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Continuous Flow Microreactor Systems for Intensified Synthesis of Fine Chemical Intermediates

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Abstract--- The position of fine chemical intermediates in manufacturing economics is a difficult one: They are too large in volume to be efficiently processed in batch flasks; too small in volume to justify an economical continuous process; and often must be produced by a transformation that is violently exothermic and unstable species are involved or must be produced in a manner that is so selective that it is hard to achieve in a continuous process. This position is directly reversed by continuous flow microreactor systems. They decrease channel sizes to the micro- or millimetre size scale, increase surface/volume ratios by many orders of magnitude, and shorten diffusion paths to the micrometre scale, which means that transport and safety become no longer the limiting factors in the potential selectivity that can be achieved. This review discusses the engineering principles underlying this intensification, reactor formats used and reported performance of flow systems in the synthesis of fine chemical intermediates. The three mechanisms by which intensification is achieved are discussed: mixing in a matter of milliseconds, operation of strongly exothermic steps near isothermally and near-ideal plug-flow residence time distributions. The role of telescoped multistep sequences, in-line work-up and hazardous intermediate generation are discussed in the context of documented examples, and scale-up strategies of numbering-up and dimension enlargement are compared, including their economics. Automation and statistical optimisation are seen as the development-speed multiplier, that makes the flows competitive at intermediate scale. As a result, the review highlighted the following: transport intensification is now well established, and the limiting factors are binding constraints related to separation science, solids handling, and absence of validated life-cycle and techno-economic data.

Keywords--- Flow Chemistry, Microreactor, Process Intensification, Fine Chemicals, Intermediates, Scale-Up, Telescoped Synthesis.

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I. Introduction

The fine chemical industry, which includes pharmaceutical intermediates, agrochemical precursors, dyes/pigments, flavour/fragrance chemicals and specialty surfactants, faces a chemistry versus equipment problem. The disadvantage of the batch stirred tank is that it is flexible and forgiving, but it takes time to remove heat, add things to it, and is not a self-replicating process from one tank to another. The consequences are very common to any process chemists—yield that drops with scale up, impurity profiles that are different in different vessels, and even routes that get dropped since the chemistry can be done but not safely or reproducibly. It is precisely these constraints that have been changed in continuous-flow reactors with channel dimensions in the micro- or millimetre range, and thus, these reactors have gained widespread use in organic synthesis (Gutmann et al., 2015). Their most representative properties are very rapid heat and mass transfer (Gutmann et al., 2015) and for all but the fastest reactions, very rapid mixing is possible in these microstructured devices (Gutmann et al., 2015). Both transport processes are enhanced by the same geometric move: both the diffusion distance across a channel is proportional to the channel diameter, and the heat-exchange area per unit volume, on the other hand, is inversely proportional to the channel diameter. As a practical consequence, the problem of trapping heat, hot spots and potential thermal runaway can be avoided and the total process safety is greatly enhanced even using severe reaction conditions (Gutmann et al., 2015). A parallel literature exists describing the same technology using the language of green chemistry and hazard elimination. Flow reactors enhance the mass and heat transfer, resulting in rapid reaction mixing, and enable a precise control over the reaction

parameters, increasing the overall process selectivity, efficiency and safety (Movsisyan et al., 2016). The goal is to make chemistry approachable for its use in the laboratory and industry without use of toxic, reactive, and explosive chemicals (Movsisyan et al., 2016). This review is an intermediate one and that is not by chance; there are three reasons to do it. The volume of intermediates (tens to hundreds of tonnes per year) is sufficiently high to warrant the capital cost of a dedicated continuous plant, but not so high as to warrant bulk-chemical process demands. They are usually synthesized in several steps and the in-line work-up and telescoping are often important not only for economy but also for the elegance of the synthesis. Moreover, they are the class of compound most likely to be derived from a hazardous transformation as the functionality that makes an intermediate valuable the nitro group, the azide, the diazonium salt, or organometallic species is also the functionality that makes it hazardous to accumulate.

