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# Polymerizations in Continuous Flow: Recent Advances in the Synthesis of Diverse Polymeric Materials

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## ABSTRACT

The number of reports using continuous flow technology in tubular reactors to perform precision polymerizations has grown enormously in recent years. Flow polymerizations allow highly efficient preparation of polymers exhibiting well-defined molecular characteristics, and has been applied to a slew of monomers and various polymerization mechanisms including anionic, cationic, radical, and ring-opening. Polymerization conducted in continuous flow offers several distinct advantages, including improved efficiency, reproducibility, and enhanced safety for exothermic polymerizations using highly toxic components, high pressures, and/or high temperatures. The further development of this technology is thus of relevance for many industrial polymerization processes. While much progress has been demonstrated in recent years, opportunities remain for increasing the compositional and architectural complexity of polymeric materials synthesized in a continuous fashion. Extending the reactor processing principles that have heretofore been focused on optimizing homopolymerization to include multi-segment block copolymers, particularly from monomers that propagate via incompatible mechanisms, represents a major challenge and coveted target for continuous flow polymerization. Likewise, the spatial and temporal control of reactivity afforded by flow chemistry has and will continue to enable the production of complex polymeric architectures. This Viewpoint offers a brief background of continuous flow polymerization focused primarily on tubular (micro)reactors and includes selected examples that are relevant to these specific developments.

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## Introduction

Performing chemical reactions under conditions where the product is generated in a continuous manner holds many advantages. The continuous production of chemical components via reactions performed in a tubular reactor, for example, presents inherent safety improvements during highly exothermic processes. Heat dissipation is more easily realized in a tubular reactor, with high surface-to-volume ratios, than in batch reactors holding in some cases more than a ton of reactants. Additional benefits include straightforward scalability, and as such continuous flow technology is increasingly applied in the manufacturing of commercial chemicals and polymers.

The utilization of continuous synthetic processes is standard practice in several commodity chemical and polymer manufacturing arenas, but is typically limited to relatively simple processes such as the manufacturing of homopolymers and copolymers containing polyethylene terephthalate (PET) or polystyrene (PS). This is in contrast to the elegant continuous flow processes that produce complex molecules by telescoping multi-step organic synthesis. The complementary development of both flow technology and synthetic methodology has enabled coupling reaction sequences that employ several orthogonal mechanistic transformations.<sup>1-2</sup> The pharmaceutical industry has enthusiastically adopted continuous chemistry for both scale up and library synthesis of diverse molecular scaffolds.<sup>3-4</sup>

Harnessing the potential of multi-step continuous flow chemistry in polymer science requires developing systems capable of implementing the sophisticated synthetic protocols required to make complex polymer compositions, architectures and functional nanomaterials. While batch polymer synthesis (*i.e.* reactions performed in flasks) and successive isolation, functionalization, and polymerization sequences provides access to increasing complex materials, the high synthetic cost can hinder translation. Increasing the complexity of polymer materials using *continuous flow technology* may provide *commercially realistic pathways* to bespoke constructs that have heretofore been considered niche materials. Furthermore, rationally designed flow polymerizations may enable the production of new materials with properties that are prohibitively difficult to obtain by other means.

While many reports have emerged describing the concept of flow polymerizations, there remains ample opportunity for further progress. Several recent reviews have captured the historical development of flow polymerizations, and as such are beyond the scope of this viewpoint.<sup>5-13</sup> Additionally, major advances have been reported in commercially important arenas (e.g., olefin polymerizations) related to continuous processes, but these remain outside the scope and recent reviews offer a comprehensive coverage of the topic.<sup>14</sup> While much progress has been made in the development of flow technology generally in the last 50 years,

1 the previous decade has seen a resurgence in interest owing largely to the emergence of  
2 advanced reactor engineering and (photo)controlled polymerization techniques. We primarily  
3 focus on continuous polymerizations in tubular (micro)reactors, wherein the reaction contents  
4 are continually traversing through the reactor. The innovative aspects of recent developments  
5 are largely attributed to the application of emerging controlled polymerization within a tubular  
6 reactor. Contemporary catalytic systems can often benefit from (micro)tube reactors, providing  
7 access to materials with well-controlled molecular characteristics. Here we briefly review the  
8 current state of the art in development of the technology applied to polymerizations, and  
9 provide some perspective into where we think the field is headed. We suggest several areas  
10 where we think flow polymerization technology will evolve in the coming decades and provide  
11 an overview of proposed strategies to achieve these aspirational goals.

### 12 13 **Block polymers via continuous flow**

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15 Block polymers are segmented macromolecules composed of at least two sequences  
16 of different repeating units that are covalently connected.<sup>15</sup> Polymers having immiscible blocks  
17 tend to self-organize into a variety of well-defined nanostructures.<sup>16-17</sup> These nanostructured  
18 materials have found use as precursors in an astounding range of potential applications, from  
19 drug transport vehicles to selective membranes for separations.<sup>18-20</sup> Increasingly complex  
20 nanostructures with expanded phase spaces can be readily accessed by incorporating three,  
21 four, or more different types of repeating units.<sup>21-25</sup>

22 Just as with multi-step organic synthesis, multi-step preparation of block polymers  
23 typically proceeds via individual reactions for each specific block, which is collectively energy  
24 and resource intensive owing to iterative workup and purification.<sup>26</sup> This is particularly true for  
25 block polymers in which mechanistically incompatible monomers are incorporated. This is  
26 often accompanied by the need for additional functionalization steps to convert end-groups  
27 into appropriate initiators for subsequent transformations.<sup>27-29</sup>

### 28 29 **Block polymers from macroinitiators**

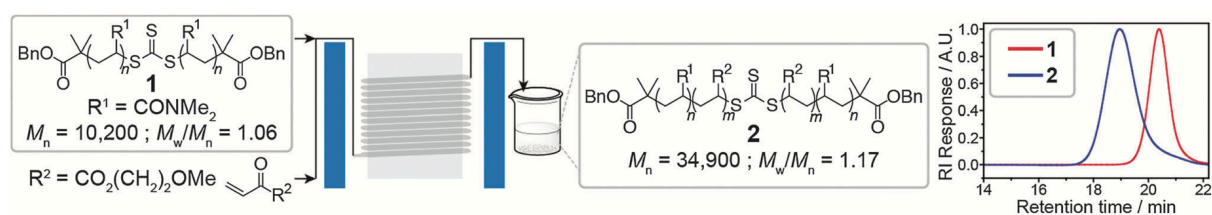
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31 Synthesizing a block polymer from a macroinitiator in flow is essentially an extension of a  
32 single-step polymerization, but additionally requires tuning reaction conditions to  
33 accommodate a starting solution with a high viscosity and different dielectric properties.  
34 Nevertheless, several notable examples described herein provide an important proof-of-  
35 concept for chain extension to meet the requirements of translating this concept to in-line,  
36 multi-step polymerization of different monomers in a sequential manner.

