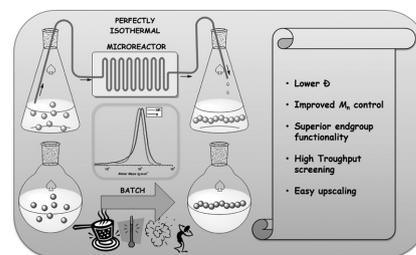


Precision Polymer Design in Microstructured Flow Reactors: Improved Control and First Upscale at Once

Thomas Junkers

Continuous flow synthesis techniques have in recent years conquered laboratory scale synthesis, yet within the field of precision polymer synthesis its use is still not fully established despite the large advantages that can be gained from switching from classical batch-wise chemistry to flow chemistry, often already by using relatively simple chip-based or cheap tubular micro- and mesoscaled reactors. Translating a polymerization from batch to continuous flow marks not only a mere change in reactor engineering, but also leads to numerous advantages in the polymerization with respect to kinetics of processes and especially product quality. In flow, polymerizations are not only speed up, they also provide materials with better dispersities and higher chain end fidelities when conditions are chosen accordingly. The underpinning effects causing these improvements are demonstrated and discussed. Further, also information on required laboratory equipment and recent developments in online reaction monitoring are highlighted to give newcomers to the field an idea about the potential of continuous flow polymerization.



1. Introduction

Controlled chain growth polymerization techniques, ranging from anionic to radical routes have truly revolutionized the possibilities of bench chemists with regards to target structures, definition, dispersity and purity. Macromolecular

structures and materials compositions that were not just two decades almost unthinkable to synthesize are nowadays available from comparatively simple and cost-effective synthetic procedures. Especially deactivation reversible radical polymerization methods (including reversible addition fragmentation chain transfer, RAFT,^[1] atom transfer radical polymerization, ATRP^[2] and nitroxide mediated polymerization, NMP^[3] to name the most prominent) in combination with various click-type chemistries^[4,5] have shown the greatest potential in this respect. Yet, serious issues have remained when addressing scalability of the processes. While almost any possible macromolecular structure has

become available, reactions are usually carried out on milligram scale and often barely enough material is obtained to allow for a full characterization of the product. This poses significant hurdles when it comes to either commercialization of a new complex material, or simply when upscaling of the reactions is required for further material testing.

In any way, research in recent years has moved away from developing synthesis routes towards new targets, but focuses more on refinement of existing techniques or development of alternative, but yet more efficient synthesis pathways. The latest developments in the realm of multiblock copolymerization are a good example for the first,

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while development of ultrafast click methods exemplifies the latter.^[6–9]

Another convenient way to improve control of reactions is to look at the process parameters itself, a strategy often not applied in synthetic chemistry. In research labs, reactions are carried out in flasks in batch processes. “Flask-chemistry” is simple and versatile. Reactions can be conveniently scaled between few milliliters up to liter(s). Heating and cooling is arranged by immersing the flasks in baths or by using heat mantles. Other advantages of such approaches is the relatively easy dosing of reactants (dripping funnels, syringes) and that direct postprocessing (i.e. distillation) is conveniently available. Yet, batch chemistry also suffers from severe drawbacks. Heating and cooling is in most cases non-ideal and temperature gradients exist throughout the reaction mixture and hotspots may exist. Furthermore, if reactions are exothermic – as polymerizations always are – heat may not be efficiently dissipated and the success of the reactions becomes consequently dependent on the reactor geometry. In essence, reactions are thus not fully upscalable (as heat transfer must be facilitated when volumes are increased). More severely, not only yield and conversion, but also the quality of the products is dependent on the type of reactor chosen as changed temperature profiles result in changed kinetics that govern the chain growth reactions.^[10–12]

Figure 1 demonstrates this effect for the RAFT polymerization of bulk butyl acrylate at 100 °C. In this particular case, 20 mL of acrylate were polymerized in a round bottom flask. Conversion of the reaction was followed by in-line infrared spectroscopy and by a thermocouple to determine the exact temperature profile inside the reactor. As initiator, AIBN was employed, which was added to the degassed reaction mixture after approximately



