in a microreaction setup, as shown in Figure 1, fitted with a stainless steel coil tube microreactor of 900 µm internal diameter and 6 m length. The microtube reactor was coiled around a stainless steel
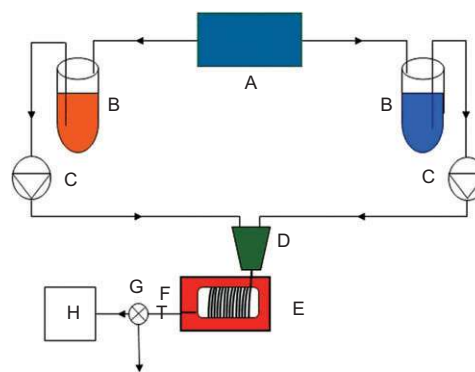

Figure 1 Microreactor setup for polymerization of (co)polymer (A) nitrogen generator, (B) reservoirs, (C) HPLC pumps, (D) micromixer, (E) microreactor inside the oven, (F) back pressure regulator, (G) three way valve, (H) GPC online platform (CORSEMP).

core and kept in a thermo regulated oven at 60°C. The micromixer, which is present outside the oven, receives two streams of reactants and delivers a single stream to the reactor. To study the effect of mixing different types of micromixer, T-junction, HPIMM (IMM, Mainz, Germany) and KM (Fujifilm Corporation, Kyoto, Japan) were used, as shown in Figure 2. The working principles and dimensions of the micromixers used in this study are given in Table 1. The microreactor setup was equipped with two 307 HPLC Gilson piston pumps, to control the flow rate, so as to achieve the desired residence time varying from 5 min to 4 h. A back pressure regulator was attached at the end of the reactor to control the pressure inside the coiled tube reactor (CT).

2.3 Polymerization

The ATRP technique was used for the synthesis of copolymers. As shown in Figure 1, the mixture of monomers and EBIB was pumped from one reservoir and the solution of isopropanol, CuBr(I) and HMTETA was pumped from the other one and passed through a micromixer before entering the microreactor. The flow rate ratio of the pumps was adjusted in such a way that the molar ratios in-between the reactants are kept constant and equal to the typical recipe of the batch process (see below). Before supplying to the reactor, both reservoirs were purged with nitrogen for 20 min. To maintain a uniform condition of polymerization, the pressure within the microreactor was adjusted to 1.0–1.5 bar by the back pressure regulator present at the exit of the microreactor. Samples for each residence time were collected once the reactor reached its steady state, which was determined from gel permeation chromatography (GPC) traces by means of the CORSEMP online GPC
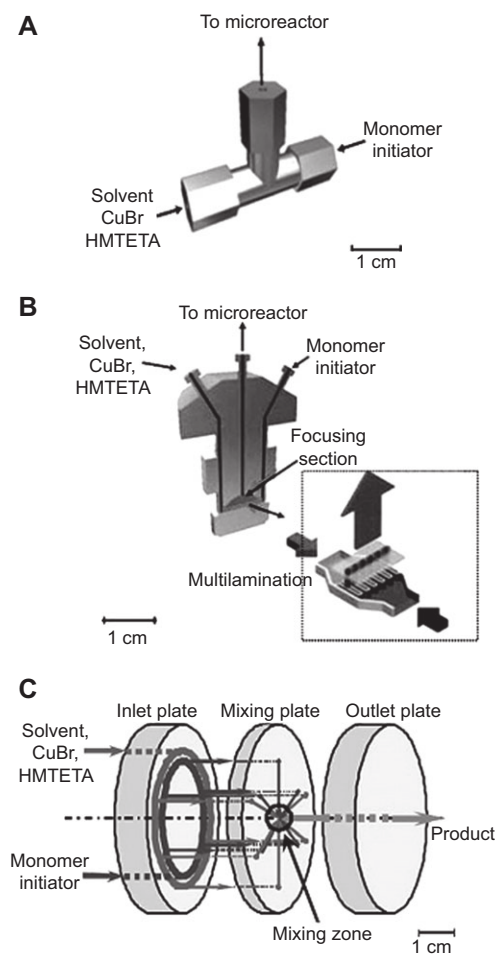
Figure 2 (A) T-Junction, (B) high pressure interdigital multilamination micromixer (HPIMM), (C) KM. Typical characteristic dimensions and mixing principles are given in Table 1.

apparatus [30, 31]. Then, a polymer solution aliquot was collected and cooled by ice to terminate the reaction.