The review is carried out in the following sequence: Section 2 introduces the fundamental concepts of transport that underpin the reasons for the intensification of miniaturisation. In section 3, the various reactor formats used are compared. Section 4 discusses Hazardous and Unstable intermediates, Section 5 covers quantification of intensification, and Section 6 deals with Telescoped multistep synthesis and in-line work up. The sections on automation and optimisation (7) and scale-up and economics (8) are followed by sustainability and techno-economics (9). The other barriers are identified in Section 10.

II. Transport Fundamentals: Why Miniaturisation Intensifies

Mixing and the Suppression of Disguised Selectivity

An addition of a reagent in a batch vessel frequently takes a long time to homogenise compared to the reaction time. This gives rise to a spatial variation in concentrations: the sections close to the feed point have a high concentration of reagent added there, the bulk has a lower concentration, and different local concentrations are sampled in the competing reactions. In the next step, selectivity is determined by the mixing equipment and not by the catalyst or the intrinsic reaction rate. The arithmetic is different with microreactors. The mixing times are much shorter than the standard mixing times of the order of seconds (milliseconds) because the diffusion distance is minimized and the mass transfer in one phase or between two phases is also strengthened (Hessel et al., 2024). The word "within one phase" is important: even single-phase reaction processes can profit, since the mixing problem is frequently the mixing of a concentrated reagent plug into a lean stream or the dispersion of a concentrated plug into a lean stream. One quantitative example is a microreactor that was used for the dehydration of fructose to 5-hydroxymethylfurfural in the presence of HCl as catalyst and operated at short reaction time and high temperature; the mixing time was measured by particle image velocimetry monitoring as 0.03 to 4.8 s (Hessel et al., 2024). The HMF yield was 50% noted by the authors, which is one of the best yields reported in the literature for this transformation (Hessel et al., 2024). There are two lessons to be learned. First, the mixing times are measured in seconds to tens of milliseconds, so fast they are not important, but slow they are enough to measure. Second, it was achieved not by altering the chemistry, but by running at a temperature and residence time that would not have been considered safe by a batch vessel; the same mixing argument leads to the heat-transfer argument below.

Heat Transfer and Isothermal Operation

When the heat transfer occurs, the temperature remains constant. During the heat transfer, the temperature is still the same. If a fast exothermic reaction is taking place, the heat from the reaction should be dissipated over an area. Due to the inverse proportionality between area and volume of a channel, the area of heat transfer that can be achieved in a channel of sub-millimetre diameter is two orders of magnitude or greater than that obtained in a channel of centimetre diameter. It is not a refinement; it alters the allowable operating range. When it comes to the point, it does not seem to be much of a hardware statement, it is more of a regime statement. In the case of thermal runaway or explosive conditions, microreactors are capable of transferring heat, and transforming from strong (adiabatic) heat release to controllable isothermal heat release (Hessel et al., 2024). A popular hardware realisation is a stack of plates containing alternating reactor and heat microchannels Hessel et al., (2024) which is also well suited to scaling out as each plate is a self-contained heat-exchange unit instead of an integral part of a larger vessel. Isothermal operation has a chemical consequence (safety). If the temperature cannot be controlled, then the reaction is preferable to be conducted at the temperature the cooling system can handle, usually well below the kinetically optimum temperature. If it can be avoided, the operator can raise the temperature to increase rate of the desired pathway and decrease the thermal side reactions potential to be caused by a hot spot. That is the reason why flow systems are frequently able to achieve selectivities that cannot be obtained in a batch process at nominally the same conditions.