1 Several controlled radical polymerization strategies have been demonstrated under  
 2 continuous flow conditions, whether in microreactor type setups or larger tubular reactors. For  
 3 example, reversible addition-fragmentation transfer (RAFT) polymerizations using various  
 4 thiocarbonate chain transfer agents (CTAs) have been shown to be effective for generating  
 5 homopolymers with narrow molar mass distributions and targeted molar mass.<sup>30-31</sup> Building  
 6 upon this premise, block copolymers of various acrylates were produced by the sequential  
 7 isolation and chain extension using a single microreactor. In this manner, up to five different  
 8 blocks were incorporated, with each extension performed using macroCTAs. While perfect  
 9 end-group fidelity was not observed, each subsequent polymerization resulted in a clear  
 10 increase in molar mass, suggesting the formation of pentablock terpolymers.<sup>32</sup>

11 Junkers and coworkers demonstrated the same strategy of sequential polymerizations  
 12 employing an alternative mechanism of photo-induced radical polymerization mediated by a  
 13 copper catalyst.<sup>33</sup> The sequential isolation and macroinitiator strategy for block formation was  
 14 utilized, where fairly high end-group fidelity and living character was identified based on SEC.

15 Johnson and Chen reported the use of a photoactivated CTA in the RAFT  
 16 polymerization of several functional monomers including dimethyl acrylamide and ethylene  
 17 glycol methacrylate in a tubular reactor.<sup>34</sup> They further demonstrated the efficacy of using a  
 18 symmetric macro-chain transfer agent to prepare ABA-type triblock copolymers through a two-  
 19 step polymerization (Figure 1). Photoiniferter RAFT polymerization is an alternative  
 20 mechanism, in which chain transfer agents are used that do not require an exogenous radical  
 21 source to initiate polymerization.<sup>35-36</sup> Photoiniferter RAFT polymerization of n-BuMA and  
 22 methyl acrylate (MA) was described shortly thereafter in a microreactor, with very high end-  
 23 group fidelity observed.<sup>37</sup> This allowed for the successful synthesis of block polymers from  
 24 these two monomers via the macroinitiator (i.e., macroCTA) strategy.

25



26

27 **Figure 1.** Macro-chain transfer agent trithiocarbonate used to prepare ABA triblock  
 28 copolymers in a tubular reactor upon exposure to UV radiation. SEC traces of the starting  
 29 material **1** and resulting block copolymer **2** after extension are shown. Adapted and  
 30 reproduced with permission from ref 34. Copyright 2015 Royal Society of Chemistry.

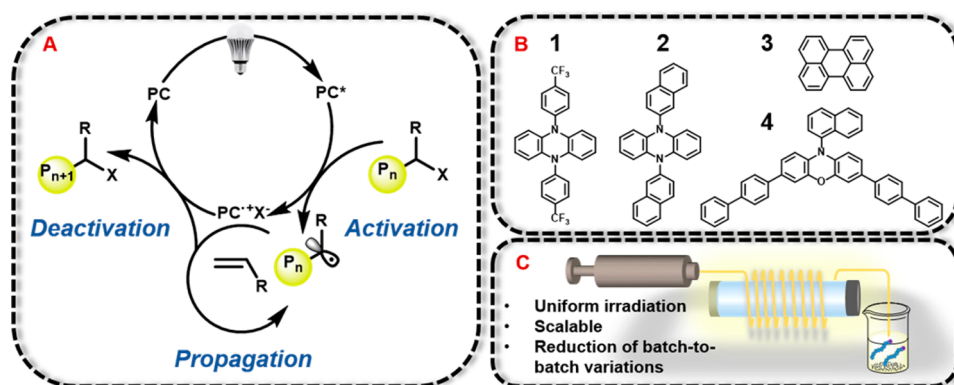
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32 Guo and coworkers describe the synthesis of graft block copolymers generated via  
 33 reversible deactivation radical polymerization (RDRP) mechanism employing a copper  
 34 catalyst.<sup>38</sup> The block polymers were synthesized starting from a macroinitiator consisting of

1 poly(vinylidene fluoride-co-chlorotrifluoro ethylene) [P(VDF-co-CTFE)], which was prepared  
2 separately in a batch process. Thus, flow polymerization was used to polymerize MMA  
3 initiated from the chloro groups situated along the P(VDF-co-CTFE) backbone. Junkers and  
4 coworkers also described a copper-catalyzed, light mediated controlled polymerization of  
5 MMA in a tubular reactor demonstrating low dispersities and well-controlled molar masses.<sup>39</sup>  
6 They subsequently employed the isolated PMMA-Br homopolymer as a macroinitiator to  
7 initiate polymerization of methyl acrylate (MA) to form PMMA-b-PMA copolymers. RAFT  
8 polymerization was also recently employed to make block polymers from commercially  
9 relevant styrene and isoprene monomers to make thermoplastic elastomers.<sup>40</sup> This was done  
10 in a rapid photoiniferter RAFT polymerization by isolating a polyisoprene macroinitiator and  
11 subsequently chain extending with styrene.

12 The emergence of several highly effective organic photoredox catalysts for ATRP has  
13 opened many new opportunities in photocatalyzed polymerizations, including the increased  
14 efficiency of performing these polymerizations in tubular reactors.<sup>41-45</sup> Photoredox organic  
15 ATRP (O-ATRP) conducted in a continuous flow tubular reactor emerged very recently after  
16 the first mechanistic reports (Figure 2).<sup>46</sup> Block polymers were formed by first preparing a  
17 PMMA macroinitiator and, after isolation, performing chain extensions via polymerization of  
18 BnMA or EtMA.

