Enabling Continuous-Flow Chemistry in Microstructured Devices for Pharmaceutical and Fine-Chemical Production
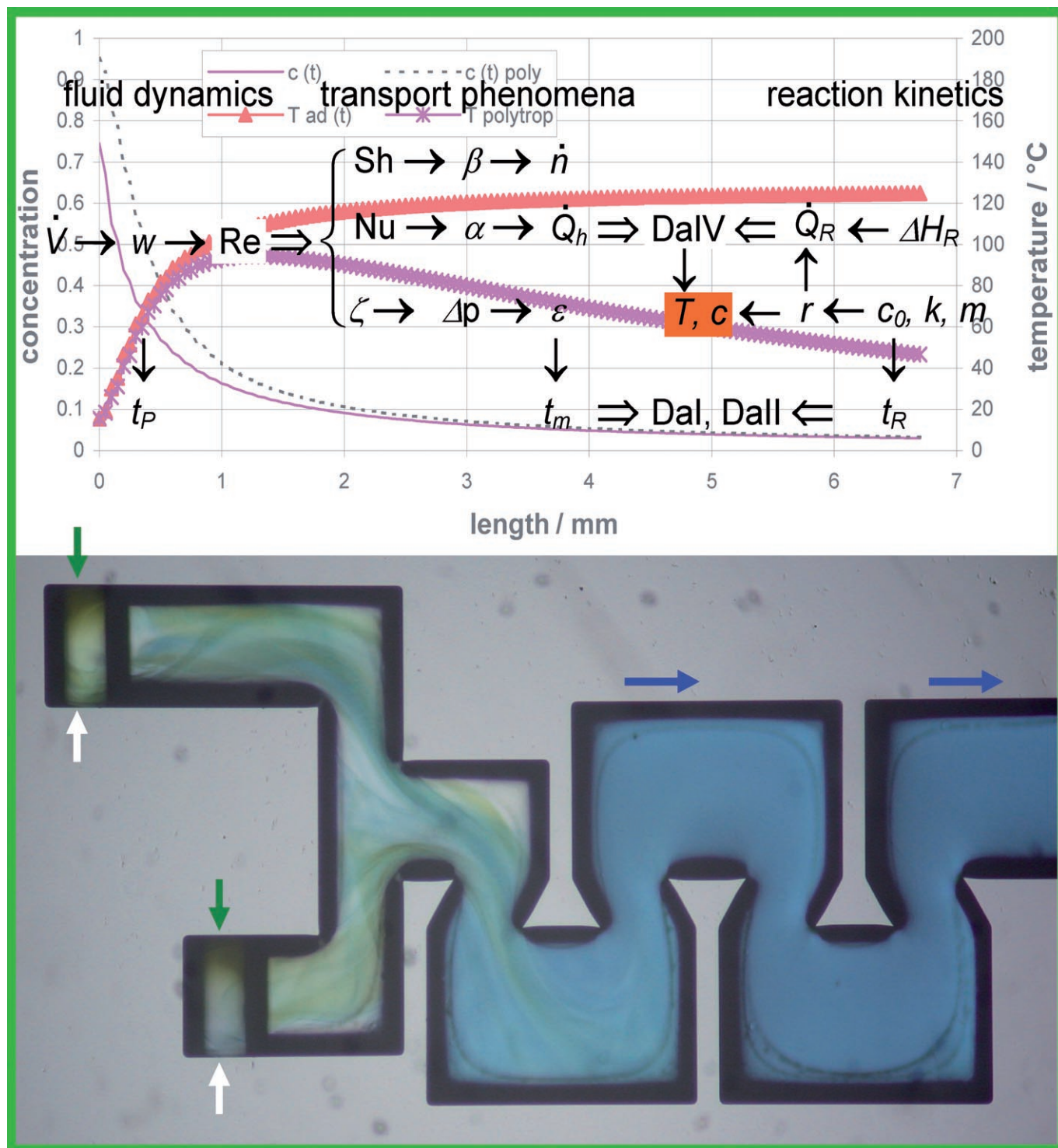
Norbert Kockmann,*[a] Michael Gottsponer,[a] Bertin Zimmermann,[a] and Dominique M. Roberge[b]

Abstract: Microstructured devices offer unique transport capabilities for rapid mixing, enhanced heat and mass transfer and can handle small amounts of dangerous or unstable materials. The integration of reaction kinetics into fluid dynamics and transport phenomena is essential for successful application from process design in laboratory to chemical production. Strategies to implement production campaigns up to tons of pharmaceutical chemicals are discussed, based on Lonza projects.