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2 min. As can be seen from the IR transmission (directly proportional to monomer concentration), a very rapid polymerization is observed (within expectations for a high-temperature acrylate polymerization). At the same time, the reaction temperature increases tremendously due to insufficient heat dissipation in the reactor. In less than a minute, an increase in temperature of more than 30 °C is reached. This increase in temperature leads to a high acceleration of the initiator decay in the system. While AIBN decomposes with a half-life time of ≈ 490 s at 100 °C, 20 times faster decomposition must be expected at the peak of the heat increase. As a consequence, more dead chains are produced throughout the polymerization than

theoretically anticipated,^[7,13] leading to increased broadening of the distributions, loss of end-groups and loss of block structure in case block copolymers were targeted.^[12]

The consequence is seen in Figure 2. The batch process, where exothermicity disturbed the reaction, yields a polymer with identical number-average molecular weight as an identical flow process, yet, dispersity is higher for the batch reaction. The peak molecular weight is shifted towards higher masses which is accompanied from a low-molecular weight shoulder, stemming from increased termination levels. The difference might seem to be small, but the effect accumulates quickly, especially when further upscaling the reaction.

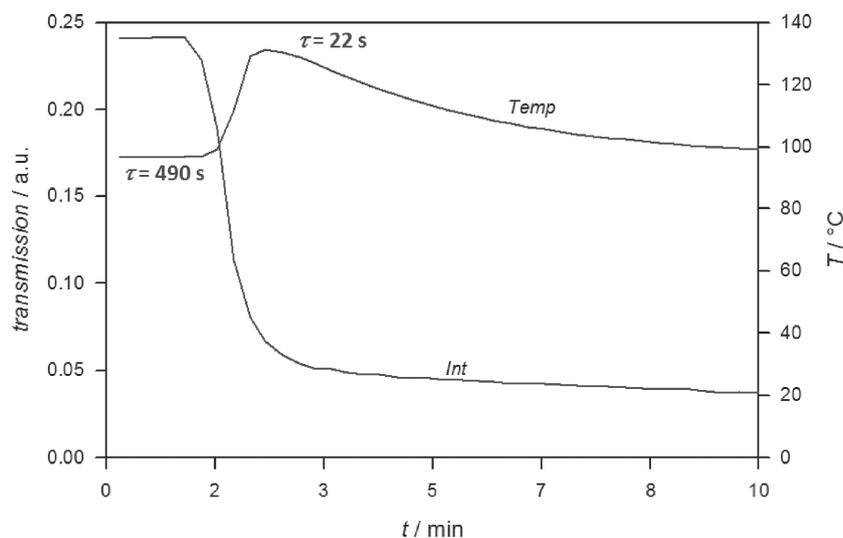


Figure 1. Temperature profile and monomer concentration in a RAFT-mediated bulk butyl acrylate polymerization at 100 °C.