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23 **Figure 2.** (A) O-ATRP conducted by a photoredox process using (B) various photoredox  
24 catalysts conducted using a (C) continuous flow polymerization in a tubular reactor. Adapted  
25 and reproduced with permission from ref 46. Copyright 2017 American Chemical Society.

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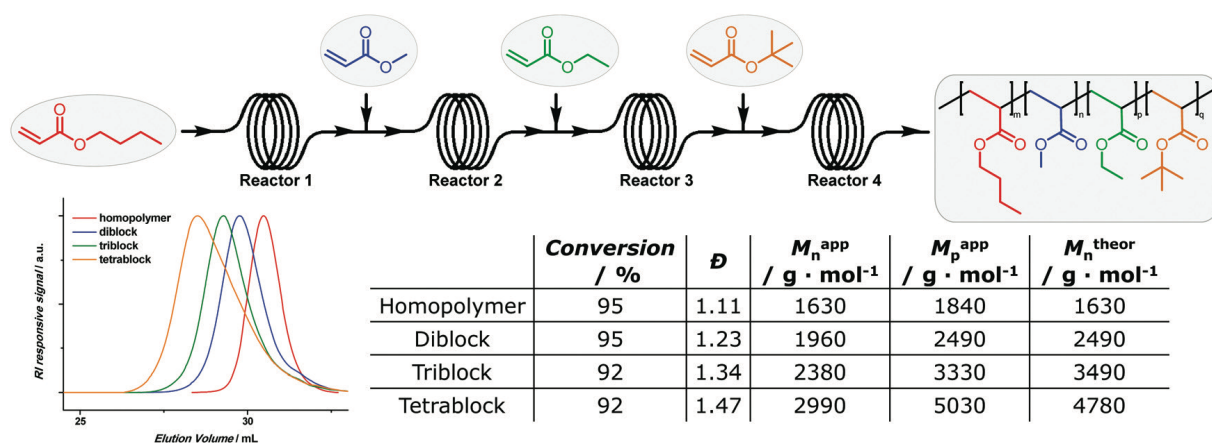
27 Similarly, Junkers and coworkers described the coupling reaction between two  
28 preformed polymers utilizing a copper-catalyzed click reaction. Interestingly, they employed a  
29 two stage reactor, where chain end-functionalization was performed in flow before combining  
30 the two components for the final coupling reaction.<sup>47</sup>

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## **Block polymers from sequential monomer polymerization**

One of the first reports of controlled radical polymerization employing a microfluidic device for continuous production was demonstrated with ATRP by Beers and coworkers.<sup>48</sup> This was pioneering for translating a controlled radical polymerization process conventionally conducted in flasks (i.e., batch reactors) to continuous production in a flow microreactor. Soon after, the concept was extended to the synthesis of block copolymers.<sup>49</sup> Haddleton and coworkers showed the ATRP of MMA in flow could be regulated to reach 90% monomer conversion after 4 h at 90 °C in flow. High conversions are an essential attribute of polymerizations to form block copolymers in one pot, ensuring sharp block junctions and minimizing gradient block transitions. While unambiguous evidence for defined block architectures was missing in this report, the experiment paved the way for the further development of multi-stage, sequential monomer polymerization. More recently, the concept of O-ATRP using a photoredox catalyst has been shown to be effective for preparing block copolymers in a tubular reactor in series, whereby a fluorinated methacrylate and MA were sequentially polymerized.<sup>50</sup>

The group of Zhenping Cheng and Lifan Zhang have recently described the extension of RAFT polymerization to aqueous and sequential two-stage reactions using a tubular reactor that yield water soluble block polymers from 3-sulfopropyl methacrylate potassium salt and poly(ethylene glycol) methyl ether methacrylate.<sup>51</sup> This was an important extension of the RAFT polymerization concept, demonstrating that the intermediate functional homopolymer from the first polymerization step needn't be isolated before conducting the chain extension. The Junkers' group also reported the so-called cascade RAFT polymerization to prepare multiblock copolymers in a single stream continuous microreactor system.<sup>52</sup> They sourced from a wide variety of acrylates and acrylamides, ultimately showing that flow polymerization was effective at incorporating up to four separate monomers to produce tetrablock quarterpolymers (Figure 3). Junkers and coworkers went on to report the well-controlled preparation of block polymers through sequential monomer addition in an photoiniferter RAFT polymerization strategy.<sup>53</sup>



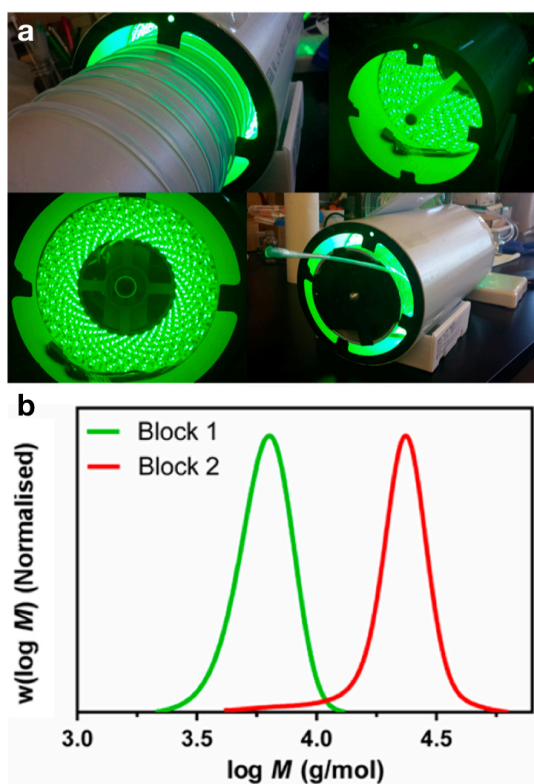
**Figure 3.** Cascade flow microreactor for the synthesis of tetrablock quarterpolymers in a single stream. Adapted and reproduced with permission from ref 52. Copyright 2017 Royal Society of Chemistry.

