This chapter is a comprehensive introduction to the field of micro reaction engineering – an increasingly relevant and rapidly expanding segment of Chemical Reaction Engineering and Process Intensification. Here emphasis is placed on the definition of the term "*micro-reactor*," which is often used in various contexts to describe different equipments such as micro-mixers and micro-heat-exchangers. The more well-recognized term is *microstructured devices*. The advantages and limitations of these microstructured devices are compared to conventional chemical production equipments.

1

1.1 Introduction

Every industrial process is designed to produce a desired product in the most economical way. The large-scale production of chemicals is mostly carried out using different equipments, such as mixers, reactors, and separators with typical dimensions up to a few meters. The process classification is often referred to as *"scale"* and depends on the volume and quality of the product. The classifications are bulk chemicals, intermediates, and fine chemicals processes. The bulk chemicals are produced in large quantities in dedicated production units. The intermediate scale products and fine chemicals are produced in the plants mostly dominated by batch processing. Batch reactors are flexible and can be easily shared between multiple products. Therefore, they are considered to be suitable over centuries and there has been no radical change in the batch processing technology. However, in many cases conventional equipment is not sufficiently efficient. In this context, there is a need to develop chemical industries implementing sustainable technology.

There are two main approaches to reach this target: chemical and engineering. In the first one, the improvements are achieved by alternative synthesis and processing routes, for example, developing highly selective catalysts and using special reaction media – a typical chemical approach. In the second one, the mass- and heat-transport rates are improved, for example, by increasing the specific interfacial area and thus reducing the diffusion path lengths. This in

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turn helps to enhance the safety by virtue of the lower hold-up and superior temperature control, even for strongly exothermic reactions. In addition to this, the reactor performance is enhanced operating reactors dynamically [1, 2], and using non-conventional energy sources. This overall development is often referred to as "Process Intensification", which can be defined in various ways depending on the application involved. However, a generic definition summarising the above discussion is given in the following [3]: "Any chemical engineering development that leads to a substantially smaller, cleaner and more energy efficient technology is Process Intensification!" Micro-technology is one of the powerful tools to attain the goals of process intensification.

1.2

What are Microstructured Devices?

The concept of process intensification using *miniaturized equipments* was pioneered by Professor Ramshaw and his group at Imperial Chemical Industries (ICI), UK, in the late 1970s, who considered how one might reduce equipment size by several orders of magnitude while keeping the same production rate [3]. The objectives were to reduce cost (smaller equipment, reduced piping, low energy, increased reactivity – higher yields/selectivity, reduced waste, etc.), to enhance safety (low hold-up and controlled reaction conditions), to make a compact size of the plant (much higher production capacity and/or number of products per unit of manufacturing area), and to reduce plant erection time and commissioning time (time to market). These miniaturized systems are the chemical processing systems in three-dimensional structures with internal dimension in submillimeter range. They are referred to as *microstructured devices, microstructured reactors, or microreactors*, and the research field is referred to as *"microreactor"* or *"microreactor"* technology.

The advantages and limitations of these devices come from the dimensions increasing greatly the transport processes and the high specific surface area (surface to volume ration). This is described in the following subsection.

1.3

Advantages of Microstructured Devices

1.3.1 Enhancement of Transfer Rates

Let us consider Fourier's law to describe the influence of transfer scales on heat transfer rates. For simplicity, Fourier's law for the flux in one-dimensional space can be written as

$$\frac{\mathrm{d}Q}{\mathrm{d}t} = \dot{Q} = \lambda \cdot A \cdot \frac{\mathrm{d}T}{\mathrm{d}z} \tag{1.1}$$

where Q is the heat energy (J), λ is thermal conductivity (W mK⁻¹), and A is the heat transfer surface area (m²). The temperature gradient dT/dz is the driving force for heat transfer. From Equation 1.1, for a given temperature difference, a decrease in the characteristic dimension results in an increase in these gradients and thus in higher heat transfer rates. The same analogy of concentration and momentum gradient could be applied to mass and momentum transfer resulting in higher mass transfer rates.