Keywords: lithiation · microreactors · reaction dynamics · reactor design · transport phenomena

Introduction

Microstructured devices offer unique transport capabilities for rapid mixing, enhanced heat and mass transfer and can handle small amounts of dangerous or unstable materials. Continuous processes offer many advantages ranging from controlled process conditions to high flow rates and mass throughput. In bulk chemistry nearly all chemical processes benefit from continuous operation. Fluid dynamics determine the characteristics of continuous-flow equipment, the pressure loss, residence time, heat transfer and mixing time.[1] Yield and selectivity of chemical reactions are greatly influenced by flow situation, if their kinetics possesses a typical timescale in the range of the flow processes. The combination of continuous-flow processes with microstructured devices allows us to use the benefits from both areas in the laboratory and production environment. In contrast, batch processes prevail in operation and production in specialty chemistry, fine chemistry, or pharmaceutical production. Batch vessels are versatile for many kinds of reactions and can handle multiphase systems in multipurpose plants.[2] Vessels can be arranged in various constellations to perform different reaction routes and can also handle certain workup steps like distillation or extraction. On the other hand, heat transfer and mixing is often limited in stirred vessels, which need high dissolution, long operation times or even do not permit highly exothermic reactions.[3] Hence, the versatility of batch vessels should be combined with the safety, reproducibility and high transport capabilities of continuous-flow

[a] Dr. N. Kockmann, M. Gottsponer, Dr. B. Zimmermann
R&D Exclusive Synthesis, Process Optimization
Lonza AG, 3930 Visp (Switzerland)
Fax: (+41) 27-947-6580
E-mail: norbert.kockmann@lonza.com

[b] Prof. D. M. Roberge
University of Ottawa
Department of Chemical Engineering, 161 Louis Pasteur
Ottawa, K1N 6N5 (Canada)

microstructured equipment. Lonza has developed a toolbox approach[4,5] with various types of reactors for various types of mixing- or temperature-sensitive reactions or unstable compounds. Each reactor type can be applied for a wide range of chemical reactions and a certain range of flow rates. These reactors are dedicated to chemical production and reaction screening and have to be distinguished from small devices for analysing purposes and molecule synthesis. These devices belong to the field called Lab-on-a-Chip with small channels ($< 100\ \mu m$), low flow rates ($\approx \mu L\,min^{-1}$) and low Reynolds numbers (Re < 10). The main emphasis is given to good optical and chemical observation for data generation. The microreactors dealt within this paper have relatively large channels (0.1–1.5 mm), moderate flow rates (10–100 mL min^{-1}) and Re numbers in the transitional regime (100–3000). The production of pharmaceutical intermediates or active pharmaceutical ingredients (API) can vary from few milligrams for first studies to hundreds of tons per year for a successful pharmaceutical blockbuster. This production range demands various production devices on different length scales for which the production process has to be transferred to. First laboratory studies work with few milligrams in glass flasks, but continuous-flow devices with integrated microchannels are also used for this purpose.[6] Process development[7] leads from small-scale production, sample production over pilot scale to large-scale production. Often, stirred vessels serve as devices to perform the reaction on wide-ranging production scales with scale-up of the chemical process. However, in stirred vessels scale-up problems often occur concerning transport limitations in mixing, heat and mass transfer.[8]

This concept paper shows the design and successful application of various microstructured devices in the laboratory for process design, chemical synthesis, and for production on various scales. The design and characteristics of microstructured devices is explained by a handful of equations to give an overview about transport phenomena and reaction kinetics.[9] Due to their small internal volume, microreactors are well suited for process screening and parameter evaluation. Sample production is the next step in pharmaceutical product development that is also feasible with microstructured devices in laboratory environment. The main task in further development is the transfer of laboratory data and processes into production environment. Strategies to implement production campaigns up to tons of pharmaceutical chemicals are shown on the base of real cases, here a lithium-exchange and coupling reaction, even for production under good manufacturing practice (GMP) conditions. Obstacles like fouling and plugging as well as integration into batch-wise production are treated and measures to overcome these are identified.

Design of Microchannel Devices

Continuous processing with microstructured devices allows the scale-up in mass flow rate and production time. Production time often depends on the labour organisation including laboratory environment, pilot plant, and production plant. The mass flow rate in continuous processes is limited by pressure loss in the device, but also by residence time, mixing characteristics and, last but not least, heat and mass transfer. With larger volumes in batch processes, the surface-to-volume ratio for heat transfer drops inversely to size enlargement and limits many reactions in larger vessels.