An innovative adaptation of this series of microreactors was demonstrated by employing a looped reactor setup.<sup>54</sup> In this manner, a single injection port was used for each subsequent monomer addition, greatly simplifying the setup required for accessing complex molecular architectures. This allowed for the time-efficient and structurally robust production of multiblock copolymers utilizing a thiocarbonate transfer agent for RAFT polymerization. A looped flow reactor has also been applied for the living anionic polymerization of styrene and butadiene, forming multiblock copolymers, albeit with a mixture of segment numbers for a given sample.<sup>55</sup>

In related work, Cyrille Boyer and co-workers have developed a robust RAFT polymerization system that is mediated by photoirradiation, and further largely tolerant to the presence of otherwise detrimental components such as oxygen (i.e., air).<sup>56-57</sup> In the photoelectron transfer (PET-RAFT) process, they have shown several variants of organic, oxygen tolerant systems that are activated with a variety of different wavelength radiation, demonstrating remarkable versatility.<sup>58-59</sup> Furthermore, the light-mediated nature of the PET-RAFT system is ideal for tubular reactors and microreactors owing to the very short path length inside the tubes during irradiation, and leading consequently to highly uniform reaction conditions.<sup>60</sup> This contrasts sharply with photomediated batch reactions, where light intensity decreases sharply as pathlength increases.<sup>10</sup> Boyer described tubular reactors employing PET-RAFT polymerization to prepare poly(*N,N*-diethylacrylamide) (PDEAm) by exposure to LEDs (Figure 4a).<sup>61</sup> They went on to demonstrate the formation of block polymers by adding a second monomer, *N,N*-dimethylacrylamide (DMAm). Because they did not reach quantitative conversion after the first block and did not isolate the product, they describe the polymers as block-like gradient copolymers. Nevertheless, this is a powerful demonstration of



1 an oxygen tolerant system that forms segmented copolymers, albeit containing very similar  
2 monomers (Figure 4b). Most recently, they have extended the concept of oxygen tolerant PET  
3 RAFT in a series of tubular multistage reactors to elegantly demonstrate the straightforward  
4 synthesis of di- and triblock polymers.<sup>62</sup>



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7 **Figure 4.** (a) Reactor setup showing LED illumination surrounding a tubular reactor wrapped  
8 around a column. (b) SEC chromatograms of the first and second blocks after sequential  
9 monomer introduction. Adapted and reproduced with permission from refs 61. Copyright 2016  
10 American Chemical Society.

11  
12 In an additional extension of this concept, Boyer and coworkers showed that the  
13 dispersity ( $\mathcal{D}$ ) could be finely tuned in homopolymers *and* block copolymers in a dual tubular  
14 reactor by introducing monomers in series.<sup>63</sup> They demonstrated this elegantly via  
15 photoiniferter RAFT polymerization of DMAM, *N*-acryloyl morpholine (Nam) and benzyl  
16 acrylate (BzA), accessing a variety of block compositions having various targeted MMDs. This  
17 is a well-known strategy to tailor the physical properties of block polymers.<sup>64</sup>

18 Anionic polymerization has also been demonstrated in a continuous flow tubular  
19 reactor, during which very fast polymerizations can be realized to generate polymers with low  
20 dispersities and well-defined molar mass.<sup>65</sup> This concept was also extended to sequentially  
21 polymerize styrene and 4-*t*-Butylstyrene to form block copolymers.<sup>66</sup> This was among the

1 earliest examples of sequential block copolymerization in a continuous flow tubular setup.  
2 Exquisitely detailed experiments showing diblock and triblock polymers via anionic  
3 polymerization were later described by Yoshida and coworkers.<sup>67-69</sup> These experiments  
4 represent a powerful development in this technology by combining monomers with very  
5 different reactivities. Furthermore, they showed that the livingness of the anionic chain ends  
6 could be extended and the reactivity attenuated by capping with a diphenylethylene group.  
7 This functionalization reaction was carried out within the continuous flow reactor, as one step  
8 in the multi-stage sequence. They also showed high end-group fidelity consistent with the  
9 corresponding chain extension as measured with size-exclusion chromatography (SEC).<sup>68</sup>

10 A similar approach was described several years later by the Noh group, in which the  
11 preparation of PS-*b*-PMMA block copolymers was demonstrated using anionic  
12 polymerization.<sup>70</sup> Yoshida and coworkers also went on to demonstrate multistage anionic  
13 polymerization of various fluoro-containing (meth)acrylate derivatives to form high surface  
14 energy block copolymers.<sup>71</sup> These results showed similar end-group fidelity and chain  
15 extension efficiencies as their previous work. Utilizing a similar reactor setup, the group of  
16 Yoshida has also employed cationic polymerization to afford block copolymers from  
17 polymerization of various vinyl ethers.<sup>72</sup> They demonstrated equally impressive block integrity  
18 during the sequential polymerization of *tert*-butyl vinyl ether and *n*-butyl vinyl ether.

19 Ring-opening transesterification polymerization (ROTEP) of cyclic lactones has also  
20 been reported on several occasions, including for block polymers produced by sequential  
21 polymerization in a tubular reactor. Kai Guo and co-workers have reported the successful  
22 preparation of block polymers based on poly( $\delta$ -valerolactone) (PVL) and poly( $\epsilon$ -caprolactone)  
23 (PCL) using an organocatalyst for the ring-opening polymerization.<sup>73</sup> Enzymatic catalysis was  
24 later employed to prepare similar copolymers in continuous flow conditions.<sup>74-75</sup> The same  
25 group has also reported the synthesis of other block polymers produced from lactone  
26 monomers including *d,l*-lactide (LA) and cyclic carbonates in a microreactor.<sup>76</sup> The evidence  
27 for chain extension and corresponding block polymer formation was primarily supported by  
28 SEC measurements. While photoinduced polymerizations have been recently described for  
29 the ROTEP of LA, the demonstration of this technology in continuous flow has not yet been  
30 reported to our knowledge.<sup>77-78</sup>

31 Very recently, the groups of Boyer, Junkers, and Zetturlund have collaborated to show  
32 that synthesis of block polymers can be combined with polymerization induced self-  
33 organization into micellar assemblies.<sup>79-80</sup> This represents a major step towards the fabrication  
34 of complex nanostructures in a continuous stream combined with the synthetic protocols  
35 employed to prepare the macromolecular building blocks.