Besides the effect of decreasing linear dimensions on the corresponding gradients, the effective surface area for exchange processes has to be considered. Let us integrate Equation 1.1 for a unit volume of reactor:

$$\frac{\dot{Q}}{V} = \dot{q} = U \cdot \frac{A}{V} \cdot \Delta T = U \cdot a \cdot \Delta T$$
(1.2)

where $U = (k/\Delta z)$ is the overall heat transfer coefficient (W·m⁻² K⁻¹) and *a* is the specific surface area (surface area per unit volume, m²·m⁻³). For a circular tube, $a = 4/d_t$, where d_t is the tube diameter. Thus, with decreasing characteristic dimensions, the specific surface area of the system increases leading to higher overall performances.

The surface to volume ratio for microdevices can be as high as 50 000 m² m⁻³ [4]. For comparison, the specific surface area of typical laboratory and production vessels seldom exceed $100 \text{ m}^2 \text{ m}^{-3}$. Moreover, because of the laminar flow regime within microcapillaries, the internal heat transfer coefficient is inversely proportional to the channel diameter. Therefore, overall heat transfer coefficients up to 25 000 W m⁻² K⁻¹ can be obtained, exceeding those of conventional heat exchangers by at least 1 order of magnitude [5]. Indeed, conventional heat exchangers have overall heat transfer coefficients of less than 2000 W m⁻² K⁻¹ [6]. Similar performance enhancement could be realized by the miniaturization for mass transfer leading to efficient mixing. For multiphase systems within microdevices, the interfacial surface to volume ratio between the two fluids is notably increased. Indeed, the miniaturized systems possess high interfacial area up to 30 000 m² m⁻³. The traditional bubble columns do not exceed a few 100 m² m⁻³ [7].

The characteristic time of chemical reactions, t_r , which is defined by intrinsic reaction kinetics, can vary from hours (for slow organic or biological reactions) to milliseconds (for high temperature oxidation reactions) (Figure 1.1). When the reaction is carried out in an eventual reactor, heat and mass transfer interfere with the reaction kinetics.

The transfer rates presented above results in the characteristic time of physical processes (heat/mass transfer) in conventional reactors ranging from about 1 to 10^2 s. This means that relatively slow reactions ($t_r \gg 10$ s) are carried out in the kinetic regime, and the global performance of the reactor is controlled by the intrinsic reaction kinetics. The chemical reactor is designed and dimensioned to get the required product yield and conversion of the raw material. The attainable reactant conversion in the kinetic regime depends on the ratio of the residence time in the reactor to the characteristic reaction time (t_r).



Figure 1.1 Time scale of chemical and physical processes [8]. (Adapted with permission from Elsevier.)

Depending on the kinetics and the type of the reactor, the residence time should be several times higher than the characteristic reaction time to get conversions >90% [9, 10].

For fast chemical reactions, the characteristic reaction time is in the same order of magnitude as the characteristic time for the physical processes (Figure 1.1). The performance of a conventional reactor is influenced in this case by mass and/or heat transfer. For very fast reactions, the global transformation rate may be completely controlled by transfer phenomena. As a result, the reactor performance is diminished as compared to the maximal performance attainable in the kinetic regime, and the product yield and selectivity is very often reduced.

To avoid mass and heat transfer resistances in practice, the characteristic transfer time should be roughly 1 order of magnitude smaller compared to the characteristic reaction time. As the mass and heat transfer performance in microstructured reactors (MSR) is up to 2 orders of magnitude higher compared to conventional tubular reactors, the reactor performance can be considerably increased leading to the desired intensification of the process. In addition, consecutive reactions can be efficiently suppressed because of a strict control of residence time and narrow residence time distribution (discussed in Chapter 3). Elimination of transport resistances allows the reaction to achieve its chemical potential in the optimal temperature and concentration window. Therefore, fast reactions carried out in MSR show higher product selectivity and yield.

The relative heat and mass transfer performance of microstructured reactors with respect to conventional reactors is depicted in Figure 1.2. As can be seen, both in terms of heat and mass transfer, as explained above, microstructured devices offer superior performance.

A simplified algorithm for a single step homogenous reaction that could help in choosing conventional and microstructured devices based on kinetics, thermodynamics, and transport rates is presented in Figure 1.3. Here t_r , ΔH_r , and t_{mx}



Figure 1.2 Benchmarking of microstructured reactors. (Adapted from Ref. [11]. Copyright @ 2009, John Wiley and Sons.)

are characteristic reaction time, heat of reaction, and characteristic mixing time, respectively. In the case of heterogenous reactions, mixing time would be replaced by characteristic mass transfer time. For a thermodynamically favored reaction, the chemical kinetics could be obtained for different operating conditions such as temperature, pressure, concentrations rendering a reaction rate equation allowing process optimization.