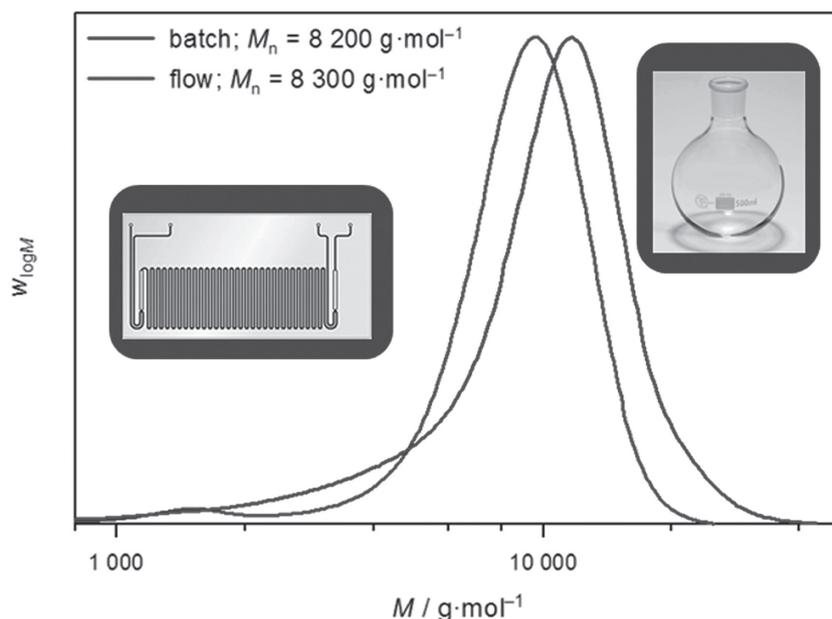


Figure 2. Molecular weight distributions for (block) copolymers obtained from RAFT polymerization in flow (left) or batch (right) operation under identical reaction conditions and monomer conversions of roughly 75%.

As already indicated in Figure 2, flow chemistry opens a convenient way to overcome or to at least significantly reduce these problems.^[10,11] In recent years, microreactor technology (MRT) has matured into a broadly available technique that allows for lab-scale synthesis of a large variety of compounds. Especially in the field of classical organic chemistry, MRT has found entry into everyday synthesis,^[14,15] but also in the polymer synthesis an increasing number of applications is found.^[16] Microreactors are comparatively cheap and allow for the synthesis of milli- to kilogram scale of products. While reactor types may differ from each other, all have in common that they provide an excellent heat transfer (by keeping an optimal surface to volume ratio) to avoid the above described problems.^[11] In this way, rapid reactions or highly exothermic reactions become easily manageable and may be performed under otherwise unusual reaction conditions, i.e. lithiations may be carried out at room temperature instead under extensive

cooling. At the same time is operation under slight overpressure rather unproblematic for most reactor systems, thus broadening the temperature range available for reactions. At pressures of only few bars, operation up to 200 °C or higher employing conventional organic solvents is feasible without restrictions. MRT also allows intrinsically for an easy scale up of the reactions. By retaining the heat transfer capabilities, a relatively simple and non-demanding upscale of reactions can be reached. Increasing volumes and tubing diameters inevitably lead to approaching heat transfer complications as in batch reactors; yet by facile design of reactors, these effects can be limited and surprisingly high amount of product is available from larger scale flow reactors that in principle operate under almost the same conditions as their microreactor counterparts. Commercial systems that allow for the fast transfer of reaction protocols from the micro- to pilot plant scale are available. Generally, the advantages of MRT are:

- (i) Perfect isothermicity of reactions
- (ii) Simple scalability from milli to kilogram scale
- (iii) High reproducibility of processes
- (iv) Stable reaction conditions
- (v) Continuous production of materials
- (vi) Simplified handling of hazardous chemicals and intermediates

In combination, microreactors are convenient synthesis tools. They can be used for production of significant product amounts without batch-to-batch variation. At the same time, they provide an almost perfect tool for reaction optimization due to their broader operation window and small scale, especially when combined with online reaction monitoring. In fact, MRT may be seen as a high-throughput experimentation tool not unlike parallel synthesis techniques. Very often, also as a result of the better optimization of the reactions, large accelerations are observed in flow reactors and reactions that usually take hours to proceed may be accessible in minutes or even seconds of reaction time in flow.^[17] In the following, the specific advantages of MRT in the field of precision polymer synthesis are discussed, which mostly manifest in the aforementioned benefits, but also – as discussed above on the example of RAFT polymerization – in a better definition of the obtained materials. It is especially this feature that allows for innovative polymer chemistry as a switch from batch to flow processing not only marks a simple change in process technology, but also allows for the synthesis of materials otherwise inaccessible (regarding purity, functional group control and dispersity). Applying flow chemistry to polymer synthesis is thus not a simple question of engineering, but has also a direct effect on the products obtained itself. It can hence not be stressed enough that flow chemistry has a vast synthetic potential that has not been claimed to date.

2. Flow Reactor Types Applicable to Polymer Reactions

Obviously, a hurdle that needs to be overcome for flow reactors with respect to polymerization reactions are limitations in medium viscosity and handling of risks of blockages. Thus, for many continuous flow processes it is mandatory to keep viscosity low. Various strategies may be applied to reach this aim, be it limiting molecular weights to the oligomeric regime ($<10\,000\text{ g mol}^{-1}$), using high dilution, increased pressure and temperature or by working in biphasic (droplet based) systems, in which the overall viscosity is less determined by molecular weight. Yet, viscosity effects are often overestimated and continuous production of highly viscous mixtures or even heterogeneous systems is possible with the currently available laboratory techniques. While the exact viscosity limitations will depend on the reactor type in use, generally reaction in solution and slightly elevated temperatures are often favored. Use of solvents is often unavoidable, yet flow polymerization processes with less than 50 wt.% of solvent are common for controlled polymerizations. Increasing temperature concomitantly helps to speed up reactions, and is hence partly also a requirement to reach economically feasible reaction conditions. While in batch processing higher temperatures are often avoided due to side reactions, flow reactors are as described more stable and allow to work in better defined temperature intervals, thus allowing to reach good product qualities even under temperature conditions that in batch would be regarded as less favorable.

A further important factor in using flow reactors is user friendliness and costs. Commercial systems exist from various companies, both for chip type and tubular reactors. Reactors can be highly automated and computer

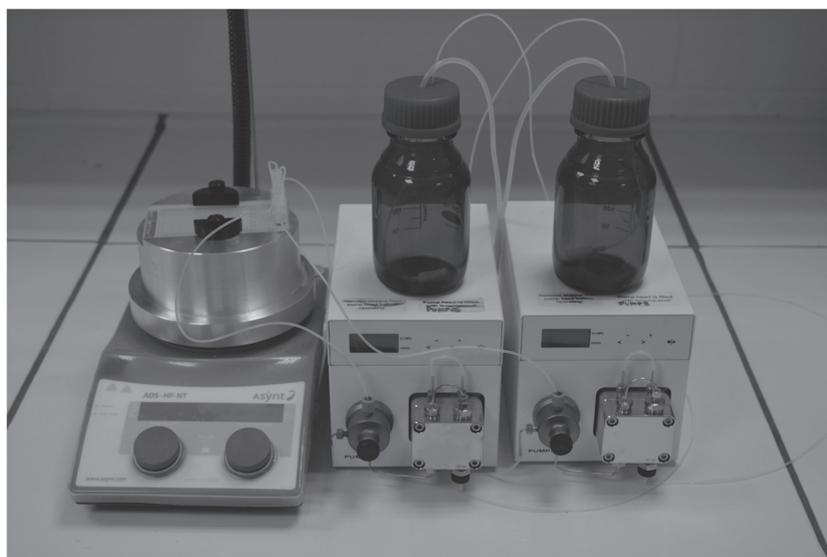


Figure 3. Typical setup for a chip-based flow reactor connected to HPLC pumps for delivery of the starting materials.

controlled, or more simple and comparable in use to classical lab chemistry equipment. Costs range from few thousand EUR/USD to very significant numbers for high-end multipurpose reactor systems. For polymerizations, often simple reactor setups are favored. Since polymer precipitation at joints and other reactor parts need to be avoided, often flow reactors only consist of pumps, a micromixer for effective mixing of starting materials, a residence unit and eventually a pressure and mass flow controller. Simple fluoropolymer tubing is normally sufficient for a broad range of reactions and materials, and most other parts are available from regular HPLC suppliers. For pumps, HPLC pumps or syringe pumps can be used. HPLC pumps are simple to use, but should be employed with caution as mass flow may not be accurate when highly viscous solutions must be pumped through the reactor. Syringe pumps often deliver better results, but reach quickly significant costs when larger volumes and increased pressures are required to be handled.

Figure 3 shows a typical example for a laboratory-scale flow reactor. Starting materials are delivered via two HPLC pumps, which are connected

to a chip-based flow reactor. The reactor is designed to facilitate good mixing, hence no separate mixing unit is required. Heating of the chip is provided via an aluminum block on a classical magnetic stirrer. Tubular reactors can alternatively simply be immersed in an oil bath, hence also there no specific heating/cooling equipment is required compared to classic batch chemistry. Products can be collected at the reactor outlet in a flask, whereby the reaction time is chosen via the flow rate of the combined flows and the amount of crude product is given by the overall runtime of the reactor. Overall, using such equipment is not more difficult than most other regular laboratory equipment. A system as depicted (2.5 mL internal reactor volume) is typically able to deliver tens of grams of precision polymer within a short time span depending on the reaction and monomer type chosen.