Residence Time Distribution and Plug-Flow Character

Selectivity in a consecutive reaction network is determined by the time that is spent in the reactor for each fluid element. If the residence time distribution is broad, there will be material that has already over-reacted and material that has not reacted enough; for example, if the process sequence is A → B → C, the fraction of material that has "over-reacted" will convert B to C, while the "under-reacted" fraction will still contain A, and the yield of B will be limited below the kinetic maximum. The approach to plug-flow behaviour of a microchannel is more pronounced than would be predicted from its laminar velocity profile due to rapid diffusion radially across a narrow channel. The other end of the spectrum is segmented gas–liquid flow, where internal circulations are introduced in each liquid segment, such as in a microreactor that operates in the Taylor flow regime, where there is very little axial dispersion and the residence time distribution is very good, with the reactor approaching the ideal plug flow reactor (Gemoets et al., 2015). In this regime the film theory is directly applicable to the calculation of mass transfer coefficients so that Taylor-flow reactors are unusually amenable to rational design as opposed to empirical tuning (Gemoets et al., 2015). The residence time in a plug-flow reactor of volume at volumetric flow rate is, which is independent of the reactor size and a dialled variable. That is the operational property that allows kinetic optimisation in flow to be much faster than in batch.

III. Reactor Formats and Their Selection

Four different formats are used predominantly for the fine chemical intermediates and the selection depends on the phases involved and the heat duty.

Coil and tube reactors are the work horse. The cost, known volume, well defined residence time and excellent heat transfer characteristics of a length of perfluorinated or stainless tubing in a temperature-controlled bath. Coils are also the natural geometry for high pressure applications, and they can be used in continuous flow systems at a nominal backpressure without which many high temperatures flow processes would not be possible – continuous flow systems are normally operated at a level of backpressure, allowing solvents to be used above their atmospheric boiling point while ensuring reaction homogeneity as the solution flows between reactor coils at different temperatures (Britton & Raston, 2017). A microreactor made of a chip has more precisely engineered channels, integrated mixing structures and optical access, but has a lower flow rate, and is susceptible to particulates. They are used for screening and very exothermic and very fast reaction, where minimizing the inventory is the goal. Packed-bed reactors are employed when the catalyst is a solid (heterogeneous catalysis) and for immobilized chemicals and scavengers. Their hydrodynamics are less ideal: channeling and dead volumes widen the residence time distribution, and axial dispersion is only neglected when the Péclet number is high enough, which should be checked empirically before kinetic data obtained from such a reactor can be trusted. Between oscillatory and segmented-flow devices lie oscillatory and segmented flow devices utilizing gas slugs or vortices created by baffle flow to achieve plug-flow-like behavior at higher flow rates and throughputs than are possible with a single narrow channel, thus breaking the channel diameter/throughput trade-off. In gas–liquid transformations (hydrogenation, aerobic oxidation, carbonylation, chlorination), the performance is more dependent on the contacting principle than on the channel size. The flow regime of interest is “Taylor flow” which is characterized by a large specific interfacial area and a well-defined liquid film, and the resulting devices can be modeled as near-ideal plug-flow reactors with high mass transfer rates (Gemoets et al., 2015). For intermediates, the most practical implication is the conversion of gas–liquid steps that tend to be the most time consuming in a batch cycle, especially hydrogenations.

IV. Hazardous and Unstable Intermediates

In the fine chemical industry, much of the commercial case for flow chemistry is not in terms of yield, but in enabling chemistry that batch cannot do safely at all. The traditional argument for the natural applicability of microreactor technology is that reactions that involve highly unstable or even explosive intermediates are natural candidates for the microreactor (Gutmann et al., 2015). As the principle is demonstrated in three families. Other highly exothermic electrophilic substitutions, such as nitration. The heat of reaction is big, the reaction is fast, and the selectivity for mono- and over-nitration is temperature dependent. If the heat can be removed rapidly enough as it is generated, a reactor can be operated at the concentration and temperature which are optimum for the formation of the mononitro product, but a batch vessel will need to be operated dilute and at a low temperature. Diazonium, diazo and azide chemistry. The species are also thermodynamically unstable and dangerous to isolate but they are also useful. The azide can be produced in a small volume reactor