In the following, design strategies for continuous processes are shown in a simple way to illustrate the pathway. First calculations give an orienting view; then, for critical steps, detailed calculations must be performed and can be found in common literature. Spreadsheet calculations can assist this design method.[10]

Single-channel devices are easy to handle and clean, and provide defined process conditions for precipitating flow or varying fluid properties along the reaction path. A typical setup is shown in Figure 1.
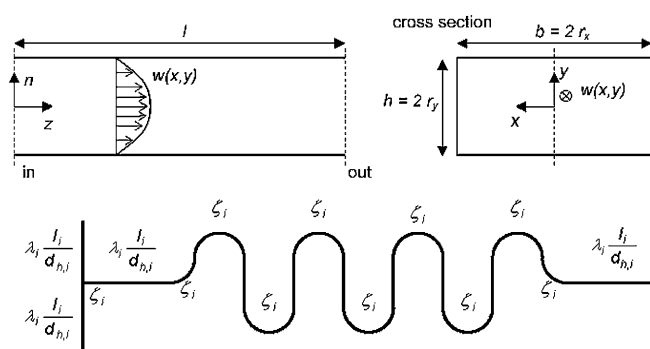

Figure 1. Geometry of a typical microchannel, rectangular cross section (top); contacting element and meandering channel with related pressure loss coefficients or friction factors (bottom).

The volume flow rate ($\dot{V}$ [m^{3}s^{-1}]) or mass flow rate ($\dot{m}$ [kg s^{-1}]) gives the mean flow velocity (w) in the related section with the density (ρ) of the fluid and the cross-sectional area (A) of the smallest channel section or dominating channel section [Eq. (1)].

Abstract in German: *Mikrostrukturierte Bauteile bieten überragende Transporteigenschaften für schnelle Vermischung, erhöhte Wärme- und Stoffübertragung und können geringe Mengen gefährlicher oder instabiler Stoffe handhaben. Die Integration der Reaktionskinetik in die Transportvorgänge ist wichtig für erfolgreiche Anwendungen von der Prozesssynthese im Labor bis zur Produktion. Scale-up-Strategien für die Produktion von pharmazeutischen Chemikalien werden anhand von Lonza-Projekten gezeigt.*

$$\dot{m} \xrightarrow{(A\rho)^{-1}} w \tag{1}$$

In a straight laminar flow, the maximum velocity in the channel centre is $2w$. The mean residence time of the fluid in the channel depends on flow velocity and channel length $t_P = l/w$. The flow regime in the channel is determined by the Reynolds number Re and the ratio of inertia to viscous forces by fluid viscosity (ν [m^{2}s^{-1}]) [Eq. (2)].

$$w \xrightarrow{d_h/\nu} \mathrm{Re} \xrightarrow{(d_h/R)^{1/2}} \mathrm{Dn} \tag{2}$$

In Equation (2) the hydraulic diameter $d_h = 4A/P = 2bh(b+h)^{-1}$ indicates the characteristic length scale of the flow cross section and perimeter P. With increasing Re number starting from unity (Re < 1 is always laminar flow), the flow regimes can be categorised in the following order: from straight laminar flow (Re < 10) the first vortices appear at flow bends (disturbed laminar flow), at first steady fluctuations, then periodic and chaotic, leading finally to turbulent flow (Re > 10 000) with chaotic, statistically distributed flow structures like vortices or swirls. The related Re numbers differ in a certain range, depending on channel geometry and flow situation. Microchannels with high mass throughput often operate in the transitional region of disturbed laminar flow to turbulent flow.

A simple way to calculate the Re number from the volumetric flow rate ($\dot{V}$ [mL min^{-1}]) for water (20 °C) in channels with hydraulic diameter (d_h [mm]) is the correlation Re = 16.6 $\dot{V}/d_h$. This correlation can easily be adapted to other flow rates, dimensions, and fluids for rapid estimation of the Re number. More detailed analysis of flow regimes in fluid mechanics textbooks.[11,12] The Dean number Dn [Eq. (2)] indicates vortex formation in bend flow often occurring in microchannels.

