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Scale-up concept of single-channel microreactors from process development to industrial production

Norbert Kockmann*, Michael Gottsponer, Dominique M. Roberge

Lonza AG, Exclusive Synthesis, Process Research, 3930 Visp, Switzerland

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ABSTRACT

Microreactors can perform chemical reactions in tiny channels using continuous-flow processes. The microreactor team at Lonza has designed and tested a series of microstructured devices in continuous-flow plants, and performed lab studies of pharmaceutical reactions with successful transfer to commercial production. Microreactor design and scale-up concept is guided by simple correlations, which are described here and displayed in comprehensive diagrams for hydraulic diameter over typical range of flow rate. This leads to a consistent and straightforward scale-up pathway for single-channel microreactors avoiding parallelization from lab development to pilot-scale production.

1. Introduction

Biology is a paradigm for many technical systems, since nature has generated many efficient, perfectly adapted systems, continuously improving them through evolution. Organisms use tiny channels to transport fluids to supply cells and limbs or to perform chemical reactions and separations [1]. Microreactors constitute a similar system, where complex chemical reactions are performed in tiny, highly adapted channels for improved process conditions [2].

Microreactor technology is a new field in chemical engineering and organic synthesis that embodies the principles of Green Chemistry [3,4]. In tiny channels smaller than a millimeter in diameter, chemical and biochemical transformations can be carried out that dramatically enhance mixing and heat transfer. The small internal volume also lowers the consumption of energy and raw materials, thereby increasing safety and economy. To achieve optimal performance of the microreactors, engineers and chemists have to know exactly how the interplay between flow, mixing, heat transfer and chemical reaction works. Typical reactions are rapid or hazardous [5] or with unstable intermediates, but can be safely operated under intensified process conditions [6].

This contribution describes a modular, multipurpose microreactor platform and the consistent design for scale-up from process development to ton-scale production of pharmaceuticals. The reactor consists of modular, microstructured plates in close contact with the heat transfer medium. The microstructured plates ensure the closed handling of hazardous reagents in a single pass with defined mixing and residence time conditions. Only one single channel is employed due to better flow and process control of meta-stable reagents, which can precipitate and plug the reactor [7]. The flow rate through the single channel determines flow velocity, Reynolds number, flow regimes, and pressure loss in the system. The pressure loss in the channel elements is a measure for the energy dissipation rate and the typical mixing time for convective mixing. Heat transfer in the reactor setup is composed of contributions from the reactor channel, cooling channel, and wall resistance and has to be correlated to the energy release from the reaction [8]. Here, only two typical cases are discussed, the reaction runaway in case of stopped flow, and the internal heat transfer coefficient due to convective flow. The derived correlations are displayed in design diagrams indicating reactor size for typical flow

* Corresponding author. Tel.: +41 027 948 65 80; fax: +41 027 947 65 80.
E-mail address: norbert.kockmann@lonza.com (N. Kockmann).

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Nomenclature

a_f	temperature conductivity of the fluid ($m^2\ s^{-1}$)
A_C	cross-sectional area (m^2)
A_S	wetted surface area (m^2)
b	channel width (m)
c_p	heat capacity ($J\ kg^{-1}\ K^{-1}$)
C_A	concentration of key component ($mol\ m^{-3}$)
C_f	friction coefficient
C_h	heat transfer constant
C_m	mixing coefficient
E_A	activation energy ($J\ mol^{-1}$)
d	post or column diameter (m)
d_h	hydraulic diameter (m)
$(-\Delta H_r)$	reaction enthalpy ($J\ mol^{-1}$)
h	channel height (m)
k_0	reaction rate coefficient (s^{-1})
L	channel length (m)
m	fluid mass (kg)
n	exponent
N	number of mixing channel elements
Nu	Nußelt number
Δp	pressure difference (Pa)
P	wetted perimeter (m)
Pr	Prandtl number
$\dot{q}$	specific heat flux ($W\ m^{-3}$)
r	reaction rate ($mol\ m^{-3}\ s^{-1}$)
R	universal gas constant ($J\ mol^{-1}\ K^{-1}$)
Re	Reynolds number
Sc	Schmidt number
t_m	mixing time scale (s)
t_R	reaction time scale (s)
T_W	temperature at the wall (K)
ΔT	temperature difference ($K\ m^{-1}$)
ΔT_{ad}	adiabatic temperature increase (K)
$\dot{V}$	volumetric flow rate ($m^3\ s^{-1}$)
w	mean (fluid) velocity ($m\ s^{-1}$)