As described before, the limiting factor can be the intrinsic kinetics, the thermodynamics, or the heat and mass transfer of the reacting system. The characteristic reaction time of the reaction is then obtained for the operating conditions where the reaction can be operated under temperature control and the product is not decomposed. If the characteristic reaction time is less than 1 s and the heat of reaction is more than $-50 \text{ kJ} \text{ mol}^{-1}$, the use of microstructured devices is proposed. However, even if the reaction time is high and heat of reaction is relatively low, the microstructured devices could be used to enhance the mixing leading to higher productivity.

1.3.2 Enhanced Process Safety

Process safety is an important issue for chemical industry in general and for exothermic reactions and reactions involving hazardous chemicals in particular. High hold-up of reactants in conventional batch reactors leads to very high impact in the case of accidents. A common approach to handle fast exothermic



Figure 1.3 An algorithm showing choice of reactor based on reaction kinetics, thermodynamics, and mixing rates for a homogeneous reaction.

reactions is through dilution of the reactants by solvents or using semibatch mode, which is the slow addition of one of the reactants.

Microstructured devices are safer than conventional devices because of the small amount of reactants and products inside the reactor. Indeed, in case of failure, the small amount of eventual toxic chemicals released can easily be neutralized [6]. The high heat transfer performance of microdevices allows rapid heating and cooling of the reaction mixture, avoiding hot or cold spots and providing nearly isothermal conditions [5]. Under the predominant laminar regime, the volumetric heat transfer resistance at the reactor microchannel side is proportional to the square of the reactor diameter. In principle, by using the strong dependence of the heat transfer rates on the reactor diameter, any exothermic reaction can be controlled by adjusting the reactor diameter [12].

1.3.3 Novel Operating Window

In the case of slow reactions, the transformation rate is limited by intrinsic kinetics. A drastic increase of the temperature allows exponential acceleration of the reaction rate in agreement with the Arrhenius Law. Moreover, the pressure can be advantageous to accelerate reactions, to shift equilibrium, to increase gas solubility, to enhance conversion and selectivity, to avoid solvent evaporation, and to obtain single-phase processes [8, 13]. The overall transformation rate of such reactions could be significantly increased in these *novel operating windows*.

Using microstructured devices, these reactions could be performed in novel operating windows under more aggressive conditions than in conventional devices. The pressure can easily be increased to several hundred bars because of the small reaction volumes and low mechanical stress. The microdevices allow an easy control of process parameters such as pressure, temperature, and residence time. Thus, an unconventional operating window, that is, high temperature, pressure, and concentrations could be used within microstructured devices even in explosive and thermal runaway regimes [8].

Operating MSR under novel process windows, the key performance parameters can be increased by a few orders of magnitude. A few examples are presented here. In the case of esterification of phthalic anhydride with methanol 53-fold higher reaction rate between 1 and 110 bar for a fixed temperature of 333 K was observed [14]. A multiphase (gas/liquid) explosive reaction of oxidation of cyclohexane under pure oxygen at elevated pressure and temperature (>200 °C and 25 bar) in a transparent silicon/glass MSR increased the productivity fourfold. This reaction under conventional conditions is carried out with air [15]. Another example is for the synthesis of 3-chloro-2-hydroxypropyl pivaloate: a capillary tube of 1/8 in. operated at 533 K and 35 bar, superheated pressurized processing much above the boiling point, allowed to decrease reaction time 5760-fold as compared to standard batch operation [16]. The condensation of o-phenylenediamine with acetic acid to 2-methylbenzimidazole in an MSR is an impressive example of the reduced reaction time from 9 weeks at room temperature to 30 s at 543 K and 130 bar [17].

1.3.4 Numbering-Up Instead of Scale-Up

Microstructured devices bring in fundamental changes in the approach toward the step from laboratory to industrial scale. Conventionally, the size of the laboratory reactor or flask is upgraded to a few cubic meters to meet the target productivity through different steps including pilot scale studies. This involves cost and time expense scaling up. The numbering-up (also referred to as *scale-out*) concept consists of an increase in the number of parallel operating units preserving the advantages of MSR, particularly their high surface to volume ratio. This approach

is simpler and faster than the conventional processes (no redesign and pilot plant experiments), thus, decreasing considerably the time between discovery and production and hence shortens the time to market. The break-even point of the cash flow curve could be reached at an earlier point of time, which renders the whole concept more appealing. Moreover, the numbering-up strategy allows to adapt the production to the market demand by increasing or decreasing the number of units as well as an earlier start of production resulting in a lower cost.