coil prior to use in a next step in the process, thus minimizing the amount of azide present at any time in the process of flow (Britton & Raston, 2017). A documented synthesis of amides went in 86% yield in 18 h in the same manner (Britton & Raston, 2017). The safety benefit is structural, i.e., in the inventory, not in the operator's care. Chemistry of Organometallics and Strong-Bases. Both failure modes are present: halogen–metal exchange and Grignard formation are fast, strongly exothermic reactions, a reactor with a narrow residence time distribution and a large heat-transfer area can overcome both reactions. There is no free lunch for these benefits, and an honest account will say so. The flow reactor is not a way of eliminating the need to manufacture, charge and store the hazardous reagent upstream of the flow reactor; nor is it an excuse to forgo a complete system hazard review. Where the risk is and how much material is exposed at any one time. The generation of dangerous reagents when needed continues the argument. In this case, the generation of a reagent like the Vilsmeier reagent in continuous flow makes the sequence safer for the operator, and also enhances the safety metrics since the reagent does not need to be transported and stored (Britton & Raston, 2017). Chemical warfare-adjacent and high-toxicity reagents—such as phosgene, hydrogen cyanide, hydrazoic acid, ozone, peroxides—have all been handled in this way, and for an intermediate manufacturer, for example, it's often the key selling point: the hazardous species is only a transient in a few millilitres of tubing.

V. Quantifying Intensification

Table 1: Representative Reported Performance of Continuous-Flow Systems Relevant to Fine Chemical Intermediates. Values As Published; Conditions Are Not Directly Comparable

Transformation / target	Reactor and conditions	Reported outcome
Etodolac key intermediate (batch vs flow comparison)	Continuous flow, 230 mL min^{-1}	100% conversion, 75% yield, increased purity, decreased byproducts Britton & Raston, (2017)
Vildagliptin key intermediate via in-flow Vilsmeier reagent	Flow generation and consumption	5.8 kg h L^{-1} Britton & Raston, (2017)
Amide via in-situ azide generation	Small-volume reactor coil, 18 h operation	86% yield Britton & Raston, (2017)
Three drug scaffolds	16 numbered-up 3D-printed metal microreactors (16N-PMR)	20 g in 10 min of operation Hessel et al., (2024)
HMF from fructose, HCl-catalysed	Coiled microchannel, high temperature, short residence time	Mixing time 0.03–4.8 s; 50% yield Hessel et al., (2024)
2-Ethylhexyl nitrate	Microreactor, Box–Behnken design, four factors at three levels	Kilogram-scale synthesis Hessel et al., (2024)
Rufinamide (multistep batch → flow)	Stepwise conversion of a multistep batch route	756 kg CO_2-eq per kg API reduction; average 45% reduction across LCIA potentials Rogers & Jensen, (2019)

The extent of process intensification is often claimed but not measured. Three metrics make up the bulk of the weight, and these can't be substituted for each other. The space–time yield is the most flow-oriented metric, being mass of product per reactor volume per unit time, and normalised not with the calendar, but with the reactor. Even if the reaction is rapid, a batch vessel with one shift per week has a very low STY while a flow system uses much less volume to achieve the same annual output. In academic research, the most commonly used productivity measure is productivity per unit volume (kg h^{-1} L^{-1}). For fine chemicals, a representative value is 5.8 kg h L^{-1} for the key intermediate of vildagliptin, which is formed using a series of reactions in which the hazardous Vilsmeier reagent is generated in flow (Britton & Raston, 2017). Figures of this order make the technology economically interesting, a litre of reactor volume making kg/h is a different ball game than a litre of a batch vessel making grams per day! The third axis is yield, purity and impurity profile; the transport argument makes its appearance here. The key intermediate of etodolac was synthesized in 100% conversion and 75% yield; a direct comparative study between batch and continuous flow showed that the reaction can be translated to continuous flow resulting in increase in yield, purity and conversion, while the byproduct formation decreased (Britton & Raston, 2017). The high fluxes (230 mL min-1) in that system are orders of magnitude higher than typically seen in an academic setting Britton & Raston, (2017) and this is important

because it indicates that the intensification is not confined to microlitre scale. The representative reported outcomes are summarised in table 1 for the various reactor types and transformations. Telescoping and Multistep Sequences. Table 1 collects representative reported outcomes across reactor types and transformations.