Greek symbols

α	heat transfer coefficient ($W\ m^{-2}\ K^{-1}$)
β	eigenvalue
ε	energy dissipation rate ($m^2\ s^{-3}$)
ζ	pressure loss coefficient
η	dynamic viscosity ($N\ s\ m^{-2}$)
λ	heat conductivity ($W\ m^{-1}\ K^{-1}$)
λ_f	friction factor of channel flow
ν	kinematic viscosity ($m^2\ s^{-1}$)
ρ	density ($kg\ m^{-3}$)

rates leading to a consistent scale-up procedure. Together with the modular concept of pumps, heat exchangers, Lonza reactors allow flexible and versatile set-up for laboratory development up to pilot plant production. In one such Lonza plant, a multi-ton campaign for a pharmaceutical intermediate was carried out in 2009.

2. Microreactor characteristics

Complex microstructured channels with meandering curves, corrugated walls, or repeated contracting and diverging channel elements generate secondary flow structures at high flow velocities, which lead to efficient and fast mixing. Large internal specific surface enables enhanced heat transfer and good temperature control leading to good control of reaction rates and heat release. Together with the small internal volume, microreactors allow for safer process conditions compared to batch processes.

The above described characteristics indicate what kind of chemical reactions are suitable for continuous flow, microstructured reactors. The reagents have to flow through the tiny channels without precipitation. Hence, starting material, intermediates, side products and products have to be soluble in the working fluid. Reaction kinetics and enthalpy determine characteristic reaction time and adiabatic temperature rise of the reagents. Competitive reactions such as consecutive or parallel reactions lead to side product formation, which lowers the yield and may complicate work-up processes. Based on the characteristic reaction time, the following classification was set up to facilitate the reactor design [9].

- Type A reactions have a characteristic reaction time below 1 s and are mixing controlled. The generated reaction heat has to be removed to avoid hot spot formation and side products from parallel-competitive reactions. Rapid mixing and correct control of the stoichiometry also avoids consecutive-competitive reactions. Typical reactions are of cryogenic type such as organometallic reactions [10–14].
- Type B reactions are rapid in the range of several minutes (<10 min), but mixing in microchannels is always faster. Enhanced heat exchange over the entire reaction period leads to good yield in temperature sensitive reactions. Proper control over the stoichiometry leads to high yield and low side product formation in consecutive reactions. Examples are coupling reactions or Simmons–Smith reactions [15].
- Type C reactions are slow and show hazardous tendency. Autocatalytic reactions or decomposition potential of intermediates or product belong to this class. The excellent temperature control in microchannels as well as the low internal volume gives higher process safety [16].
- Type D reactions are all reactions not belonging to the above described classes. These reactions can be accelerated by harsh process conditions [17], such as high reaction temperature, high pressure, enhanced reaction activation, or high active reagents.

From the above classification, the question arises, how to design continuous-flow systems with microreactors, which fulfils the following purposes: proper control of stoichiometry, robust to plugging or at least fast plugging detection, modular for different reaction types, rapid mixing and volume providing, modular for different phases involving gas/liquid and liquid/liquid. The answer to these requirements is partially included in problem formulation: a modular reactor plate setup with single microstructured channel for excellent mixing and proper flow control. It has to be flexible for process development in the lab, reactor development, and production on different scales with a consistent scale-up approach.

3. Equipment overview for single channel microreactor

The microstructured reactor plates are made from corrosion resistive material and can fulfill various task in modular set up. Plates are designed for heat exchange to bring the reagents to reaction temperature. Mixing plates include a mixing channel as well as wider channel elements to provide reactor volume for residence time. Finally, reactor plates have only wide channels for heat exchange and residence time. In an approach to standardize Lonza's reactor design, the sizes chosen for the production plates are based on the European paper sheet format DIN A4, A5, and A6 standard. The plate area is doubled by each size step with the result that also heat exchange area and reactor volume are doubled. The scale-up concept becomes apparent and is related to the reaction classes. Thus, for Type A reactions, the aim will be: