Precise Macromolecular Engineering via Continuous-Flow Synthesis Techniques

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The current state of the art of polymer synthesis in (microstructured) continuous-flow reactors is given, focusing on controlled/living polymerization methods that allow for precision polymer design. Emerging trends and the most notable developments are discussed. Especially, the field of multistep reactions and online monitoring are highlighted, which in combination may give access to fully automated high-throughput polymer synthesis reactors in the future.

Keywords: Polymerization, continuous flow, automation, online monitoring, precision polymer design

1. Introduction

Flow synthesis, especially when conducted in microreactors, has in recent years opened pathways towards synthesis methods that otherwise would be inaccessible or at least very difficult to conduct. In this sense, continuous-flow techniques do not only mark a technological advance and yet merely a different approach from a chemical engineering point of view. Much more, flow technology is an enabler for the development of novel (or rediscovered) chemistry and, at the same time, delivers all advantages of a state-of-the-art technological development [1]. Batch (or better flask) chemistry is simple and easy to carry out and hence since over 150 years the standard method for chemical research up to small and intermediate scale industrial production. Continuous-flow techniques on the other hand represent a hurdle to start using them due to the on first glance less intuitive mode of operation and higher sophistication of equipment (certainly when coming from a standard pure chemistry education). Once in use, however, they unfold a potential that is inaccessible via classical methods and prove an easy mode of operation if a few points of considerations are kept in mind [2–5]. The sophistication of the equipment gives direct access to automation. The controlled way in which reagents are mixed and pumped through the reactors allows for a reproducibility that is hardly reached in batch wise operation. Furthermore, the distinct advantages of micro- and milli-structured flow reactors with respect to heat transfer (the reader is referred to literature for a discussion of these effects) allow for a direct upscale of reactions and hence shorten the way from chemical discovery to commercial production of compounds [3]. An often found criticism on flow reactions, especially in the realm of polymer chemistry where highly viscous or heterogeneous reaction mixtures are very common, is that reactors must be optimized for each reactor and that flask-based chemistry is more versatile. While this is certainly true for some types of reactions, such criticism generally is blind to the plethora of glassware modules that have been developed over decades and centuries for laboratory-scale synthesis to react to the various situations one can find themselves in during synthesis. A similar variety is possible with regards to continuous-flow techniques, and while some issues still need to be resolved, it is in the end only a matter of education to train chemists to adapt to different situations intuitively with flow technology. The increasing number of academic laboratories and industrial production facilities picking up continuous-flow synthesis is the best proof of this hypothesis.

Nevertheless, the largest advantage of flow reactors in a larger scope is probably associated with the intrinsic adaptability of the technology. Flask-based chemistry requires at all stages trained personnel and a suitable environment, hence a chemistry laboratory. Flow technology is, once a procedure has been worked out and adapted to a certain process, more mobile and can be employed in principle also outside classical chemical laboratories. Furthermore, since operation can be highly automated or at least standardized, its use becomes more available to non-experts. Much as many biochemical processes have been optimized and automated (see for example peptide synthesizers) so that they can be used by scientists with limited chemical education, flow chemistry offers the opportunity to transfer routine synthesis to the place of need: the workplace of applied science research. Whether this is a biology, pharmacy, or materials engineering workplace does not matter in this sense. Flow chemistry hence not only enables new chemistries or chemical engineering pathways but also shifts chemical synthesis from the workbench of a chemist to the user of the synthesized compounds. While not established yet, polymer research has the largest potential to benefit from this aspect.

Applied polymer research often requires systematic variation of polymer structures; be it in composition, polymer chain (or block) length, etc., most researchers do not have direct access to such libraries of materials directly (see also Figure 1 for examples). Commercially often unavailable (or associated with very high costs) materials must be sourced from experienced polymer synthesis laboratories. In these laboratories, however, emphasis is often put on development of new materials and chemical methodologies and the task to systematically vary structures is often regarded as unattractive. Scaling of methods additionally often represent a significant hurdle. Application tests often require amounts of materials that are typically not handled in synthesis labs. Due to these reasons, applied research is often hindered. If scientists would gain the ability to produce their own materials, this gap could be closed and access to more innovation would be granted. In light of this potential, the current state of the art in continuous-flow polymer synthesis is sketched, followed by an in-depth discussion of trends and future challenges in technological developments. These techniques and developments will also play a significant role outside applied science research laboratories. Also, chemical laboratories often have a need for standardized reproducible production, and obviously, industrial production is at a point where continuous-flow techniques become a serious alternative for batch-based chemistry below multi-ton production scale. Any future development in flow technology will of course have a direct impact in these realms as well.