VI. Telescoping and Multistep Sequences

Single step intensification is helpful, multistep integration is transformative. If the consecutive transformations are not separated by any intermediate step, the intermediate step is never stored as a material, never has to be dried before use, never has to be transported to another part of the process, and never has to be released before the next step in the transformation can be performed. The practice is called telescoping; in the flow version, there is one significant difference from the flask version: In-line purification and reagent addition at specific positions in the sequence can be achieved, which is not possible through the flask version (Britton & Raston, 2017). The logic of telescoping also shifts the metrics that get better. The combination of telescoping and optimisation with automation allows for swift investigation of synthetic processes in a minimum number of experiments, leading to a reduction in the number of experiments performed and a large reduction in process mass intensity values (Boyall et al., 2024). In this configuration, each step is directly transferred to the next step in a one environment Boyall et al., (2024) and process control is improved, heat and mass transfer is improved, and footprints of plants are smaller when using flow chemistry than traditional batch chemistry (Boyall et al., 2024). All the staffed floor area, the solvent stock and number of isolation trains are combined. It's not the reaction, it's the work-up. Some of these processes, such as solvent exchange, phase separation and removal of spent reagents, are less amenable to miniaturisation, and this is one of the reasons why sometimes the mass metrics of flow routes were even poorer than the mass metrics of the batch processes they replaced. The simplest case is the in-line separation of immiscible fluids, which can be accomplished with the help of liquid–liquid membrane separators, where the organic phase flows through a membrane to a new continuous-flow stream (Britton & Raston, 2017). The same application has been accomplished with gravity settlers equipped with computer vision level detection systems, and immobilized scavengers eliminate metal catalysts and excess reagents without any aqueous extraction at all. The most comprehensive examples combine synthesis, separation and formulation in a single chassis. Continued end-to-end synthesis of the U.S. Pharmacopeia (USP)-compliant drugs diphenhydramine hydrochloride, lidocaine hydrochloride, diazepam and fluoxetine hydrochloride are continuously synthesized on a compact and reconfigurable platform 1.0 m wide, 0.7 m long and 1.8 m high, thanks to advances in continuous-flow synthesis, complex multistep sequence telescoping, reaction engineering equipment, and real-time formulation (Adamo et al., 2016). The platform generates enough per day to feed hundreds to thousands of doses, either oral or topical, of liquid formulations (Adamo et al., 2016). What matters for intermediates isn't the molecules, it's the architecture: A plug-and-play system in which the modules are reconfigured instead of rebuilt transforms a capital asset from a single-product plant into a multipurpose one, the kind required by an intermediate manufacturer whose products are all low-volume.

VII. Automation and Statistical Optimisation

Flow systems are inherently more easily automated than batch vessels; all the variables are setpoints on pumps, heaters, or valves and once a steady state is achieved it is maintained without intervention. Most incidents occur at transient states, such as start-up, shutdown, reagent charging, and a process spends a lot of time at steady state, spends a lot of time at its best characterised state. The flow coupled with in-line analysis and experimental design reduces development time. A Box–Behnken experimental design (BBD) was systematically used to vary the process parameters for a statistical development of a micro reactor process to make 2-ethylhexyl nitrate at a 1 kg scale (Hessel et al., 2024). This is an important methodological comment, as the conditions are defined by the reactor volume and the flow rate, not the vessel, so the parameters optimised in the lab are the ones to be taken to pilot. A design space mapped on, say, a few millilitres, is valid on a numbered-up module, but not on a batch design space mapped in a flask. The transfer is confirmed by reported outcomes. Recently, the scale-up of sub-second micro-flow synthesis has been carried out by numbering up 3D-printed and laminated metal microreactors: a single one-flow-reactor synthesis has been extended to a single 4N-PMR module containing four numbered-up microreactors, and finally 16 microreactors has been integrated into a single 4N-PMR module to produce 20 g of three drug scaffold products in 10 min (Hessel et al., 2024). This was the transition from one reactor to sixteen, without a change in chemistry, which is all the numbering-up philosophy says.