## 1 **Block polymer self-organization outlook**

2  
3 Block polymers described in the literature are often prepared with a specific  
4 nanotechnology in mind. The various technologies in which block polymers are envisioned  
5 exploit the inherent nanoscopic dimensions associated with the organized mesophases that  
6 are typically adopted. However, conventional wisdom is that the segregation strength ( $\chi N$ )  
7 between the constituent segments must be above a critical value for adopting these structures.  
8 The strategy for accessing well-defined morphologies typically lies in choosing components  
9 that are intrinsically immiscible, having either incompatible functional groups or surface  
10 energies. The immiscibility that arises from the contrast in atomic/molecular structure often  
11 necessitates very different conditions for synthesis. Therein lies the challenge in applying a  
12 single stream, “one-pot” system like flow polymerization in series to prepare block polymers  
13 with highly immiscible segments.

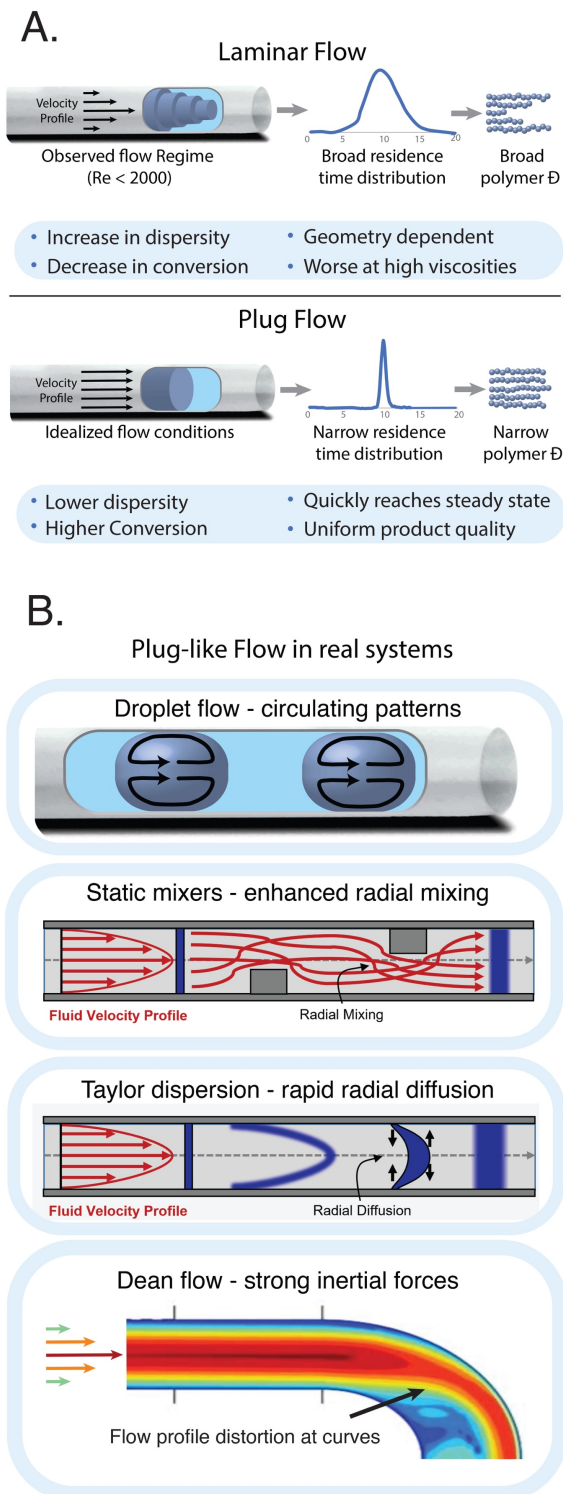
14 Without exception, the block polymers described in the examples provided in this  
15 Viewpoint have employed a single mechanism. Often, methacrylates or acrylates were the  
16 monomers of choice. Many (meth)acrylate repeating units have low intersegmental interaction  
17 parameters ( $\chi$ ), with the obvious exception of fluoro-derivatives. Thus, purely (meth)acrylate  
18 block polymers rarely undergo microphase separation. An additional challenge lies in  
19 transitioning between different mechanisms within a single continuous flow reactor series in  
20 order to polymerize monomers that are mechanistically incompatible. As an additional  
21 complication, transitioning between mechanisms often necessitates post-polymerization  
22 functionalization steps after the first block is prepared. For example, the preparation of end-  
23 functional polymers via functionalization strategies receives abundant attention in the  
24 literature.<sup>29, 81-83</sup>

25 Nevertheless, the technology of flow chemistry has been developed to an advanced  
26 stage for the synthesis of complex organic molecules requiring multiple synthetic steps.<sup>1, 84</sup> As  
27 such, the barrier to applying complex conditions in what is essentially a multi-step synthesis  
28 to generate block polymers with various segments can be overcome. This holds the potential  
29 to facilitate the transition of complex polymer architectures and nanotechnologies from an  
30 academic curiosity to a commercial manufacturing reality.

## 31 **The influence of fluid dynamics on polymer attributes**

32 The flow profile of fluid flowing through a tube has a significant impact on the resulting  
33 polymer structure, molar mass, composition, and molar mass distribution (MMD).<sup>85</sup> Recent  
34 studies have illuminated quantitative relationships that relate polymer residence time  
35 distribution (RTD) to polymer structure (Figure 5A).<sup>86-87</sup> RTD is defined as the distribution of  
36 time it takes for simultaneously injected fluid to fully traverse and exit a flow reactor.  
37