The pressure loss is an important parameter in continuous-flow devices and determines the mixing and transport phenomena, described by pressure loss coefficient ζ or the channel friction factor λ_f [Eq. (3)].

$$w, \mathrm{Re} \xrightarrow{\text{geometry, flow regime}} \lambda_f, \zeta \xrightarrow{(l/d_h)(\rho/2)w^2} \Delta p \tag{3}$$

In long channels [Eq. (4)] the ratio is important, but in short channels, simply the pressure loss coefficient is considered as the channel length is not important [Eq. (5)].

$$\Delta p = \lambda_f \frac{l}{d_h} \frac{\rho}{2} w^2 \tag{4}$$

$$\Delta p = \zeta \frac{\rho}{2} w^2 \tag{5}$$

In laminar flow, the channel friction factor is inversely proportional to the Re number $\lambda_f = C_f/\mathrm{Re}$, in which the constant C_f is 64 for circular and 56 for rectangular cross sections. For disturbed laminar flow, the pressure loss coefficient can be given by empirical correlations, for example, $\zeta = 37.5/\mathrm{Re}^{1/3}$ in T-shaped microchannel junctions for $100 < \mathrm{Re} < 600$. For turbulent flow, λ_f and ζ have constant values.

The pressure loss is the starting point for describing the heat and mass transfer at the channel wall and the mixing performance. We start with heat and mass transfer at the wall, which is also described by simple correlations. Here, we concentrate on heat transfer; mass transfer is important for heterogeneous catalytic reactions and transport at the wall. The heat transfer at the wall is described by the heat-transfer coefficient and the driving temperature difference from bulk to wall [Eq. (6)].

$$\frac{\dot{Q}_h}{A} = \frac{\dot{Q}_h}{P l} = \dot{q} = \alpha \, \Delta T_w \tag{6}$$

The area A is the channel surface available for heat transfer. The Re number is the starting point to calculate the heat transfer [Eq. (7)], with the heat conductivity of the wall being λ.

$$\mathrm{Re} \xrightarrow{\zeta, \mathrm{Pr}} \mathrm{Nu} \xrightarrow{\lambda/d_h} \alpha \xrightarrow{\lambda, s, A} k \xrightarrow{A \, \Delta T_{tot}} \dot{Q}_h \tag{7}$$

The heat transfer is expressed with a dimensionless number, the Nußelt number [Nu, Eq. (8)],[13] which is determined by the pressure-loss coefficient, the Re number, and the Prandtl number $\mathrm{Pr} = \nu/a$, in which a is the temperature conductivity.

$$\frac{\alpha \, d_h}{\lambda} = \mathrm{Nu} = 0.404 (\zeta \, \mathrm{Re}^2 \mathrm{Pr})^{1/3} \tag{8}$$

The characteristic heat-transfer timescale (t_h) is determined by Equation (9), which means that a small diameter and a high heat-transfer coefficient result in short transfer times.

$$t_h = \frac{\rho c_p d_h}{4 \alpha_R} \tag{9}$$

The wall mass transfer can be described with the same correlations substituting the Pr number with the Schmidt number $\mathrm{Sc} = \nu/D$ and the Nu number with the Sherwood number $\mathrm{Sh} = \beta d_h/D$. Then, the wall mass transfer, $\dot{n} = \beta A \Delta c_w$, is calculated from the mass transfer coefficient β, the transfer area, and the concentration difference from bulk to wall.

The entire heat transfer from the channel to the cooling/heating fluid is determined from the sum of all resistances along the heat-transfer path, that is, heat transfer in mixing channel α_R, heat conduction in the wall λ_f/s and heat transfer in cooling/heating channel α_c. The heat-transfer area changes along its path, which complicates the calculation. An estimation of all contributing resistances gives a first indication of the entire heat-transfer coefficient k, which is always lower than the smallest contributing element. The entire heat transfer in the device is given by Equation (10) and includes the total temperature difference over the device.

$$\frac{\dot{Q}_h}{A} = \dot{q} = k \, \Delta T_{tot} \tag{10}$$

The overall heat-transfer coefficient is normally in the range of 500 to 5000 $\mathrm{W\,m^{-2}\,K^{-1}}$ depending on device material, employed fluids and solvents, temperature and channel geometry. A helpful measure for a device is its heat-transfer capability, given in $\mathrm{W\,K^{-1}}$.

A typical micromixer consists of a contacting element (Y-mixer, symmetrical or asymmetrical T-mixer, tangential mixer or injection mixer), in which the components get in contact for the first time. This element is often not sufficient for complete mixing, hence, succeeding mixing channel elements form the mixing channel and lead to a homogeneous mixture. These can be meandering structures with sharp or round corners, winding channels (caterpillar mixers), corrugated walls (Herringbone mixer), Tesla valves, or split-and-recombine elements with flow splitting.[14,15] Mixing channels for convective micromixers often consist of meandering channels with round bends and short distances in between, resulting in a low pressure loss and chaotic flow behaviour with excellent mixing characteristics.