As a reference, polymerization was done in batch mode using a Schlenk flask. A mixture of copper (I) bromide (22.80 mg, 0.159 mmol), HMTETA (47.6 µl, 0.1749 mmol), DMAEMA+BzMA (31.8 mmol) and isopropanol (5.4 ml, 50 wt.%) was placed in a Schlenk flask and degassed with argon for 20 min. Then, EBIB (0.3101 µl, 0.159 mmol) was added to the mixture as the initiator and

Type of micromixer	HPIMM	KM	T-Junction
Working principle	Digital multilamination	Impact mixing	Kinetic energy and long diffusion distance
Number of channels per inlet stream	15	5	Internal diameter 1.6 mm and length 9.14 mm
Channel width (µm)	45	100	

Table 1 Characteristics of micromixers.

the Schlenk flask was stirred under argon atmosphere at 60°C. A composition of 20% and 40% of comonomer (BzMA) was used. Samples were withdrawn from the Schlenk flask by a degassed syringe, for analysis.

2.4 Analysis

The unpurified polymer solution was used to determine the molecular weight and polydispersity index (PDI) by GPC in tetrahydrofuran (THF) (at a flow rate of 1 ml/min, at 35°C). GPC apparatus was equipped with a PL-GPC 120 Platform, consisting of a Shimadzu LC-10AD liquid pump, a column (PL-gel 5 µm MIXED-C, Polymer Laboratories, 300 mm) and four online detectors: a Knauer K-2501 UV detector (operating at 254 nm), a single capillary viscometer (length 20 cm; inner diameter 0.5 mm), a dual angle-light scattering detector (MALS) and a PL-refractive index detector (RI). Molecular weights (Mn) and PDIs were calculated from a calibration curve obtained with narrow linear polymethyl methacrylate (PMMA) standards for RI detection. The data from detection were processed with cirrus GPC software. Conversion of monomers, as well as the composition of the copolymers, was determined by proton NMR (Bruker 300 equipped with TopSpin software) using deuterated acetone as the solvent (see Supplement, Figure S1). Analyses were performed on an unpurified sample for the determination of the conversions, while dried polymer samples were used for evaluating the composition (see Supplement, recovery procedure section). The rheological behavior of unpurified polymer solutions was obtained from a shear rate sweep in a dynamical rheometer equipped with a cone and plate (Physica MCR 301, Anton Paar). To avoid the evaporation of the solvent during the analysis, the shear rate sweep was kept at under 2 min.

3 Results and discussion

Statistical (co)polymers of DMAEMA and BzMA, with 20% and 40% BzMA composition, were synthesized in batch and continuous-microflow reactors. Polymerization conditions in microreactors were maintained the same. The flow rates were varied to get the required molar ratios and residence time. It was observed that whatever the micromixer employed, the polymerization rate in the case of the microreactor is higher than for the batch reactor (Figure 3). Synergy of efficient heat transfer and enhanced diffusion in microscale, even at high viscosity, can be seen as a remarkable increase in conversion. Indeed the conversion of both comonomers was higher by 31 to 35 points at a residence

time of 4 h (see Supplement, Table S2). One can notice that, for the longest residence time investigated, there is not much difference in the final conversion of the comonomers, whatever the micromixer employed. This suggests that the final conversion is independent of the initial quality of the mixing at the entrance of the microreactor, but depends rather on the time available for diffusion. However, the copolymer characteristics will be quite different, as seen in the following section. A change in composition of BzMA in the inlet stream has no significant impact on conversion of DMAEMA and BzMA in the continuous-microflow process. However, in batch polymerization, an increase in the conversion of both comonomers is observed, with an increase in the composition of BzMA (Figure 3). Since the composition of the copolymers follows the initial composition of the comonomers in the polymerizing solution (see Supplement, Tables S1 and S2), indicating reactivity ratios close to one, the observed increase in conversion of the comonomers might result from concentration gradients in the batch reactor.