There are two ways of numbering-up of microstructured devices: internal and external (Figure 1.4). For external numbering-up, multiple identical units are operated in parallel. The advantage is that each single unit is independent of the others and performs as the developed lab-scale unit. However, as each unit will need individual equipment (such as pumps, tubing, flow meters), the costs of external numbering-up are considerable.

When numbering-up is carried out internally, the amount of equipment is reduced and thus the cost is lower. The fluids in this case are contacted in a mixing zone and subsequently are distributed into the reaction channels, where conditions are similar to the lab-scale single channel device. The plates or chips fabricated or the standard microtubes that are used as MSR are assembled in two types of geometries: monolith geometry and multiplate geometry. In the former case the inlet stream is distributed simply between all the channels through a large distributor, while in the second case, the inlet stream is first divided into different plates/layers and then distributed into channel plates.

The main problem for internal numbering-up to overcome is the equal distribution of fluids to the multiple channels. Equal distribution is indispensable to



Figure 1.4 Schematics of Numbering-up of microstructured reactors: (a) external numbering-up, (b) internal numbering-up [18]. (Adapted with permission from Elsevier.)

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obtain identical reaction conditions in each channel to ensure high reactor performance and safety. The eventual maldistribution in the microchannels leads to a broad residence time distribution and can even result in the clogging of some of the channels, thus affecting product yield and selectivity [18].

The flow nonuniformities generally occur because of two reasons: a poor reactor design and manufacturing tolerances. The manufacturing tolerances usually cause variations of local temperature in the range of about 5%; the former reason can cause flow ratios in different channels more than a factor of 4 [19].

A further disadvantage of internal numbering-up is the absence of reaction control in the mixing zone. As soon as both reactants are contacted, reaction is initiated and heat is generated. However, heat can be efficiently removed from the channels placed after the distribution section. Possible solutions to overcome the mentioned problems are discussed in chapter 5.

1.4 Materials and Methods for Fabrication of Microstructured Devices

The steps in the selection and use of suitable microstructured devices for a particular chemical production are depicted in Figure 1.5. Majority of steps corresponds to the procedure that is followed for conventional equipments. However, more emphasis is placed on fabrication techniques as it involves structures in micro-, nanometer scale requiring very precise fabrication techniques. In addition, they should be able to accommodate, either individually or combined, these structures and sensors that are required to control the process.

Different materials such as metals, glass, polymers, and ceramics are used to fabricate the microstructured devices. Various techniques such as etching, lithog-raphy, electroplating, molding, polymer microinjection molding and embossing are applied to make the microscale channels of different cross-sectional geometries (e.g., circular, rectangular, square).

Some of the commonly used techniques to fabricate complex structures of microdevices are summarized briefly in the following.

1) The LIGA (German acronym Lithographie, Galvanoformung und Abformung of Lithography, Electroplating, and Molding) process: The LIGA process can be expected to be superior to other methods for fabrication microstructures with high aspect ratios (ratio of height to width) and to produce microstructures of complex shapes [21]. This technique is suitable for a broad range of

Figure 1.5 Steps in the selection and use of microstructured devices for chemical production.

materials, including metals, alloys, polymers, as well as ceramics and composites to fabricate net-shaped high aspect ratio components. In this technique a layer of photo resisting resin is deposited on a base plate and exposed to high-energy X-rays to the area that is to be etched [22]. The irradiated portions of the photoresist are dissolved and eliminated with a solvent obtaining a three-dimensional structure. The metal is deposited on this structure by electroforming. This metal structure can either be used as it is or it can serve as a mold for making a large number of parts through injection molding or stamping. This technique also uses an inexpensive Ultraviolet (UV) light source, but precision is an issue in this case.