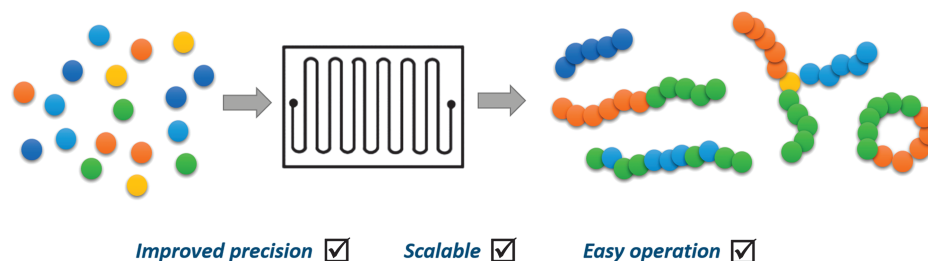* Address for correspondence: tanja.junkers@uhasselt.be

Improved precision ☑   *Scalable* ☑   *Easy operation* ☑

Figure 1. Precision polymer engineering via continuous-flow reactors

2. Current State of the Art

Continuous-flow polymerizations are in use since decades for large-scale industrial production. However, only in the past decade they have found access to research and development laboratories to a larger degree [2]. A good historic overview on continuous-flow polymerizations and polymer modification is found here [6]. Practically, all types of polymerization have been investigated in flow micro- or milli-reactors [7]. Step-growth polymers are studied hereby to a lesser extent, while the main focus is various types of chain growth polymerizations. High-molecular weight polymers can be obtained, for example, from free-radical polymerization; however, viscosity is hereby often a limiting factor. To avoid blockages of reactors, high molecular weight polymers are often synthesized in heterogeneous flow conditions, often in the form of polymer particles (emulsion or suspension based) and beads (oil-in-water droplet phase flow conditions) [4]. Solution polymerizations are typically limited to several ten thousand Da in size, which is, however, for many precision polymers more than sufficient to achieve desired polymer properties [8]. In this respect, controlled and living polymerizations are the most interesting polymerization methods to be applied to flow chemistry, also because already small product amounts can gain very significant commercial value. Here, a differentiation between radical pathways (reversible deactivation radical polymerization, RDRP) [9–11] and ionic polymerizations (including ring-opening polymerizations, ROPs) must be made. The earliest examples for flow polymerizations are anionic polymerization [4, 12]. These polymerizations are typically difficult to perform due to their high sensitivity towards moisture and impurities of all kinds. Flow reactions can be highly advantageous as impurities and residual water adsorbed in the equipment can be easily consumed in the beginning of a flow run during reactor stabilization, hence allowing to produce high-definition polymers with comparative ease. Of course, the usual advantages of flow chemistry, such as improved mixing and better temperature control, are fully retained, allowing for unusually fast reactions, as was impressively demonstrated by Yoshida and coworkers [13, 14]. Next to anionic polymerizations, similar advantages could also be identified for cationic polymerizations, which can be carried out at very high temperature under flow conditions without inducing side reactions typically observed in batch or microwave reactions [15]. ROP has also been found to work efficiently in flow conditions (it should be noted that most ROPs are only formally anionic polymerizations and are typically catalyzed by tin compounds, organocatalysts or enzymes) [16, 17].