To have a better understanding of the effect of micromixers on macromolecular characteristics, molecular

weights were determined. Interestingly, it was found that, even at 5 min of residence time, the molecular weights obtained by different micromixers and batch processes were different, and that they were arranged in a distinctive order (Figure 4); batch process gave the lowest molecular weight while the HPIMM micromixer gave the highest. Among the micromixers, the lowest molecular weight was obtained when T-junction was used as a micromixer. This may be attributed to poor initial mixing achieved by bilamination, which is also highlighted by the highest PDI (see below). The effect of initial inhomogeneity becomes more prominent as the polymerization time increases. The slow increase in molecular weight can be attributed to poor mixing, whereas better mixing results in a faster increase of molecular weight, as in the case of HPIMM.

More insight into polymerization and the behavior of polymerizing solutions inside a microreactor can be seen from Figure 5. It can be observed that for both BzMA compositions (20% and 40%) and for low overall comonomer conversion (<50%), evolution of molecular weight for batch and continuous-microflow reactors follows the predictable theoretical behavior. However after 1 h of residence time, corresponding to comonomer conversion >50% (see Figure 3), the difference between theoretical and actual molecular weight (evaluated on non purified samples) starts to increase for both processes. It is also the time after which PDIs of copolymers start to increase (see Figure 7). It is worth noting that after a residence time of 1 h, the availability of monomer diminishes and the viscosity of the solution increases significantly, which may lead to poor growth of macromolecular chains and unwanted termination. Therefore, a deviation in growth from the theoretical molecular weight towards lower values is observed.

Amplification of inhomogeneity was also clearly visible in GPC traces. For both compositions (20% and
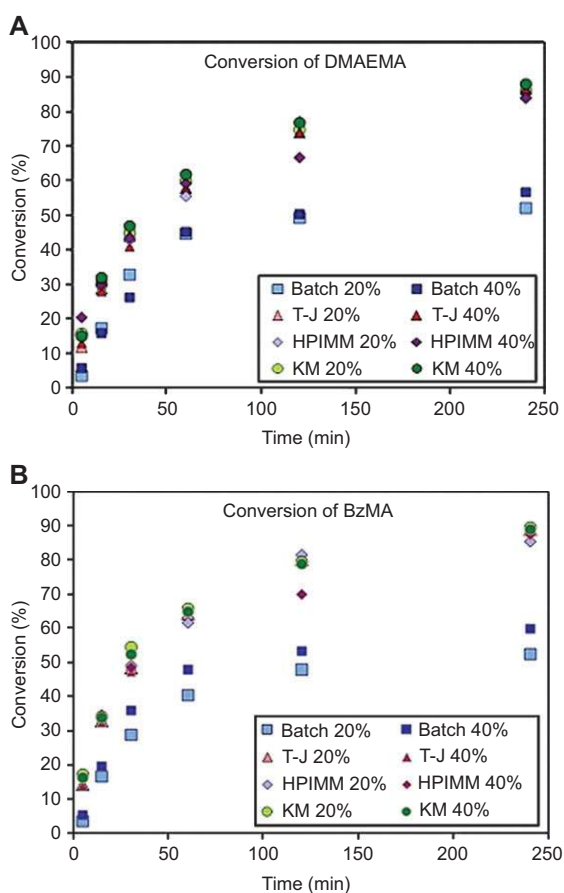