Mixing is the homogeneous distribution of components over an entire domain and related to interface enlargement and distance reduction. The energy dissipation is a measure for the interface generation between the components. We distinguish between macromixing (vortex generation and interface generation), mesomixing (mixing or blending of a stream into bulk flow), and micromixing (mixing by diffusion) on the smallest length scale of a fluid vortex. In microchannels with convective mixing, the vortex structure is very small, so that macro- and mesomixing are on a similar length scale. Again, the Re number is the starting point to determine the timescale of the mixing process [Eq. (11)].

$$w, \mathrm{Re} \xrightarrow{\rho} \Delta p \xrightarrow{w(l\rho)^{-1}} \varepsilon \xrightarrow{(\nu/\varepsilon)^{1/2}} t_m \tag{11}$$

The pressure loss is mainly consumed by vortex generation, which depends on the energy dissipation rate [Eq. (12)].

$$\varepsilon = \frac{\Delta p \, w}{\Delta l \, \rho} \tag{12}$$

Typical values for well-stirred vessels are in the range of 10 $\mathrm{W\,kg^{-1}}$, while micromixers generate an energy dissipation rate of more than 1000 $\mathrm{W\,kg^{-1}}$. The mixing timescale in various microreactors was determined in an intensive literature study [Eq. (13)].[16]

$$t_m = C \left(\frac{\nu}{\varepsilon} \right)^{1/2} \tag{13}$$

The constant C rates from 17 to 25, depending on the geometrical setup and flow situation. This timescale is also valid for mixing in stirred tank reactors indicating the dominant role of vortex motion and engulfment.

With chemical reactions, a new timescale and energy transport gain importance, described by reaction kinetics. The reaction is defined by the rate coefficient and reaction

order, but the reaction rate depends also on the starting concentration and reaction temperature [Eq. (14)].

$$k_R, m \xrightarrow{T, c_0} r, t_R \rightarrow c(t)$$
$$r, \Delta H_R \qquad \xrightarrow{\dot{Q}_h} T(t) \qquad (14)$$

The reaction rate r and the reaction enthalpy ΔH_R determine the reagent temperature, which influences the rate coefficient itself, described by the Arrhenius correlation [Eq. (15)].

$$k_R = k_{R,0} \left(\frac{k_R}{k_{R,0}} \right) = k_{R,0} \cdot \exp \left(\frac{E_A(T - T_0)}{R\,T\,T_0} \right) \qquad (15)$$

The temperature of the reagents along the reaction channel is determined by the reaction rate, the heat capacity of the reagents, and the heat transfer to the ambient. The temperature of the reagents themselves determines the reaction rate and the concentration development for an irreversible reaction [Eq. (16)].

$$r = \frac{\dot{n}_i - \dot{n}_{i,0}}{\nu_i \rho_m V} = k_R c_i^m \qquad (16)$$

The characteristic reaction time indicates the timescale for comparison with mixing and heat-transfer characteristics [Eq. (17)].

$$t_R = \frac{1}{k_R c_0^{-1}} \qquad (17)$$

The reaction enthalpy and the energy balance with heat transfer and fluid temperature change gives the transient behaviour and temperature development along the reaction channel (plug flow) [Eq. (18)] for an exothermic reaction with temperature T_c of the cooling fluid.

$$\frac{dT}{dz} = \frac{1}{\rho w c_p} \left[k_R c^m \Delta H_R - k \frac{4}{d_h} (T - T_c) \right] \qquad (18)$$

This equation can not be solved analytically; Figure 2 shows a numerical solution of a typical concentration and temperature development of an exothermic reaction along the reaction channel.
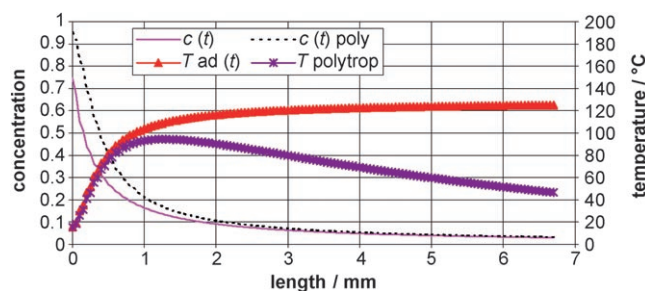

Figure 2. Concentration and temperature development along the microchannel for model reaction.