With RDRP methods, all major types of polymerizations have been successfully applied to flow reactors, be it thermal reversible addition fragmentation chain transfer (RAFT) [18, 19], photo-induced RAFT and photoelectron-transfer RAFT [20–23], atom transfer radical polymerization (ATRP), single electron transfer living radical polymerization (SET-LRP) [24, 25], nitroxide-mediated radical polymerization (NMP) [26], or cobalt-mediated radical polymerization [27]. Without doubt, any solution-based controlled chain growth process can be applied to flow processing. Typical advantages are a lowering in dispersity of the product, an effect that can be traced back to the improved isothermicity of the reactors (which prevents unwanted termination reactions) [28]. As a further advantage, the better temperature control also allows to carry out polymerizations outside the typical temperature window known from batch processing. In consequence, reactions can be accelerated significantly without losing control over the reactions. Examples for this effect are numerous, and the number of reports on polymerizations in flow reactors is consequently increasing quickly over the recent years (see Figure 1). Next to linear polymers, the same effect is also observed for branched polymer systems, such as hyper-branched polymers [29], star polymers [30] of block copolymerizations [31], and polymer modifications, such as endgroup conversions or click-type polymer conjugation [32, 33].

Photoreactions can be carried out with high precision and efficiency in continuous-flow reactors [34, 35]. The small optical pathlengths allow for full illumination of reaction solutions, which leads to acceleration of reactions of orders of magnitude. This effect is also nicely visible for photopolymerizations, which gives an additional advantage to such flow processes [36]. Most photopolymerization techniques have by now been tested in flow reactors and have been generally found to be more efficient and economic compared to their batch counterparts [32]. In that respect, photopolymerization is a significant driver in application of flow techniques to polymer systems, as photo-induced polymer reactions undergo currently a renaissance and gain increasing significance in the field [37, 38].

3. Multistep Reactions

Homo- and statistical block copolymers can be made in virtually any chain length (up to a reactor-dependent viscosity limit), dispersity, and functionality. Flow reactors do not limit the synthetic possibilities, yet allow as described above for an improvement of reaction outcomes. In this sense, flow polymerizations have already matured to a high degree. Nevertheless, especially when targeting precision polymer synthesis, more than a single reaction is required. Either sequential polymerization steps, modular click reactions, or post-polymerization modifications are required to achieve a selected goal. While flow synthesis can be used independently as well as in combination with batch processing in subsequent reaction steps, a large potential is unfold when reactions are carried out consecutively in a continuous fashion. Such multistep flow procedures, sometimes also referred to as reactor telescoping is far from trivial. Addition of several reactor stages (and hence reactant injection points) increases the complexity of the processes, and requires that questions such as intermediate product purification or solvent switch must be addressed. Inline purification of polymer systems is not fully explored to date; only few examples exist where, for example, counter-flow extractions are used to remove side products or residual monomer from a polymerization [39]. The question of how to switch solvents in a continuous reactor system is still largely unresolved, not only for polymer flow reactions. Consequently, most multistep flow reactions focus on reactions that

do not require purification steps or changes in solvent polarity. The best example for such reactions is block copolymerizations or postmodification reactions after polymerization. If designed carefully, such processes allow to create libraries of compounds in an efficient manner. Synthesis of diblock copolymers from various techniques is widespread, but also higher order block copolymers have been synthesized in telescoped reactors before [40].

Figure 2 depicts the outcome from such reaction as an example for this type of multistage reactions. In this case, thermal RAFT polymerization was used to polymerize a variety of acrylate monomers. The difficulty in setting up such reactor is that high monomer conversions must be reached in each individual reactor stage, as residual monomers cannot be removed between reactor stages. Hence, very detailed knowledge on the reaction kinetics is required in order to correlate residence times with polymerization progress. Furthermore, every injection of monomer leads to a volume increase and dilution of the actively propagating polymer. This has direct influence on the kinetics and on the residual flow rates. As a rule of a thumb, with every reactor stage, the volume of the reactor needs to be doubled in order to provide constant residence times. This factor needs to be accounted for when designing multistage flow reactions. Increasing volumes lead additionally to longer reactor stabilization times, making kinetic investigations material- and time-consuming. Also, addition of several reactors also requires use of a large number of pumps, which can become a significant cost factor quite rapidly. Nevertheless, once set-up, such multistage reactors resemble true high-throughput reactor systems. Control of these reactors can be automated (see below) and connected to online monitoring, giving then access to systematic data in a very short amount of time. Compared to classical batch-based synthesis robots (i.e., chemspeed robots) [41], such multistage reactors can form a cost-effective alternative. With the example shown above, already without any computer-control and online monitoring, a large library of block copolymers was synthesized in a short amount of time, providing materials on a significant scale (suitable for material tests), some in quantities of several 100 g over overnight synthesis run [36].

To date, few multistep polymer reactions are reported in literature, but a significant increase in number of studies can be expected for the nearer future. With increasing availability of in-line purification methods, hurdles in applicability will be removed and open a much larger array of reactions to be used. The potential to access complex polymer materials simply from monomers is highly attractive and will certainly find application in all areas where such materials are required either in systematic product libraries or where specific products need to be resynthesized frequently. In both cases, the additional effort in setting up reactor assemblies is economically justified.

4. Online Monitoring and Reaction Automation

Flow reactors are optimal for automation of equipment. Since processes are designed to operate continuously without manual intervention, all steps can be controlled by computers. Process parameters are typically flow rates (and hence concentrations and reaction times) and temperature, which are both easily accessed electronically. It is hence quite easy to use simple computer programs to steer and carry out flow protocols. However, to reach a true form of reactor automation, more effort is required. Ideally, an automated reactor is able to monitor the reaction outcome and can adjust its process parameters in case the desired product is not detected in the target yield. With proper online analysis, self-optimization of reactions can be achieved by relatively simple algorithms [42, 43]. Such reactor already exists, e.g., for synthesis of pharmaceuticals, and the first algorithms for reactor optimization of polymer products have surfaced recently [44]. Nevertheless, the most significant hurdle for the setup of self-optimizing automated flow reactors is the choice of adequate online-monitoring tools [45]. Generally, any online-monitoring technique should be ideally non-invasive and have short response delay times. The most common tool for that purpose is Fourier transform infrared (FT-IR) spectroscopy [46]. FT-IR spectra can be sampled on a very short time scale, and sufficient knowledge on the product (and intermediate) spectra provided allows for highly accurate quantitative detection of chemicals. Ultraviolet–visible (UV–vis) spectroscopy is also easily applied and wide spread as detector. Other spectroscopic tools such as low-field nuclear magnetic resonance (NMR) or mass spectrometers have equally found their way in online reactor monitoring [47].

Polymer characterization typically uses the abovementioned techniques, yet these are often not fully sufficient to gather all relevant information. In the industrial field, technical solutions
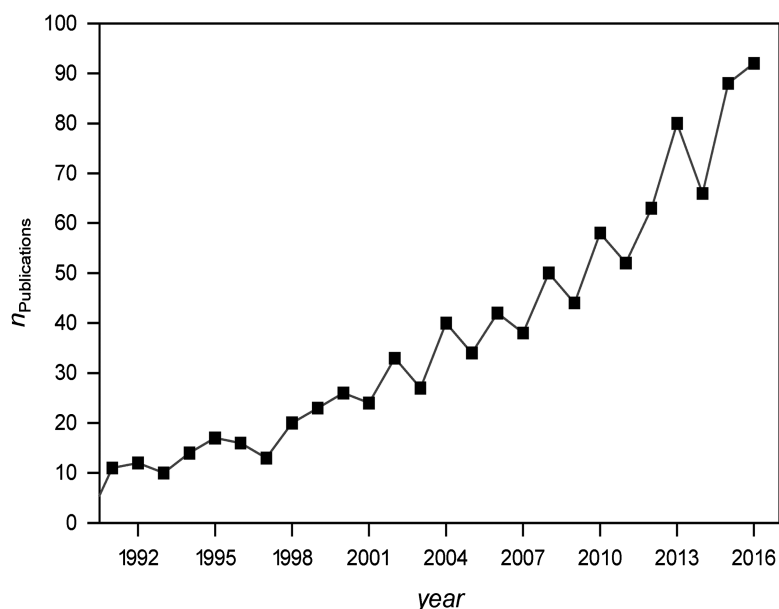