3. Radical Polymerizations in Microstructured Flow Reactors

A large number of studies on (micro-)flow polymerization have

been conducted on anionic polymerization systems. Anionic polymerizations are ideal candidates for MRT because of their partly very fast reaction rates and high demand for pure reaction conditions, which can both conveniently be matched in flow reactors. A review on various anionic flow polymerizations is given elsewhere.^[18,19] Controlled radical polymerizations (from reversible deactivation radical polymerization techniques) are less well studied. Yet, for each major reaction methodology, examples can be found in literature and thus allow comparing the outcome of the reactions with batch processes. As a measure for the success of a reaction, the dispersity of the obtained polymer may serve as a quality indicator. It is thereby acknowledged that the success of a controlled polymerization should be assessed based on further parameters such as end-group fidelity and ability for chain extension, yet dispersity allows for a quick comparison. If the dispersity is low, fast initiation is indicated alongside a usually high livingness of the process. A direct comparison of dispersity data is, however, challenging. Not only must experiments between batch and flow be carried out under identical conditions to allow for meaningful conclusions, also various flow reactors may be in use, which can likewise affect the result. A variation in reactor type (chip or tubular reactor) as well as reactor volume (micro- or milliliter scale) can have a

significant impact on the outcome of the reaction.

Table 1 gives examples for such comparison for a number of radical polymerizations. It must be noted that not all flow reactions found in literature display lower dispersities for the flow process. However, as stated above, not many studies allow for a direct comparison since often different reaction conditions are used in flow compared to batch reactions. Regardless, the number of studies in which larger dispersities are observed is very small. Indeed, almost all literature reports on improved reaction outcomes. Tubular reactors are most commonly applied in various sizes and materials, but also chip-type reactors have been applied for CRP reactions,^[23,26–29] nevertheless, no significant difference is seen in the quality that can potentially be reached. For ATRP, a significant decrease in dispersity (at otherwise similar conversion and M_n) was observed by Haddleton and coworkers.^[19] By using a rather large volume tubular PTFE reactor, a decrease in dispersity from 1.24 to 1.07 was observed. Likewise, Bally et al. found a decrease from 1.99 to 1.71 also for a MMA ATRP.^[20] The rather broad distributions in that case are due to the use of branching agents to produce hyperbranched polymers. Interestingly, not only somewhat more narrow distributions were observed in the flow process, also

improved branching efficiencies were achieved. As for ATRP, also for NMP and RAFT, similar increases in reaction efficiency were observed for a number of monomers (see Table 1 for details),^[21–23] which can also be attributed to the more constant temperature profile and thereby much better control in the instant degree of polymerization reached at any instance of time/conversion. In fact, Derboven et al. have demonstrated by extensive kinetic modelling that the decrease in dispersity of polymers obtained in continuous flow microreactors can be directly linked to the isothermicity of the process, as described above.^[30] Next to the more constant radical flux established in flow, it was shown particularly for acrylate polymerization that flow reactions help to avoid side reactions, which lower the livingness of the polymers, and hence broaden dispersity. This effect is not limited to homogenous controlled radical polymerization reactions. Also for emulsion polymerization significant improvements of product properties in flow reactors were noted. Iwasaki and Yoshida demonstrated that free radical emulsion polymerization largely benefits from isothermal flow conditions, with decreases in dispersities from above 9 to 3.6 in some cases under otherwise identical reaction conditions.^[24] Further, Beers and coworkers also noted on the large improvements in quality and in time/yield correlation when

■ Table 1. Overview over some flow polymerization compared between batch and flow synthesis.