1 Fundamental studies have enabled the rational design of complex reactor geometries that  
2 provide more control over polymer characteristics. In particular, the majority of continuous flow  
3 polymerizations are conducted in the laminar flow regime, which is characterized by fluid  
4 moving through a tube with a Reynolds number less than 2000. A consequence of laminar  
5 flow is the development of a parabolic velocity profile that develops due to frictional forces  
6 between the interface of the moving fluid phase and the stationary tubing. This velocity profile  
7 leads to RTDs within the reactor where fluid toward the center of the tubing has a shorter  
8 residence time compared to fluid close to the outer edges of the tubing. Leibfarth and  
9 coworkers recently quantitated the detrimental influence of this RTD on the ability to control  
10 the molar mass, composition, and MMD during controlled polymerizations.<sup>86</sup> Thorough  
11 experimental data derived from various reactor geometries demonstrated that the magnitude  
12 of the RTD is highly dependent on tube diameter, residence time, and viscosity. Significantly,  
13 the RTD of a polymerization reaction was found to have a more pronounced parabolic velocity  
14 profile compared to analogous small molecule reactions due to the decreased radial diffusion  
15 caused by the higher viscosity typical of polymer solutions. In a similar study, Boyer and  
16 coworkers found that the effect of laminar flow was exacerbated for photopolymerizations  
17 because polymer near the tubing–liquid interface simultaneously experienced longer retention  
18 times, and more intense light exposure compared to liquid flowing in the center of the tubing,  
19 ultimately leading to higher viscosities and RTD amplification.<sup>87</sup> Schork and coworkers studied  
20 the RTD of a RAFT polymerization in miniemulsion droplets within a continuous flow tubular  
21 reactor.<sup>88</sup> Slippage of the dispersed droplets along the walls of the fluoropolymer tubing  
22 caused a flow profile that deviated from the expected laminar regime. This effect, in  
23 combination with the diffusive effects of each individual emulsion droplet being able to move  
24 freely throughout the aqueous continuous phase, contributes to the observed broadening of  
25 the RTD. As the aforementioned studies indicate, RTD has been identified as a crucial  
26 parameter to optimize in order to produce well-defined polymers in flow.

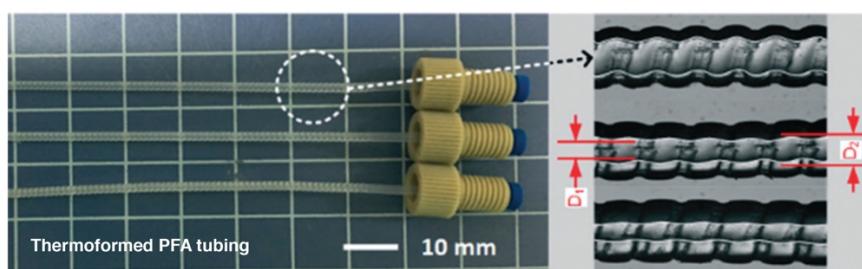


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**Figure 5.** (A) Comparison between idealized and experimentally observed fluid flow during continuous flow polymerization; (B) Strategies pursued to achieve plug-like fluid flow in continuous flow reactors. Adapted and reproduced with permission from refs 86, 89-91 Copyright 2019 American Chemical Society (ref. 86; 89); Copyright 2018 Taylor & Francis (ref. 90).

1 A variety of approaches have been pursued to minimize the influence of RTD on  
2 polymer structure (Figure 5B). Guironnet and coworkers exploited a Taylor dispersion effect  
3 that resulted in plug-like flow of even viscous polymerizations.<sup>92</sup> While this worked well to  
4 precisely control the addition of discrete building blocks for bottle-brush copolymer synthesis,  
5 the approach relies on small diameter tubing and long reaction times. An alternative approach  
6 is the use of droplet flow, where slugs of a reaction mixture are compartmentalized by an  
7 immiscible mobile phase.<sup>86-88, 93-95</sup> Each droplet has a small RTD, while recirculation within  
8 each droplet enhances mixing. Droplet flow has the added benefit of translating seamlessly  
9 between tubing of different inner diameter.<sup>86</sup> Choosing a suitable immiscible phase is crucial  
10 for droplet flow. Using an inert gas simplifies purification and can be a sustainable solution,  
11 but such a compressible fluid will change volume over different pressure and temperature  
12 regimes, thus complicating synthesis. An immiscible oil phase is less compressible, but the oil  
13 complicates purification and thus care must be taken to ensure no reagents partition into the  
14 oil phase.

15 Static mixers are a well preceded approach to enhance radial mixing and decrease  
16 RTD, although they typically lead to an increase in the pressure drop across the reactor.<sup>96</sup> The  
17 mixing efficacy with a static mixer depends strongly on the fluid flow rate, solution viscosity,  
18 and liquid miscibility. Consequently, using a static mixer in the research and development  
19 stage of a project, wherein reaction parameters may change rapidly, is not always practical.  
20 An additional limitation is the availability of small-scale static mixers for laboratory use. A  
21 recent innovation by Jensen and coworkers, however, outlined an elegant solution. The simple  
22 thermoforming of commercially available fluoropolymer tubing into a screw-like geometry  
23 using an aluminum mold was shown to improve radial mixing and substantially reduce the  
24 RTD (Figure 6).<sup>97</sup> An alternative to static mixers is to create Dean vortices that result from the  
25 centripetal forces of fluid flowing in tubes with tight curvature, coil flow inversion, and  
26 oscillatory fluid motion.<sup>98-100</sup> Such secondary flow fields, however, are challenging to create for  
27 viscous solutions, with few examples related to polymer synthesis.

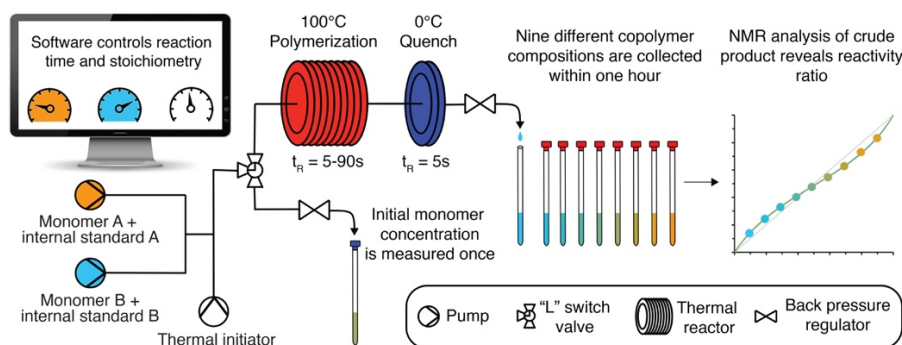


31 **Figure 6.** Static mixing devices made from the thermoforming of commercial fluoropolymer  
32 tubing. Adapted and reproduced from ref 97. Copyright 2018 Royal Society of Chemistry.