Figure 2. Number of publications in the field for continuous-flow polymerization per year since 1990 (source: ISI Web of Science, keyword search on "continuous flow," "microreactor," and "polymerization")

for paramount polymerization monitoring were established (see the so-called ACOMP system) [48, 49], yet these are only of limited applicability on the laboratory scale. Typically, spectroscopic methods give insights into the identity of a product. This is, from an online-monitoring perspective, of lesser interest (Figure 4). The type of monomers and thus the resulting polymer is typically known in a reaction a priori. More interesting is knowledge on polymerization (or polymer modification) progress and, very importantly, molecular weight. While reaction progress is monitored conveniently by the non-invasive FT-IR technique, molecular weight data is more difficult to access. NMR spectroscopy (which is limited by viscosity and data acquisition times and hence is difficult to be operated in a fully non-invasive fashion) can give indications, yet is limited in accuracy. Full access to molecular weight data, and more implicitly molecular weight distributions, is only given by size exclusion chromatography (SEC). SEC is based on high-performance liquid chromatography (HPLC) techniques and requires defined injection of samples at given point of times. Detection is hence non-continuous and time-consuming, resulting in low time resolutions and large analysis delay times. Nevertheless, despite these disadvantages, also SEC monitoring is available for flow reactors [50, 51]. Last, but not least, also end group identification is important for polymer synthesis, especially in the field of precision material design. This information is best accessed via mass spectrometry [52]. Polymer analysis, however, requires soft-ionization techniques for proper analysis, rendering electrospray ionization mass spectrometry (ESI–MS) the only viable option. While such detector can be operated fully online, it is by far the most expensive one and hence limited in application [53–55].

Figure 3 gives an overview on the above discussed detectors. More in-depth information on these detection techniques can be found in a recent review on the topic [44]. To date, the various detection techniques have mostly been applied independently from each other. Large potential is seen in the combination of detectors, which will make paramount self-optimization of reactor feasible. Especially, the combination of infrared spectroscopy with SEC or NMR with SEC is very interesting, as this would cover the most commonly applied polymer characterization methods. While MS techniques are most interesting for any reaction involving "living" polymer chains, as well as for polymer analogous reactions and click modifications (hence all reaction connected with a distinct mass change per chain length), FT-IR, NMR, and SEC will be of highest interest for polymerization reactions of any kind, be it chain growth of step-growth polymerization. NMR can be specifically useful for copolymerization reactions, as it allows for direct determination of copolymerization parameters.
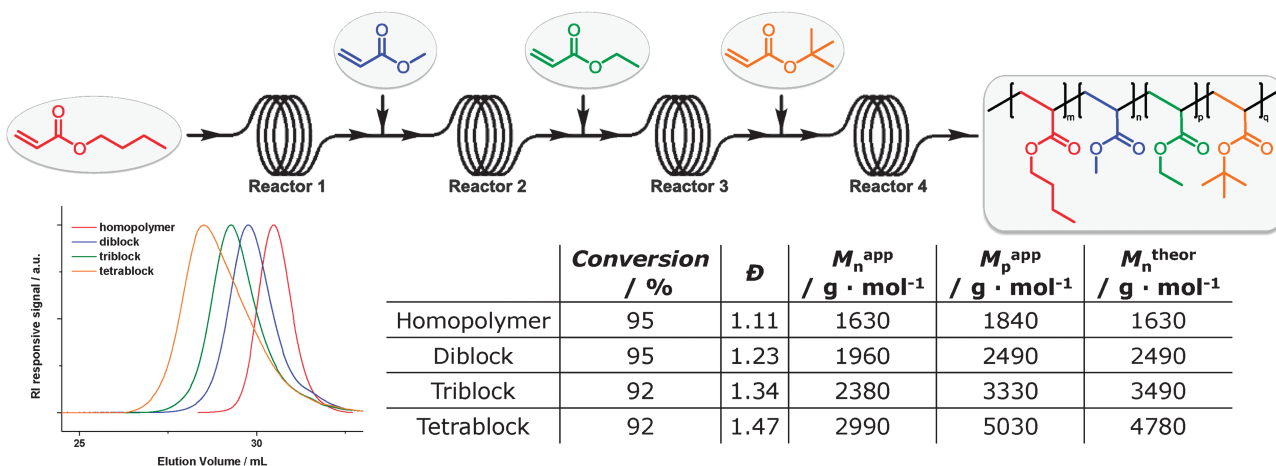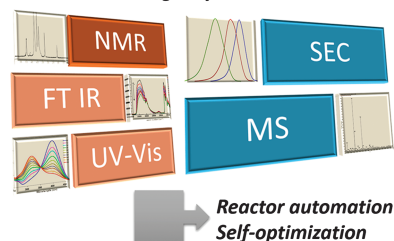