Ref	Polymerization type	$M_{n, \text{batch}}$	$\mathcal{D}_{\text{batch}}$	$M_{n, \text{flow}}$	$\mathcal{D}_{\text{flow}}$	Reactor type
[20]	ATRP, MMA	9820	1.24	13200	1.07	Tubular, 10 mL
[21]	ATRP, MMA hyperbranched	3000	1.99	2400	1.76	Tubular, 14 mL
[22]	NMP, STY	16700	1.26	18500	1.19	Tubular, 0.79 mL
[23]	NMP, BA	29700	1.80	26600	1.44	Tubular, 1.8 mL
[24]	RAFT, <i>n</i> BA- <i>b</i> - <i>t</i> BA	8100	1.36	8300	1.14	Chip, 20 μ L
[25]	FRP, BA	10000	9.6	33000	3.6	tubular, 7 mL
[24]	FRP, MMA	7800	2.26	8500	1.83	tubular, 7 mL

performing enzymatic ring-opening polymerization of caprolactone,^[31] an effect that has also been seen for cationic and anionic ring opening polymerizations.^[32,33]

A further significant improvement that flow reactors can provide is found for photopolymerization processes.^[34] (Radical) Photopolymerization is in principle known since decades, yet outside of curing techniques, photoreactions have not gained much interest. This stems mostly from the low scalability of photoreactions in general. While successful on small scale, reactions become ineffective at larger reaction volumes as light is quickly absorbed by the initiating chromophore at the reactor walls, limiting light penetration typically to only few millimeters. Reactions hence cannot be carried out in the bulk, requiring very high light intensities (that in turn cause side reactions), and extensive reaction times. Next to the development of low-cost LED light sources, continuous flow techniques have given a boost to the application of photopolymerization in the synthetic field. In flow reactors, optical pathways are at all times short, hence allowing for much better illumination and light efficiencies in such reactors. Also for polymerizations tremendous efficiency gains have been noted (often reducing reaction times from hours to minutes), while retaining the general improved features of flow polymerizations as described above.^[35–39] In consequence, a true renaissance of photochemistry also in the polymer field is observed, and with certainty continuous flow reactors will play an important role in the implementation of these reactions in regular laboratory procedures, not only due to the simplicity of such flow reactors, but also since these are scalable and allow for production of precision polymer materials on a significant scale.^[40]

4. Upscaling of Precision Polymer Synthesis

Upscaling of flow reactors can be reached by different strategies. In the simplest case, runtimes of reactors are increased, which directly correlates to the amount of material produced. A second possibility is reactor parallelization in which the same reaction is carried out in identical, yet independent reactor setups. Due to the typically very high stability and reproducibility of flow reactors such strategy is easier than in conventional batch synthesis, yet reactor parallelization becomes tedious due to a large amount of pumps, reactors and other parts that need to be exactly synchronized. Hence, most often, a volume increase is considered also for continuous flow processes. The above described advantages of continuous flow reactions diminish when reactor volumes – and specifically channel widths and volume to surface ratios – are increased. However, within reasonable windows, upscaling is possible with large retention of the improved product properties and reactors with large volumes are nowadays available that still retain the excellent heat transfer properties of microscale reactors. Synthesis of kilograms of materials, and in principle ton scale, is feasible within hours in dedicated reactors, and a large variety of reactor types have been designed by various manufacturers for this purpose. Yet, academic literature is somewhat scarce in this area, yet interesting examples have been provided by various groups with very promising results.^[41,42] It should be noted though that even simple reactors, as shown in Figure 3 can allow for synthesis of very significant amounts compared to classical batch chemistry. Especially highly complex precision polymers that are obtained in tedious reaction sequences are often only available in minute amounts, hindering the systematic exploration of their

properties. Grams of products – for example in biomedical research – are very often already sufficient to carry out most necessary tests, yet may not as easily be accessible via non-flow techniques.