The temperature development along the channel influences not only the reaction rate, but is also responsible for the possible generation of side products in complex reactions; for degradation of thermal unstable reagents, intermediates or products and for the stability and possible runaway of a reaction. The thermal behaviour is also described by the heat production potential [Eq. (19)], in which the adiabatic temperature rise is given by Equation (20) and the time ratio of reaction and cooling is given by Equation (21).

$$S' = \frac{-\Delta T_{ad}}{T_c} \frac{E_a}{RT_c} \qquad (19)$$

$$\Delta T_{ad} = -c_0 \rho_m \Delta H_R / (\rho c_p) \qquad (20)$$

$$N = \frac{t_R}{t_c} = \frac{1}{k_R(T_c) c_0^{-1}} \frac{4k}{\rho c_p d_h} \qquad (21)$$

The heat-production potential (S') should be in the range of 15 or lower and the time ratio above 28 for a stable reactor operation.[17] These values give a rough estimate; the experimental investigation of the chemical reaction will give more accurate data. The comparison of the heat-release potential of the reaction and the heat-transfer capability gives another dimensionless group, the fourth Damköhler number DaIV [Eq. (22)].

$$DaIV = \frac{\rho_m d_h k_r c_0 \Delta H_R}{k(T - T_c)} \qquad (22)$$

The heat transfer, concentration and reagent temperature vary along the reactor channel, which only allows determining a local DaIV. For an allowable maximum reagent temperature, the DaIV number should be approximately unity.

As an overview, the sketch in Scheme 1 clearly shows the influence parameters on improved reaction conditions for microstructured devices. Rapid mixing below 10 ms in liq-
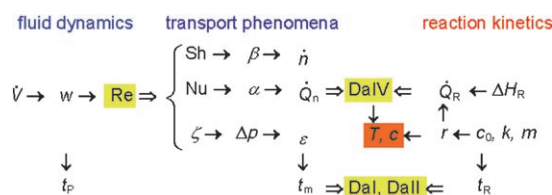
Scheme 1. Correlation scheme for fluid dynamics, transport phenomena and reaction kinetics in continuous-flow devices.

uids serves for homogeneous and stoichiometric concentration distribution over the entire microreactor. The reagents are often mixed much faster than the reaction can start; this effect can be called a "premixed reaction". Scale-up of the reactor for higher flow rates and mass throughput can be done with less risk than for reactions in batch vessels.
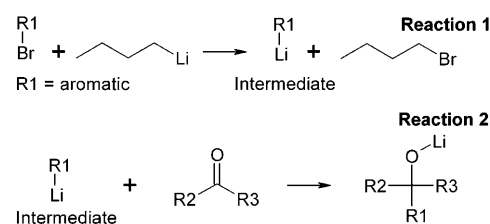
High heat-transfer rates lead to homogeneous temperature distribution along the channel with less side-products and higher selectivity and yield. The above correlations indi-

cate that continuous processes serve for controllable conditions, which can be maintained as long as necessary. They are easy to change in a certain range and can be adapted to differing entrance conditions, for example, varying starting-material concentration and quality.

Scheme 2. Organometallic and coupling reaction as example reaction.[18]

Industrial Scale-Up Example from Production at Lonza

Scale-up in process development and pharmaceutical production ranges from sample production with few grams, over kg-sample production and process optimization with many data points, to pilot-plant production in the range of tons of pharmaceutical intermediates or active ingredients in a few weeks. Continuous-flow microstructured devices allow for rapid experimental set-up of the laboratory plant for process design and optimization. Changes can be realized within minutes to hours and experiments can be performed with little reagent consumption. Process parameters can rapidly be screened, such as temperature, flow rates and stoichiometry; only a little more effort is needed to change solvent, reagents or chemical routes. Data points are rapidly generated and analysis is assisted by design-of-experiments (DOE) as statistical tool.

A chemical reaction illustrates the capabilities of pharmaceutical production in microstructured devices, in transferring from laboratory investigations to pilot-plant production. Two key steps of four reactions of an intermediate are given in Scheme 2:[18] a highly exothermic lithium-exchange reaction and a coupling step resulting in an unstable intermediate.

The entire equipment chain of the process is displayed in Figure 3 upper row. In addition to the lithium-exchange and coupling steps, the process includes protection and hydrolysis steps, followed by two separation and two workup steps. Overall the process occupies six vessels in batch operation. The lithium-exchange and coupling steps were investigated in a microreactor and a static mixer setup in the laboratory. Within short time (3–5 days), optimal process parameters were found and few kg of intermediate could be produced. Two static mixers were arranged in parallel to allow for simultaneous operation and cleaning due to plugging issues in that step.