VIII. Scale-Up: Numbering-Up, Dimension Enlargement and Economics

A key aspect of microreaction technology is that scale is obtained by replication not by enlargement. Ideally, the microreactor systems are "numbered-up," but the scale-up of microreactors is far from ideal in reality, it is still faster and more facile than for a conventional batch reactor setup (Hessel et al., 2024). There are three strategies available, which can be used in parallel: reduce operation time, increase throughput, increase flow rates; number-up: several devices run in parallel; and smart scale out: a dimension enlarging strategy (Gemoets et al., 2015). The simplest is the one that is used in most of the laboratory-scale work and is known as the first. It enables optimization of reaction parameters on small quantities of material, thus avoiding the necessity of re-optimization of the reaction protocol, or the device, and allows for the direct scaling up of the reaction to up to a few hundreds of grams of product (Gemoets et al., 2015). That is enough for discovery and early development, but is not enough for production. The strategy of numbering up is used to keep the transport regime exactly the same because each unit is hydrodynamically identical to the one that was optimised. It requires hundreds to thousands of reactors with similar size to the ones used for process optimization studies, and it enhances safety by providing better control of reactor temperature and also significantly reduces the time required for scale-up (Taylor et al., 2023). It does not however, get rid of the engineering discipline: It is essential in the design process that the hydrodynamics and transport properties remain the same throughout each scale, from lab to pilot to production (Gemoets et al., 2015). This requirement applies to the distributor design because small variations in the pressure drop causes a significant maldistribution and hence non-identical conditions in parallel channels. The number-up penalty is structural as opposed to hydrodynamic. It has a high investment cost as many reactors are needed which would not be the case in a single stirred tank reactor, and multiple process control devices (Taylor et al., 2023). A number of reasons come to mind why the approach can only be justified economically in the case of high-end products, and in cases where a drastic improvement in output has been shown (Taylor et al., 2023). The sector has been selective in its uptake of the adoption and fine chemical intermediates form part of that boundary. Analysis by an industrial process development group shows that 50% of reactions in the fine chemical/pharmaceutical industry could benefit from the miniaturisation of the reaction process, which is both a declaration and an endorsement of the result Taylor et al., (2023) that half the existing chemistry does not benefit from such miniaturisation. In practice in industry, the solution that has been adopted has been to partially intensify the process – to replace the one or two steps per route that are transport-limited or hazardous, to keep the remainder in batch, and join the two together. The opposite strategy of dimension enlargement is milli- and meso-scale devices with internal microstructures, where the surface-to-volume benefit is still present, but throughput is increased such that fewer parallel trains are required. The engineering criterion is the same in all cases; the transport characteristics of all of the scales must be reproduced in the engineering and they cannot simply be approximated.