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### Engineering innovations enable opportunities to analyze and control polymer structure

The fundamental understanding of how to control polymerization processes in continuous flow has recently translated to advanced reactor setups that provide precise reaction parameters. This understanding has enabled the systematic variation of parameters such as reaction time, temperature, and reagent stoichiometry *in situ*, without stopping the flow system. This reveals opportunities to use flow as an analytical tool for understanding polymerization kinetics. As an example, Leibfarth and coworkers developed a method for determining comonomer reactivity ratios through iteratively changing monomer stoichiometry while simultaneously controlling reaction time to ensure low monomer conversion. The approach was allowed the authors to rapidly generate libraries of copolymer samples and subsequently extract reactivity ratios (Figure 7). The work ultimately allowed the determination of previously unreported comonomer reactivity ratios in under four hours.<sup>101</sup> In a similar fashion, a droplet flow reactor was used by Lu and Wang to quantify the kinetics of ROTEP. Using a standard 6-port 2-position injection valve, a sample loop was filled with the reaction solution before being injected through the reactor by gas delivered from an upstream mass flow controller.<sup>93</sup> Material waste was minimized by avoiding the need for the system to achieve steady state between samples. Junkers and coworkers showed that microreactor technology could be used in conjunction with theoretical kinetic models to acquire insight into polymerization mechanisms. Using Predici, two different possible kinetic models were developed. Utilizing a microreactor with both rapid mixing and precise timing of initiation and quenching, high quality kinetic data was generated that distinguished which pathway the polymerization was proceeding.<sup>102</sup> Lastly, Baxendale and coworkers screened the influence of reaction temperature and time on the free radical polymerization of poly(acrylic acid) to rapidly screen a large reaction space. Using the data generated in flow, a kinetic model was constructed that successfully allowed the authors to target the molar mass of poly(acrylic acid) made through an uncontrolled chain growth process.<sup>103</sup>



29

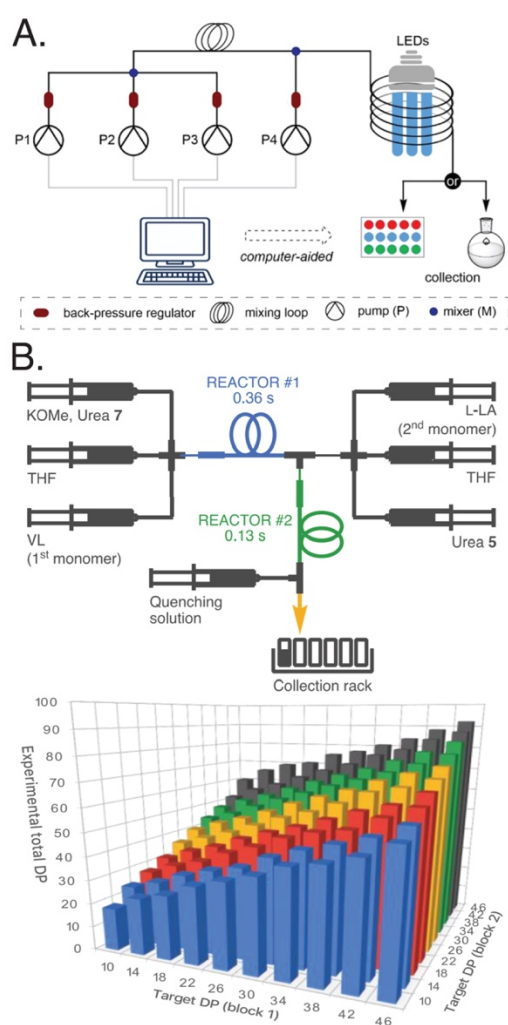
1 **Figure 7.** A flow system designed for the rapid quantification of comonomer reactivity ratios.  
2 Adapted and reproduced with permission from ref 101. Copyright 2018 Royal Society of  
3 Chemistry.

4  
5 Flow systems that provide precise and reproducible control of reaction parameters also enable  
6 complementary approaches to control polymer structure compared to traditional batch  
7 synthesis. As an example, Walsh and Guironnet demonstrated how the temporal separation  
8 of two sequential, mechanistically distinct polymerizations (ROTEP and ring-opening  
9 metathesis polymerization) provided an approach toward shape-controlled bottle-brush  
10 copolymers.<sup>89, 104</sup> Saubern and coworkers showed how slow addition of reagents in flow could  
11 be achieved using tube-in-tube reactors. The time-dependent diffusion of a comonomer out of  
12 an etched stainless-steel inner tube results in the slow addition of that comonomer into a  
13 tubular reactor at all points along the reactor. This concept facilitated the production of gradient  
14 copolymers that deviated from the reactivity ratios of the individual comonomer pairs due to  
15 the slow addition of one component from the inner tube.<sup>105</sup> The concept proved general to a  
16 wide variety of comonomer pairs, but the study was restricted to the evaluation of polymers  
17 made by a RAFT mechanism. While viscosity has long been a limitation to producing high  
18 molecular weight polymers in flow, Yundong and coworkers demonstrated the use of droplet  
19 flow with a fluoruous immiscible phase. The fluoruous oil preferentially coated and lubricated the  
20 fluoropolymer tubing walls, facilitating synthesis of polyacrylamides that exceeded a molar  
21 mass of 1 million g/mol. In-line purification methods have also provided unique opportunities  
22 to telescope multi-step procedures. Baxendale and coworkers developed a membrane ultra-  
23 filtration method to continuously purify poly(acrylic acid) from a crude reaction mixture.<sup>106</sup> Bally  
24 *et al.* demonstrated another example of in-line purification utilizing nanoprecipitation to  
25 simultaneously recover synthesized polymer and remove residual monomer and catalyst. The  
26 introduction of a non-solvent post polymerization resulted in a colloidal suspension of  
27 nanoparticles with a narrow particle size distribution.<sup>107</sup> Further innovations in the in-line  
28 purification of polymeric materials will be necessary to allow the integration of polymer  
29 synthesis with property testing.