5. Online Monitoring and Kinetic Evaluation

Continuous flow reactors display next to their synthetic potential also a very high value in the kinetic and mechanistic study of polymerization processes. Especially chip-based microreactors are perfect tools for reaction optimization. Since flow reactors are inherently easy to scale up and allow transferring reaction conditions from microreactions directly to polymerization at industrially relevant scale without adaption of reaction conditions, a wide range of conditions can be screened with only minute amounts of starting material. This is especially interesting for cases where starting materials are rather expensive and where classical synthesis approaches do not allow for paramount screening of conditions for economic reasons. The determination of kinetic rate coefficients, Arrhenius parameters, copolymerization parameters or others can be carried out quickly and in a very straight forward fashion without the requirement to take samples from ongoing reactions or massive parallelization of reactions, which is always prone to data scattering.

The true potential of microflow polymerization optimization unfolds, however, only in combination with online monitoring tools. Direct coupling of online-FT-IR, UV-vis or NMR probes is possible, giving access to a vast array of data within a short period of time. Also more polymer specific detection methods are available, such as online size-exclusion chromatography or online electrospray ionization spectrometry. Online size-exclusion

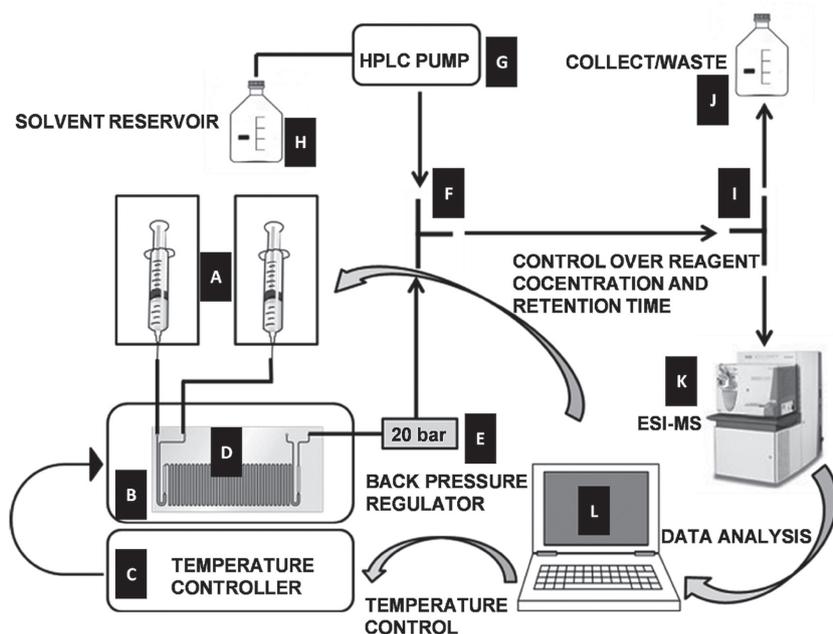


Figure 4. Schematic overview over a microreactor/ESI-MS online monitoring coupling. Reproduced with permission.^[38] Copyright 2015, The Royal Society of Chemistry.

chromatography is realized by collection of sample under stable flow conditions followed by injection into a conventional SEC system.^[43] Such process is efficient and automatable, yet still suffers from the non-continuous nature of chromatography. In this sense, electrospray ionization MS is advantageous as such analysis technique allows for continuous monitoring and hence immediate feedback.

A microreactor/ESI-MS coupling had been realized by Haven et al.^[44] The direct continuous analysis

allows to screen reactions efficiently by performing time-sweep experiments. In such experiment the reactor is set to a certain flow rate and stabilized. Then, the flow rate is abruptly changed. In the following, all possible reactor residence times that fall between the starting flow rate f_1 and the then set flow rate f_2 are screened within the timespan according to the lower flow rate. ESI-MS ionization counts can then be directly recalculated from the measured abundance at time t_m into the actual reactor residence time t_{res} via:

$$t_{res} = \frac{V_{reactor}}{f_1} + t_m \left(1 - \frac{f_2}{f_1} \right) \quad (1)$$

Figure 5 depicts the relative abundance of cyanoisopropyl-terminated chains in an AIBN-initiated RAFT polymerization, hence the amount of side products formed in the reaction. Quasi-continuous data is obtained in the experiment rather than distinct data points as typically obtained from sampling and consecutive offline measurement. The measured trace (recorded time) exhibits a delay time, which is correlated with the dead volume of the setup (see Figure 4) between reactor outlet and ESI-MS inlet. Application of Equation (1) allows transferring the data into actual reactor residence times, which can be followed by in-depth kinetic fitting. The depicted case of tracing initiator-derived end-groups in RAFT polymerization is a good example to demonstrate the amount and quality of data that can be obtained. Eventually, however, any polymer species (as long as quantitatively detectable, which may pose a significant hurdle in some cases) can be followed by the technique, opening pathways to rapid optimization procedures and in-depth kinetic screenings.