The same setup from the laboratory was transferred to a pilot plant with larger vessels (600–1600 L) for a production campaign of nearly 700 kg of isolated product. The protection and hydrolysis were performed in stirred tanks, while the lithium exchange and coupling occur in continuous-flow
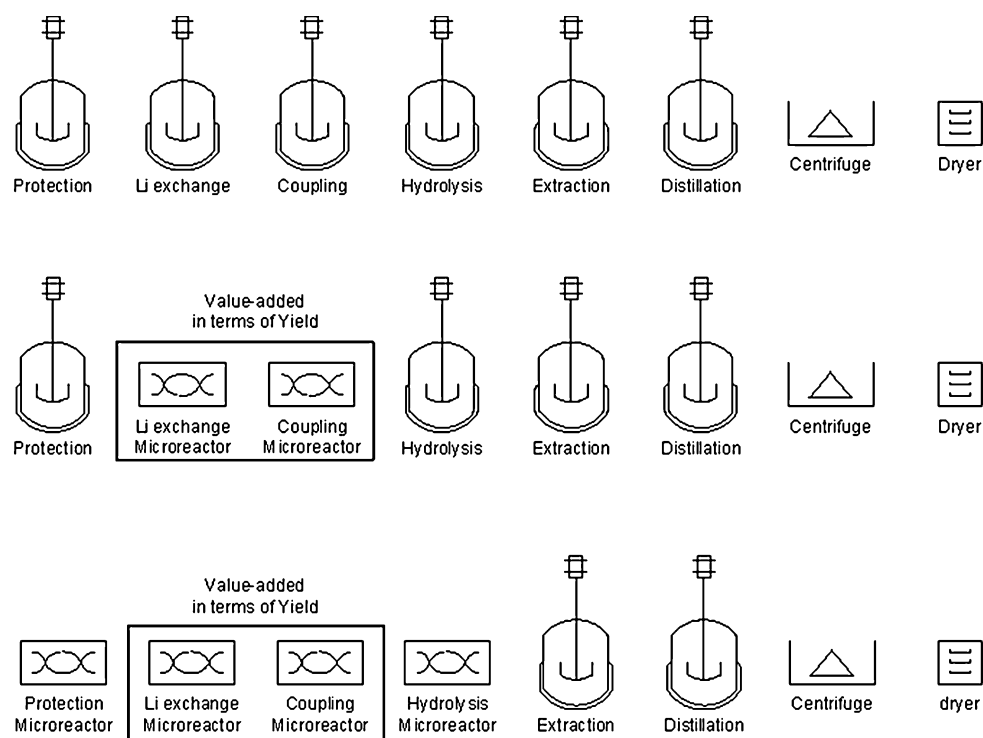

Figure 3. From batch to continuous process in several steps with optimised reaction yield and additional optimisation by continuous-flow reaction.

devices, see Figure 3 middle row. The devices including pumps, sensors and feeding lines were cleaned at the beginning of the campaign and during batch switch. Starting with parameters measured in laboratory, the plant was optimized with respect to the stoichiometry during the first day. Primarily, the plant was operated by shift workers under supervision of technicians; later, shift workers independently operated the plant. After several weeks of operation reaching the production goal, the plant was cleaned and the microreactor and static mixers were moved to the laboratory. The entire production campaign in a metal-microstructured device[19] shows reproducible product quality with no batch out of specification, which facilitated the workup procedure. Cost-saving calculations depend on the financial base and have been determined to approx. 9% compared to batch production. Economic saving potential is assumed due to wider application of continuous-flow devices,[20] see Figure 3 lower row, and is the subject of ongoing analysis.

Scale-Up Issues, Drivers, and Benefits

During scale-up and production implementation, several issues may occur depending on chemistry, periphery and especially for continuous-flow microstructured devices. Here, the scale-up concept within the Lonza approach is described for single-channel devices allowing high flow rates. The single-channel device allows rapid mixing of miscible liquid/liquid, immiscible liquid/liquid and gas/liquid systems and can be called multipurpose for a wide range of applications. It can not cover all applications, for example, heterogeneous catalysis or severe precipitation demand for different devices, often called dedicated devices. In a single channel, the flow and process conditions are well defined; plugging is measured by an increasing pressure drop. With solvent purging precipitated components can be removed; the success is measured by the outlet concentration. This is very important for production under GMP regulations, under which product contamination must be avoided.