30 Building from pioneering work by Beers and coworkers, advances in reactor design  
31 have spurred the construction of flow systems for the high throughput synthesis of diverse  
32 polymeric materials.<sup>108</sup> Leibfarth *et al.* constructed a flow system that greatly expedited the  
33 synthesis of sequence-defined polymers by semi-automated iterative exponential growth  
34 (IEG). The Flow-IEG system conducted three reactions and an in-line extraction in a single  
35 system and its increased throughput enabled a systematic study of the influence of sequence  
36 and connectivity on the thermal properties of well-defined oligomers.<sup>109-110</sup> In an approach that  
37 took advantage of chain-growth processes, Chen and coworkers demonstrated an automated



1 system that used droplet flow to simultaneously avoid problems with residence time  
 2 distribution and viscosity for photoinduced electron transfer RAFT polymerization. This  
 3 method resulted in the synthesis of a library of 11 statistical copolymers in 11 minutes (Figure  
 4 8A).<sup>95</sup> In a truly high-throughput approach, Park and coworkers took advantage of urea anion  
 5 catalyzed ring-opening polymerization of lactones and cyclic carbonates. Controlled  
 6 polymerizations were complete in residence times as low as 6 milliseconds. Furthermore, an  
 7 *in situ* catalyst switching strategy enabled the synthesis of well-defined block copolymers from  
 8 comonomers with drastically different reactivity. Interfacing this powerful chemistry with  
 9 automation facilitated the generation of a 2-dimensional library of 100 diblock copolymers in a  
 10 total reaction time of under 9 minutes (Figure 8B).<sup>111</sup>  
 11



12 **Figure 8. A:** A droplet flow system for the synthesis of copolymer libraries, where pump 4  
 13 delivers an immiscible fluid for droplet formation; **B:** High throughput block copolymer  
 14 synthesis achieved using a catalyst switching strategy. Adapted and reproduced with  
 15 permission from refs 95 and 111. Copyright 2019 American Chemical Society.  
 16

17

## 1 **Complex Reactor Geometries Outlook**

2  
3 A deeper understanding of how fluid dynamic phenomenon influence polymer structure and  
4 composition in continuous flow polymerizations has enabled the realization of powerful  
5 synthetic technology. For high throughput polymer synthesis, the ability to modulate  
6 continuous variables *in situ* provides an operationally simple method to rapidly synthesize a  
7 large diversity of polymer samples. While similar throughput could be in principle achieved  
8 through the use of robotic tools in batch, the small-footprint and easily programmable nature  
9 of continuous flow systems provide a broadly accessible and user-friendly approach to  
10 generating libraries of copolymers. The ultimate value of high throughput synthesis, however,  
11 will only be realized if relevant analytical techniques can be performed on a commensurate  
12 timescale to synthesis. While some progress has been made in this area, further innovations  
13 are needed.<sup>107, 112-113</sup> The integration of such analytical technology would enable seamless  
14 integration of the artificial intelligence algorithms to guide the synthetic hardware, thus creating  
15 a closed-loop system that optimizes polymer structure toward a desired function.<sup>114</sup> The  
16 integration of artificial intelligence and continuous flow polymerization has the potential to  
17 create complex copolymer solutions for multivariate challenges, especially those where  
18 interdependent variables make discrete structure–property relationships difficult to discern.

## 19 20 **CONCLUSION**

21 Only a tiny fraction of the range of intricately designed, multi-component and multi-  
22 segmented, architecturally diverse copolymers have been synthesized in a continuous flow  
23 setup. In some cases, the advantages of employing flow chemistry for polymerizations cannot  
24 justify the effort required to build customized synthetic setups. However, as the field  
25 progresses further, the equipment and experimental setups required to make both simple and  
26 complex polymers alike will become more readily available. Continuous flow technology may  
27 become a standard fixture in the polymer chemist’s toolbox, whereby even non-experts in  
28 chemical synthesis can make custom materials in a user-friendly and continuous process.  
29 Ultimately, continuous flow polymer synthesis represents an emerging and enabling synthetic  
30 tool to unlock polymeric materials with precisely controlled architectures and desirable  
31 properties for a wide variety of commercial applications. Further investigation, including  
32 detailed analysis of fluid dynamics, for example, will expediate this process and expand our  
33 access to new and diverse polymer constructs.

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## 5 **Notes**

6 The authors declare no competing financial interest.

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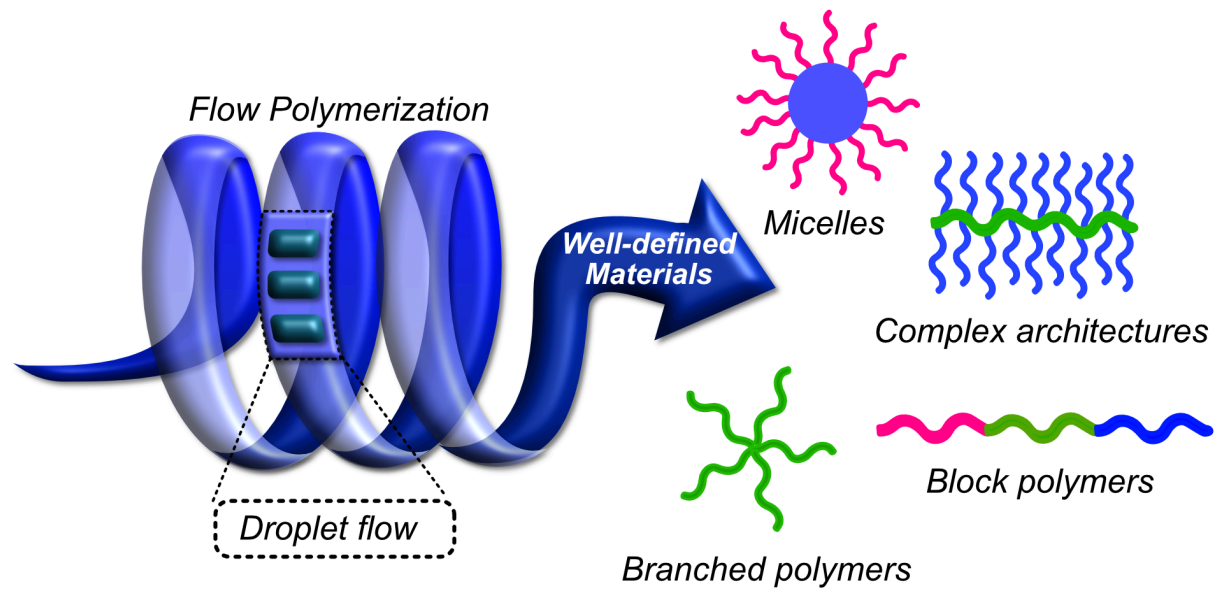


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**Polymerizations in Continuous Flow: Recent Advances in the Synthesis of Diverse Polymeric Materials**

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