Figure 4. Overview of available online-monitoring tools in continuous-flow polymer synthesis reactions

5. The Past and the Future

In many ways, flow chemistry, despite its enormous potential, has not yet moved past classical batch chemistry possibilities. In its current stage of evolution, flow chemists still orient themselves at classical batch chemistry and try to recreate their abilities. This approach tends to lead to optimization of protocols, better economy of reactions, and an increased safety of processes. However, truly original examples, hence synthesis targets that would be unreachable in classical laboratory techniques, in the field of polymer chemistry have not really been reported. A breakthrough in this sense can be expected with the ever increasing scope of organic chemistry continuous-flow activities. The polymer community is known to be delayed in its innovation by several years as protocols from organic chemistry need to be adapted to polymer systems, which requires time. Since organic chemistry already acknowledges chemical synthesis pathways that can only be carried out in continuous-flow microreactors (see, for example, flash chemistry [9] or the so-called forgotten chemistries) [1], it is only a matter of time before these are picked up in the polymer field. A specific role is here assigned to electrochemistry [56]. Electrochemistry in contemporary polymer synthesis plays only a minor role. Only few examples exist where currents are directly used for synthetic uses (if one does not count electrode surface grafting) [57]. It can be stated with some certainty that electrochemical polymer synthesis is somewhat unchartered territory, simply due to the fact that batch procedures lack any specificity. Flow processing has already provided enough evidence that synthetic electrochemistry can be carried out with high precision, and it is easily foreseeable that this advantage will also soon be applied to polymer systems.

For more conventional polymer synthesis approaches that are known from batch chemistry, a further diversification can be expected. While much attention is now given to translation

	Conversion / %	Đ	M_n^{app} / g · mol^{-1}	M_p^{app} / g · mol^{-1}	M_n^{theor} / g · mol^{-1}
Homopolymer	95	1.11	1630	1840	1630
Diblock	95	1.23	1960	2490	2490
Triblock	92	1.34	2380	3330	3490
Tetrablock	92	1.47	2990	5030	4780

Figure 3. Reactor setup for the multistage block copolymerization of tetrablock polyacrylates via thermal RAFT polymerization. Figure reproduced with kind permission from RSC [36]

of single polymerization protocols, it is expected that integration of processes in multistep reactions will become more and more important. Such integration requires to carry out different polymer reactions in sequence, but also purification steps. Further challenges are to push boundaries towards higher molecular weights, which is of high interest for certain industrial applications. Due to the inherent viscosity increases involved, such systems need to be realized via heterophase polymerization. While significant advances have already been made in this direction, no routine techniques are yet established.

As described, distinct developments in the chemistry used in flow reactors can be expected, which will almost certainly have large impact on the general development of the field of polymer synthesis. An equally profound change is envisaged for commercial use of polymers. As described in the introduction, classical batch-wise chemistry requires highly trained staff and adequate chemical laboratory environments. While the handling of chemicals will always require a certain level of expertise and safety installations, a very significant decrease in safety precautions, education of operators, and hence global costs of use is expected when purely flow procedures are applied. Flow reactors are inherently closed systems, much safer in operation, and due to the above described reactor automation able to be handled by personnel that did not go through year-long training. With this development, production of polymer products becomes available to small enterprises which at this point in time cannot afford own chemical production environments. This development will remove the need to buy polymers from third party suppliers, which in turn will not only lower costs but also foster faster innovation cycles. In this respect, flow chemistry becomes a part of the democratization of precision polymer production — away from few central players in the field towards on-site production of high-end materials. Such scenario will not hold for products that are produced in bulk on multi-ton scale (hence in situations where few global players are able to use scaling effects to reduce cost). For added-value materials that are typically only required in kilogram quantities, this development might, however, mark a very significant step.

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