- 2) Micro-EDM (Electrical Discharge Machining): This technique uses electric discharge or sparks created between a workpiece and an electrode in dielectric fluid. When the workpiece and the electrode are separated by a small gap, called as *spark gap*, a pulsed discharge occurs, which removes material from the workpiece through melting and evaporation [23]. It is possible to etch as fine as 50 µm on the surface of the contacting plate using the programmable movement of the electrode [24]. A metal form obtained with another process can also be used as an electrode in order to obtain the desired surface on the substrate.
- 3) *Wet etching:* This is a highly selective technique and involves chemical reactions. The metal plate to be etched is first covered with a resist using spincoating or lamination technique. The resist is further structured via different techniques, for example, it is irradiated with UV light through a mask giving a structured resist layer partly covering the metal. Etching of the metal in the uncovered area with subsequent removal of resist gives microstructures [25].
- 4) *Dry etching:* In this technique, an ion beam is directed on the surface to be etched. This process is easy to use, but it is rather expensive [26] and limited to a certain materials (e.g. silicon), which is not always suitable for a given application.
- 5) Recently a novel manufacturing technique for microstructured reactors was proposed [27]. This technique is based on a cheap and resource-efficient production of structured plates by using roll embossing. The stacked plates are joined by laser welding or vacuum brazing. The method allows manufactoring microstructured reactors in a wide range of throughput, pressure and temperature for homogeneous and multi-phase reactions.

1.5

Applications of Microstructured Devices

Microstructured devices have been successfully used for the continuous processing of fast and highly exothermic reactions [28] and chemical transformations involving toxic, sensitive, and explosive chemicals such as nitration [29], hydrogenations [30, 31], polymerization [32, 33], oxidation [34], halogenations [4], alkylation [35], tetrazole synthesis [36], and reaction of diazomethane [37]. With newly developed *online* monitoring techniques, MSR can be used as a powerful laboratory tool to investigate the reaction mechanism and kinetics.

1.5.1 Microstructured Reactors as Research Tool

Over the past two decades, MSR have been used in the laboratory as well as in industries. Such activities are regularly reported on various scientific meetings and conferences. One of the most important conferences, IMRET (International Conference on Microreaction Technology), was started in 1997 (Frankfurt, Germany) and is being followed up successful till date. Information on this research area is available in the form of books [7, 38–40]. In addition to the usual update through scientific journal papers, quite a few reviews are published on MSR [4, 38, 41-46]).

Microstructured devices are replacing conventional flasks or laboratory reactors as a laboratory tool. Let us take the example of an investigation of reaction mechanism and kinetics of fast and highly exothermic reactions. It is conventionally carried out using the measurements from either continuous online monitoring (e.g., stopped-flow technique [47]) or offline analysis [48]. Two difficulties arise in the former case: integration of efficient cooling to suppress temperature rise because of spectroscopic devices and separation of intermediates for identification. Therefore, only offline method combined with sample quenching (freeze/chemical) can allow catching intermediates providing information about reaction mechanism. The quenching for offline analysis is done either by adding an agent to the continuous stream [36] (referred to as *quenched-flow technique*) or to a container that collects the sample. MSR have been successfully used to overcome such problem. A slugflow MSR binds both reactants in the dispersed microliter droplets, which are carried by an inert fluid within a microcapillary. Each isolated slug acts as a micro-batch reactor. Because of the small size of the reactor assembly, it can be incorporated into commercially available calorimeters with precise temperature control. This concept has been applied for the investigation of enzymatic reaction kinetics [49], bromination of styrene [50], hydrolysis of pnitrophenyl acetate [51], high-throughput catalyst screening [52], and cyclization of Pseudoionone [53].

Besides, there are several reports on mixing and kinetics studies involving handling of hazardous reactants using both invasive and noninvasive techniques.

1.5.2 Industrial/Commercial Applications

The prominent industries that benefited from microstructured devices are pharmaceutical, specialty, and fine chemical industry. A few micro-plants have been developed and successfully tested in the laboratory as well as on commercial sites

MSR activities	Company/institute
MSR/mixer design and fabrication, process development	Fraunhofer ICT-IMM Mainz [57, 58], Forschungszentrum Karlsruhe GmbH [59], Ehrfeld Mikrotechnik BTS [60], Microinnova Engineering GmbH [61]
MSR design and fabrication, development of laboratory systems	Mikroglas GmbH [62], Mikronit microfluidics [63], Little Things Factory [64], Syrris [65]
Engineering services of MSR	Bayer Technology Services [66], Alfa Laval [67]
Development of MSR materials	Corning [68, 69]
MSR process development and demonstration of industrial production	Merck [70], SK Chemicals [71], Ampac Fine Chemicals [72], Phoenix Chemicals [73], Clariant GmbH [74], DSM [69, 75, 76], Lonza [43, 44], Sigma-Aldrich [77]

Table 1.1 Examples of industries/institutes active in microprocess engineering.