The use of online monitoring techniques, and more specifically the following self-optimization and

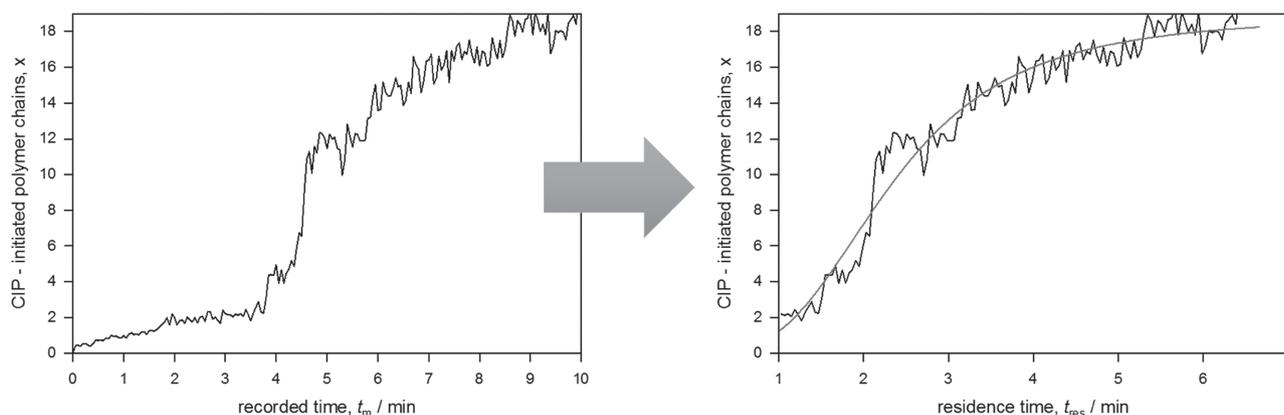


Figure 5. Measured relative peak abundancies of cyanoisopropyl-terminated polymers in AIBN-initiated RAFT polymerization measure by online microreactor/ESI-MS. Adapted with permission.^[38] Copyright 2015, The Royal Society of Chemistry.

automatization of processes that goes in principle along with it, is, however, yet in a relatively premature stage, same as for other novel trends in flow chemistry such as inline-purification. While the above proof of principle has been provided for a polymer reaction, these techniques are far from routine work, and extension towards other method such as NMR or light scattering methods is still outstanding. Yet, the combination of online monitoring and flow chemistry is highly rewarding and opens a broad field of possibilities once fully matured.

6. Conclusions

Continuous flow synthesis in and outside of the realm of polymer synthesis should not be seen as simply another way of performing chemical reactions, but also as a tool to improve the control over reactions, and eventually to design novel materials which may not or not as easily available from classical synthesis techniques. While truly novel polymerization protocols have not yet been identified for flow processes, it is only a matter of time, before online monitoring and reactor integration will allow taking this step. Regardless, precision polymers such as multiblock copolymers are already available via flow in "one-step" reactions, and also the combination of polymerization and direct post-polymerization are currently under investigation in many laboratories.

Flow chemistry techniques are simple to apply to polymerizations, and almost in all instances lead to an improvement of product quality, while providing at the same time a first upscale of reactions to the higher gram scale in common research laboratory equipment or pilot plant scale in more dedicated reactor types. Reactor couplings, online monitoring (and automatization of reaction optimization

procedures) in conjunction with the ability to easily apply reaction in a much broader range of conditions compared to classical techniques allows for out-of-the-box thinking, which has a large potential to reshape the way scientists will plan and perform their polymerizations and polymer modification reactions, and eventually give access to completely novel processes and unseen polymer designs.

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