IX. Sustainability and Techno-Economics

Flow chemistry is often touted as inherently green. The evidence is on the side of a more qualified position, and that is particularly crucial for intermediaries as compared to pharmaceuticals due to less margins. The pros are: solvent and energy. A 756 kg CO_2e reduction was accomplished when converting the multistep batch synthesis of rufinamide to flow, while an average of 45% reduction was measured for all LCA impact assessment potentials (Rogers & Jensen, 2019). A wider comparison of 7 industrially relevant APIs, which included energy use, water use, waste generation, 11 environmental impact categories for 9 planetary boundaries, capital and operating costs, concluded that on average, continuous-flow processes are significantly more sustainable, and energy efficiency, water use and waste reduction are possible paths to this improvement, including up to 97% reduction in energy consumption (Ince et al., 2025). There is just as much counter evidence here, and it should not be glossed over. The continuous process may have a greater process mass intensity than the batch process that is being replaced, due to either the greater amount of reagents required or the lower concentrations of the reagent streams that need to be fed (Rogers & Jensen, 2019). However, the advantage can switch from the pilot-plant to the batch process, as the washes mass was determined to be considerably higher in the batch process Rogers & Jensen, (2019) at the pilot-plant stage. The overall conclusion from the practitioners who have looked at matched batch–flow pairs is that continuous processing can have sustainability benefits, but can also have an adverse impact on environmental metrics. Three factors determine whether intermediates get better or worse. The first is that the mass-intensity argument is lost if the flow route is solvent, which means that the hazardous intermediate must be maintained in the solvent in high dilution. The second is the number of steps telescoped, since savings are virtually all due to eliminated isolations. The third is equipment utilisation, because an

intermittent plant is not as good as a continuous plant—let alone multiproduct reconfigurable platforms as compared to dedicated production lines.

X. Remaining Barriers

There are four constraints that restrict the wider adoption, none of which is transport related. One is solids. Fine chemical intermediates crystallize, precipitates and foul. A microchannel is a good filter and blocked channel is a dead plant. The problems of continuous crystallisation and slurry processing and fouling resistant geometries are not solved. The latter is separation. Reaction intensification is faster than work-up intensification. There is a variety of membrane separators, miniature distillation, falling-film evaporators and scavenger columns, but not much has been done in truly telescoped multistep syntheses, and the dilutions that occur at each step must be removed—an evaporator task which can offset the energy savings the reactor provided. The third one is analytical and regulatory. In-line methods have to be validated for use in continuous processes, where the acceptance of a batch in a continuous train is not as defined as it is in end-product processes, and where there is a lack of guidance in the literature on residence-time-distribution evidence to verify that material is being properly integrated through the process. In all these areas, the industry is ahead of written guidance. The fourth is data. While the number of published syntheses is high, few flow routes have been assessed by techno-economic and life-cycle analyses, meaning most of the claims of intensification are based on yield and space–time yield. Capital and operating cost comparisons at common scale will not be commonplace until then; and decisions on adoption in an industry where margins are small will remain based upon limited information.

XI. Conclusions

Three physical and not chemical characteristics of continuous flow microreactor systems are responsible for intensification of the synthesis of fine chemical intermediates: reduction of diffusion path until mixing becomes the rate limiting process and therefore selectivity is no longer limited by mixing, increase in the area-to-volume ratio in such a way that heat removal becomes the rate limiting process and therefore no longer limits the operating window, and narrowing of the residence time distribution until consecutive reaction networks no longer over and under-react. The reported results are similar for the various reactor formats (millisecond to second mixing, operation of violently exothermic steps near isothermal conditions, near-ideal plug-flow behaviour in Taylor flow, productivities of up to kg/l/h in well-optimised transformations). But the most unique aspect of the technology is its capability and not its efficiency. The substances inside the loop can be reduced to a few millilitres of tubing, and reactions which would be very explosive or highly unstable can become routine. It is that capability that can be a good justification of the capital cost of the number up option, and is defensible only for high value products and only if a significant improvement is demonstrated. The restrictions have followed suit. Solids handling, in-line separation, validated control strategies, and matched scale techno-economic data are the bottlenecks, not channel miniaturisation. Routes that isolate no steps, telescope three or four steps, and manage precipitation without fouling, as well as reporting mass and energy metrics in addition to yield, will be the next phase of adoption. During that time, the intermediate range of volumes (too large for flasks, too small for a continuous plant, and chemically too risky for either) is likely to be the first volume range where flow will become commonplace instead of the exception.

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