Table 1.1. The industries that are working in this area are Cellular Process Chemistry Systems GmbH, Fraunhofer ICT-IMM, Micronit Microfluidics, Ehrfeld BTS GmbH, Systanix, Inc., Styrris, to name but a few. In 2005 Fraunhofer ICT-IMM, Germany, has made successful runs of a continuous microstructured nitroglycerine plant (capacity 15 kg h^{-1}) at the site of Xi'an Chemical Industrial Group HAC in China [54]. This plant consists of three main parts: the mixing of sulfuric acid with nitric acid (both highly concentrated fuming liquids), the reactor, and the phase separation (washing and purification devices). On demand, glycerine and the acid mixture are fed separately into an MSR where mixing occurs within milliseconds. Such micro-plant has also been developed for the polymerization of Methyl methacrylate [32] and showed significant improvement in the control of molecular weight because of superior heat transfer efficiency. The plant constructed by numbering-up eight tubes (microreactors) was continuously operated for 6 days without any problems.

Microreactor technology is an important part of the decentralized mobile plant concept. Such plants have already been developed for biological applications (e.g., miniature analytical thermal cycling instrument, MATCI, to amplify and detect DNA via the polymerase chain reaction in real-time [6]). The objective behind chemical mobile plants is to reduce the risk associated with transporting hazardous chemicals. Rather than transporting hazardous chemicals, a distributed production strategy may be used with economic manufacturing on consumers' site, as is currently performed for oxygen and nitrogen [7]. Recently, a chemical plant has been developed by Ehrfeld Mikrotechnik BTS GmbH, Germany, in a briefcase, which can be used for a variety of applications.

Microstructured devices have several applications in pharmaceutical and fine chemicals where production amounts are often less than a few metric tons per

1.7 Summary 13

year [55]. The processes that rely on batch or semibatch mode could be operated continuously with multiple advantages over the batch processes. A review on the benefits of such devices for pharmaceutical industrial processes cites that 50% of the reactions in fine chemical/pharmaceutical industry could benefit from a continuous process [43]. In drug industry, there is always a strong time pressure to bring new molecules on the market to maximize the profit because of the manufacturing patent life of 20 years [56]. The process development time could be reduced significantly (Table 1.1).

16 Structure of the Book

The purpose of this book is to present the engineering aspects of microstructured devices. It addresses these questions: under which conditions microstructured devices are beneficial; how the devices should be designed; and, finally, in which way microstructured devices can be integrated in a chemical process. It also includes several theoretical and practical design examples on which the industry personnel have been working for several years. Some of these examples are included as exercise for the master and doctoral students in the curriculum at Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland.

This book is divided into two parts: homogenous and multiphase (heterogenous) systems. Prior to explaining homogenous systems, a chapter on the fundamentals of chemical reaction engineering is presented, which is the basis for the discussions throughout the book. Homogeneous reactions part consists of three chapters that concentrate on mixing, residence time distribution, and heat management. The chapters in the second part elaborate on fluid-solid reactions, fluid-fluid reactions, and three-phase reactions. Each chapter contains the introduction, the types of devices used in a particular application, the basic design equations, the examples depicting the design methodology for a particular application, and chemical examples.

1.7 Summary

In this chapter, the microstructured devices are introduced underlying their potential benefits for the process industries. The reduced scale facilitates the temperature control giving an opportunity to maintain the temperature within any window required. Enhanced (heat/mass) transfer rates allow control of highly exothermic and hazardous reactions. It also increases production rates and thus reduces the total processing volume. In addition, microreactors can be simply numbered up for large-scale production, avoiding the problem of scale-up of conventional reactors.

Thus, these devices are suitable when the following case-specific drawbacks are faced in the conventional processing options:

- · severe transport limitations (heat or mass transfer)
- · low yields and high wastes because of multistep reactions
- · safety issues for hazardous materials
- poor control of reaction parameters
- · failure to meet market quality demand.

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