To increase mass throughput, simple enlargement of the number of parallel channels is called numbering-up, which can be done within the device (internal numbering-up) or with complete parallel devices (external numbering-up). For homogeneous systems without any change in fluid properties (density, phase transition, precipitation and viscosity) in time or during the process, the numbering-up concept can successfully be used. Careful attention must be paid to the homogeneous flow distribution over all channels during entire production time. Flow maldistribution can lead to inhomogeneous mixing and stoichiometry, heat load or fouling and plugging of channels. In Figure 4 the scale-up concept, from laboratory to production at Lonza, is displayed for single-channel devices. The operation time is the most important parameter to increase the production rate in laboratory and pilot-plant environment. A higher pressure from the feeding pumps allows for higher pressure loss Δp over the device and increases the flow rate. The highest allowable
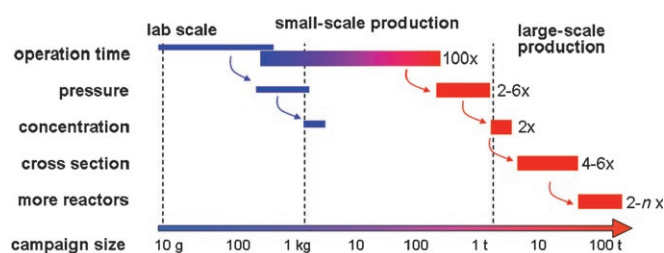

Figure 4. Scale-up concept of single-channel microstructured devices.

concentration depends on the chemical system and on safety issues. A larger cross section of the microchannel allows for higher flow rates, but it has to be checked that the transport processes in the microchannel are still sufficient for the chemical system. A good indicator is the energy dissipation rate ε, which leads to the mixing time. A larger channel cross section is compensated with a higher pressure loss for similar energy dissipation rate and mixing time. Furthermore, the heat-transfer capability must be sufficient. A reaction split with two or more injection points of one reagent spreads the reaction heat over a larger area and avoids hot spots. As a last measure, two or more devices in parallel increase the mass flow rate, going together with higher investment cost and control effort.

According to our experience at Lonza, the implementation of microstructured devices follows a learning curve with increasing experience and knowledge. Many issues must be considered and each chemical system has its own peculiarities. Fouling and plugging of microchannels is still a critical issue, but several strategies can be given to overcome this point. These measures can be substance- or chemistry-based, equipment- or process-related: Regarding the substance, an appropriate solvent can be chosen, the starting materials must be filtered and free of precipitating components, and in some cases additives may prevent fouling. Concerning the microstructured device, dead volumes should be minimized, high flow velocities generate shear stress to remove deposited layers, the surface should be very smooth and the microchannels should be only as long as necessary. Parallel devices allow for cleaning when the second device is in operation. Process conditions have a large influence on plugging behaviour: a high temperature increases the solubility, cleaning intervals should be planned and pumps should tolerate a pressure increase due to fouling.

The main driving consideration for implementing continuous-flow microstructured devices is often not cost saving, but comes from operational experience, enhanced safety and quality and less scale-up risk. Time-to-market can be shortened, but often the implementation of analytical and chemical procedures takes more time and the overall project schedule depends on external decisions. Continuous-flow devices allow for rapid implementation and scale-up leading to a faster time-to-decision as to what is the next step.

Conclusion and Future Developments

After more than a decade of microstructured devices in chemical production, the basics of engineering are roughly understood, but still experimental and theoretical research is necessary for running chemical reactions in microstructured devices. The interaction of chemistry, reaction kinetics, involved phases and transport phenomena play the crucial role for appropriate design. It is important to determine the limiting steps in timescales and heat management. Often, heat and mass transfer or mixing are sufficient for organic reactions with slow kinetics, and hence, more benefit comes from continuous-flow processing with small volumes and increased safety. With microstructured devices, it is possible to run continuous processes at the laboratory scale, which can scaled-up to production scale with low risk. This multiscale production potential from grams to tons allows a high flexibility and offers short time-to-decision in a project. This has to be demonstrated in the future with successful projects in launching pharmaceutical production from research to large-scale production. In automotive and aviation, completely computer-designed devices from series production have been reality for some decades. In analogy, it would be interesting to see, when the first molecule will appear on the market, designed on a computer and solely synthesised and produced by continuous-flow devices. This would be the first step into new era for chemistry.

Acknowledgement

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