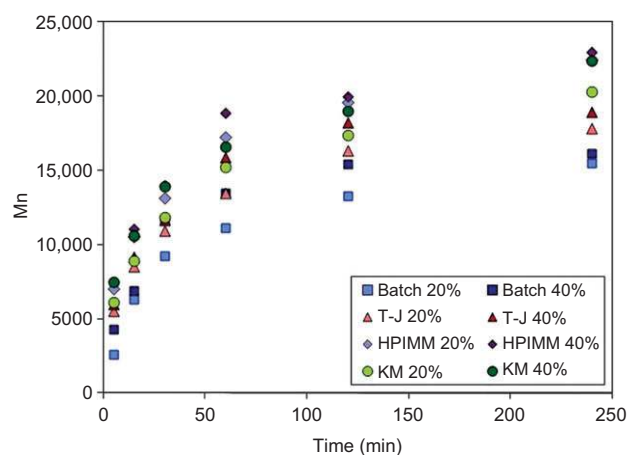**Figure 3** Conversion of monomers (in %) with time for (A) DMAEMA and (B) BzMA.
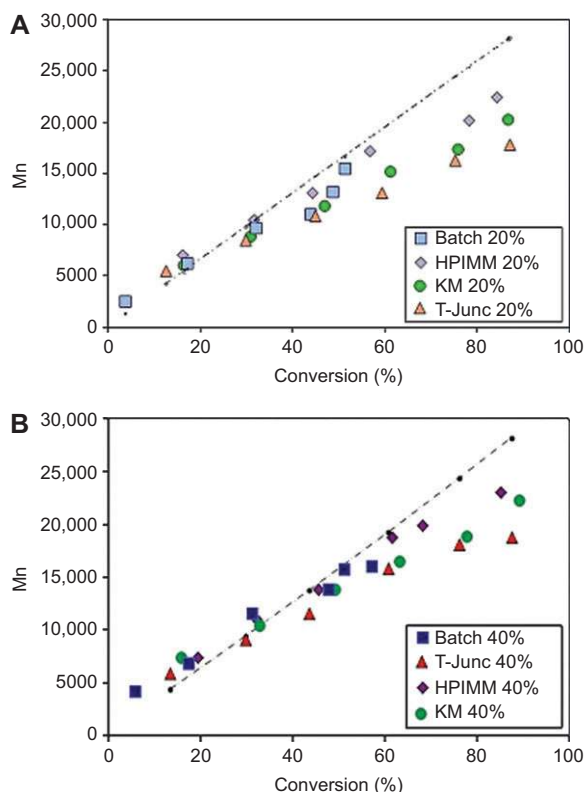

Figure 4 Evolution of molecular weight (Mn) with time.

Figure 5 Comparison of theoretical and actual molecular weights for (A) 20% BzMA and (B) 40% BzMA composition.

comonomers phase. However, a smooth GPC trace for the HPIMM mixer indicates an efficient homogenization during polymerization.

PDI is an important characteristic parameter to follow the course of the polymerization reaction, and also gives an indication of the degree of control over the process. Initial PDIs, in the case of continuous-microflow polymerization, were almost the same whatever the BzMA composition (Figure 7). As a general trend, PDIs increase with molecular weight (i.e., polymerization time) for the 20% BzMA composition, except for the continuous-microflow reactor equipped with the HPIMM mixer (Figure 7A). For the latter, one can observe a decrease in the PDI, followed by an increase past 15,000 g/mol. Moreover, this micromixer induces the smallest PDIs, especially at high molecular weights. An initial higher PDI may arise from the higher flow rate, which reduces the time availability for diffusion of molecules. As a result, the residence time distribution (RTD) reflects the laminar flow profile and induces a broadening of the molecular weight distribution. With an increase in the residence time (the microreactor length was kept constant), the time available for diffusion was increased, and therefore, better homogenization is expected. This can be seen as a decrease in the PDI with an increase in polymerization time (Figure 7). However, after 1 h of residence time, larger macromolecular sizes and an increased viscosity induce a more pronounced resistance for diffusion. Indeed, rheological measurements (see Supplement, Figure S3) showed a 100-fold increase in the viscosity of the reactive solution between 5 min and 1 h residence time. Reduced diffusion results in an unequal growth of macromolecular chains, leading to an increase in PDIs of copolymers. Such phenomenon is not very distinct in the case of mixers, like T-Junction and KM. Improper mixing obtained by these last two mixers at initial stage results in an uneven initiation of polymer chain, which remains dominant over mixing inside the microreactor, by pure mass diffusion.
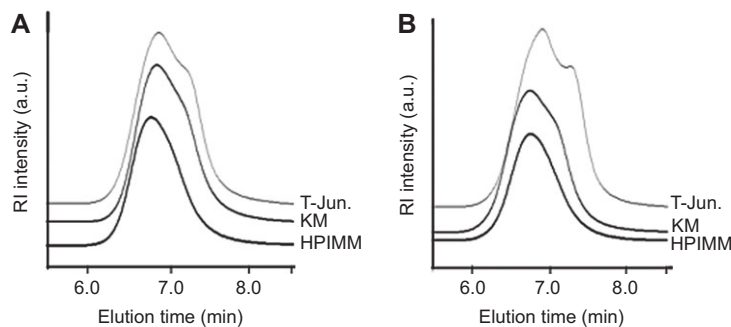
40% BzMA), a shoulder starts to appear in GPC traces at a residence time of 2 h for the continuous-microflow reactor equipped with the T-junction mixer (see Supplement, Figure S2) and becomes more pronounced at 4 h residence time. For the KM mixer, a similar shoulder also appears, but seems to be delayed in comparison with the T-junction, i.e., at 4 h residence time (Figure 6). This shoulder indicates the presence of (co)polymers with a bimodal molecular weight distribution, which may arise from polymerization in two different phases; presumably the copolymer viscous solution and the less viscous

Figure 6 GPC traces of DMAEMA-BzMA statistical (co)polymers synthesized in the continuous-microflow reactor at 4 h residence time, (A) 20% BzMA (B) 40% BzMA composition.
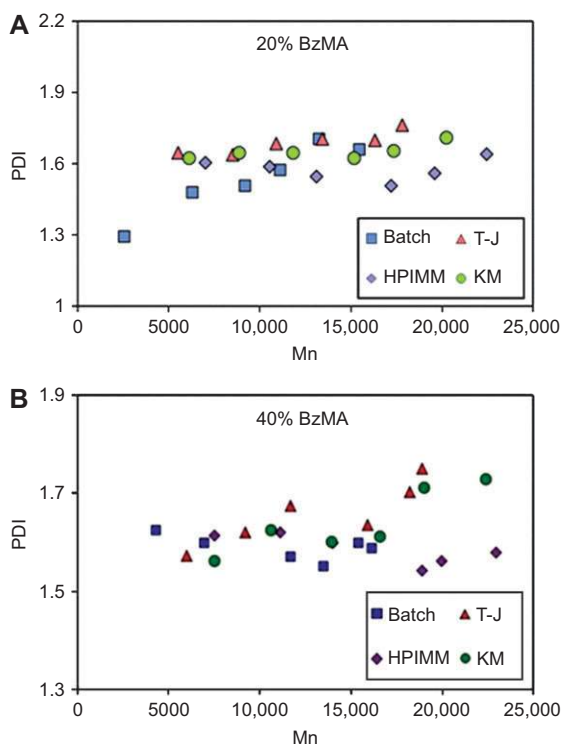
Figure 7 Plot for PDI vs. Mn of DMAEMA-co-BzMA statistical copolymers for (A) 20% BzMA (B) and 40% BzMA composition.

4 Conclusion

The synthesis of statistical copolymers of DMAEMA and BzMA was investigated in batch and continuous-microflow reactors. Process intensification is a feature of microreaction technology, which is clearly demonstrated in terms of higher overall conversion of monomers (+35 points), higher molecular weights (+8000 g/mol) and lower PDIs.

The effect of different micromixer working principles on polymerization was investigated and it was found that polymerization in a microreactor is better controlled when a multilamination mixer (HPIMM) is used to mix reactants' streams prior to entering the reactor. The HPIMM was found to impart better mixing as compared to an impact jet (KM) or bilamination (T-Junction) mixer. It was also observed that initial inhomogeneity gets amplified with increase in the polymerization time, which is more pronounced in T-Junction, as seen by the presence of a shoulder in the GPC traces. For the batch reactor and the continuous-flow reactor, whatever micromixer was used, deviation in molecular weight from the theoretical molecular weight towards the lower side, and an increase in PDI after 1 h of residence time, indicates that the viscosity of the reactive medium inside the reactor significantly affected the polymerization. However, the microreactor equipped with the HPIMM allowed adhering more closely to ideal conditions (theoretical values).

Thus it was demonstrated that even a "slow" reaction like an ATRP polymerization reaction can be accelerated significantly by means of micromixing, since a given comonomer conversion is obtained in approximately half the time required for a batch process, leading to an overall productivity twice as great. Moreover polymer characteristics can be improved in terms of higher molecular weights and lower PDIs.

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Dambarudhar Parida is a PhD student in the University of Strasbourg, France. He received his M.Tech. degree in fiber science and technology, from IIT Delhi in 2010. During his master thesis, he worked in the field of surface modification of polymers by atmospheric plasma. Subsequently, he joined the Group for the Intensification and Intrapolation of Polymer Processes (G2IP) as a PhD student, under the advisorship of Prof. C.A. Serra. Currently his research is focused on the synthesis of architecture-controlled polymers by microflow processes.

Christophe A. Serra is a Professor at the University of Strasbourg, teaching at the European School of Chemistry, Polymers and Materials (ECPM). He received his MS and PhD degrees in Chemical Engineering from the National Engineering School of the Chemical Industries (Nancy) and the Paul Sabatier University (Toulouse), respectively. His research concerns the development of intensified and integrated microfluidic-assisted polymer processes for the synthesis of architecture-controlled polymers and functional micro and nanostructured polymer particles.

Florence Bally received her Research Master's degree in Materials Science, with Polymer specialty, from the University of Strasbourg (France) in 2008. She graduated the same year from the European Engineering School of Chemistry, Polymers and Materials (ECPM) in Strasbourg. In 2011, she completed her PhD at the University of Strasbourg, in Polymer Chemistry and Polymer Engineering. She is currently working as a postdoctoral researcher with Prof. Lahann at the Karlsruhe Institute of Technology (Germany), in the Department of Functional Interfaces. Her research interests include the synthesis and processing of biomaterials based on polymers and particularly, the design of biofunctional polymer surfaces.

Dhiraj Kumar Garg is a PhD student in the University of Strasbourg, France at the Institut de Mécanique des Fluides et des Solides (IMFS). He received his B.Tech. degree from GGSIP University, Delhi, India and his M.Tech. degree from IIT Delhi, India, both in Chemical Engineering. He had worked in Nuclear Power Corporation of India Ltd, India as a nuclear engineer for 5 years in various fields, such as operation, commissioning, technical section, etc., besides working in various PHWR plants in India. His current area of research involves the numerical modeling and simulation of polymerization reactions in continuous flow reactors.

Yannick Hoarau is Associate Professor at the University of Strasbourg. He received his MS and PhD from the Ecole Nationale Supérieure d'Ingénieurs en Construction Aéronautique and the Institut National Polytechnique of Toulouse, respectively. His researches concern the accurate numerical simulation of various kinds of flows in complex geometries: turbulent flows, compressible flows, blood flows, flow in airways, reacting flows, etc.