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The Smaller, The Better – Microtechnology for a Macroresults

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Abstract

There is a well-known expression The Bigger, The Better, on which many would agree but when it comes to microreactors it is necessary to make the slight modification and say The Smaller, The Better. Reduction in reactor size emerged in many positive effects on many chemical and biochemical reactions. Faster reactions, smaller usage of reaction components, smaller amount of waste streams, safer reaction conditions, easier process manipulation etc. are just some of the advantages of microreactors. The aim of this review is to present microreactor technology in a simple way and to show its basic characteristics such as structure, advantages and disadvantages, types and general application.

Keywords: *microreactors, production, application, advantages, disadvantages*

1. Microreactors at a glance

When something is present in the science for almost half of the century it can no longer be called as new technology. However, "new" is usually an adjective related to microstructured devices. On the other hand, if we cannot talk about new technology itself, we can still relate the word new to the new concepts, new approaches and new methodologies that are for sure connected with microstructured devices. From the early days, back in 1977 this technology has withdrawn significance attention. From that time, when a microreactor was considered to be a straight tube with microchannel size (Fig. 1a), thanks to the significant scientific and technology progress, the technology itself grown to more complex systems (Fig. 1b).

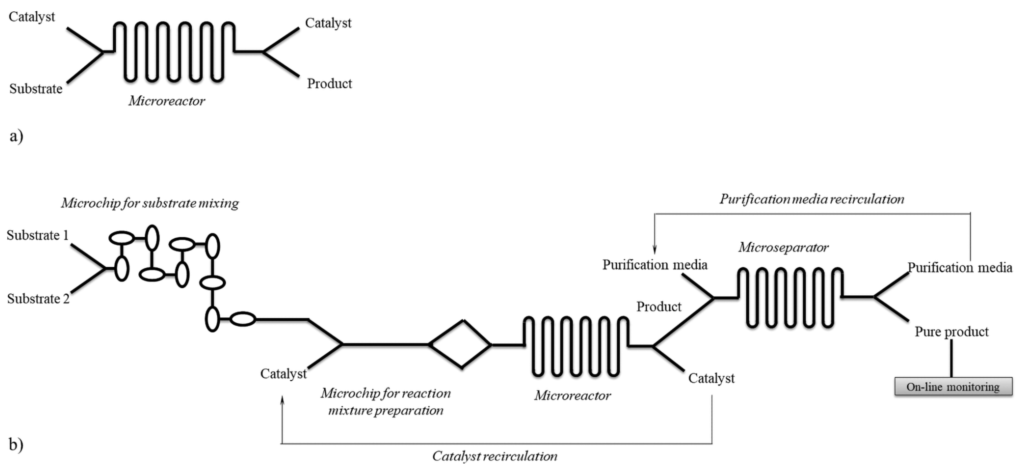

Fig. 1. Schematic diagram of a) simple and b) complex microtechnology system

Regardless to the complexity, microreactors are defined as miniaturized reactor systems constructed by using methods of microtechnology and precision engineering [1] and always consist of same structural units (Fig. 2). First of those structural units is always a microchannel. Usually in microchannels with smoot walls, parallel flow is formed and in those with rough walls, segmented flow is more typical. Flow formation is important for several reasons. First, it directly affects the size of interphase area that is important for mass transfer. Second, it affects the phase separation at the exit of microchannel and third, mathematical modelling becomes more challenging when going from parallel to segmented flow.

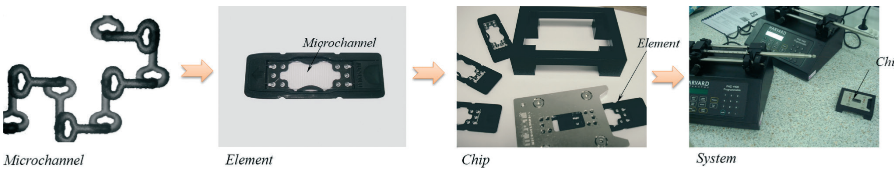

Fig. 2. Structural units of microreactor system

Microreactor is a channel etched in a solid substrate (*element*). As mentioned, *microchannel* is a basic structure of microreactor system but in order to function properly, it needs additional parts (Fig. 2). First, it is an *element*, a material/base in which a channel is positioned. Element and microchannel together form a *chip*. In order to supply microchannel with reaction mixture connection fluid lines are necessary. Together with chip, they form an *unit*. Combination of unit and all other parts of equipment (pumps, systems for analysis etc.) is called a *system* [2]. High pressure pumps are especially important since they are responsible for reaction time determination and flow regulation.

Typical diameters of microchannels are in the range from 10 μm to 500 μm. Microchannels can be in a simple, straight tube form (Fig. 3a and b) or more complex i.e. with integrated micromixers (Fig. 3c and d). Usually, they are round or rectangular in cross section. Depend-ing on a final purposes they are fabricated from different materials mainly glass, silicon, quartz, metals and polymers. The selection of material depends on its chemical compatibility with the reaction mixture and production price. In this way microreactors are adapting to the reaction not *vice versa*. The most commonly used material is glass since it is chemically inert and transparent. Several methods can be applied for etching a microchannel in to solid sub-strate like: micromilling, lithography, embossing processes and laser ablation processing [3]. Choice of method affects channel depth and surface roughness (Fig. 3a and b). Surface roughness is considered to be one of the most important factors for microreactors. Decreasing the size of the channel impact of roughness is significantly increasing and thus increases its impact on reaction. The average channel roughness ranges between 0.8 and 2.5 μm and as mentioned, it depends on microchannel production method [4].

Chemical and biochemical processes are never simple (Fig. 1b). They are usually a combination of reactant preparation, reaction(s), product separation, reactant recirculation, analysis, etc. As mentioned, this means that microreactor system can vary from a simple one to certainly complex one. Integration of different processes such as, for example, reaction and separation, in microreactor system is currently one of biggest challenges in microreactor technology.

When going on a small scale, size is not the only thing that is changing but also a lot of new physical phenomenon's are observed. They all present a certain challenge to science and usually demand a new approach to reactions that are by now well known on a macro scale. Reducing the scale a lot of new advantages [4] emerged that brought new spotlight on old processes. Microreactors are characterised as safe, reliable, scalable and robust. They allow better process control and offer rapid dynamic response. Some of the other advantages and disadvantages of microreactors are listed in Table 1.

Among all advantages, adaptability of microreactors is considered to be one of the major benefits. This is especially important for process intensification and integration. The best way to simply describe this is to identify microreactors with a LEGO system. Like them, connecting different microstructured devices complex systems can be built up. As mentioned in Table 1., under the Numbering up part, all the rules, all the chemistry that is defined on a single microreactor unit just replicates on all other units when they are multiplied in order to enhance the production capacity. This makes the transition from laboratory to the industry easier and makes the gap between them significantly smaller.

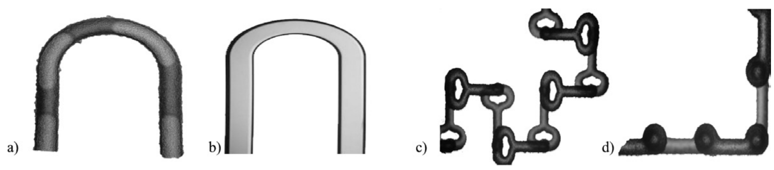

Fig. 3. Different types of microchannels: a) tubular microchannel with rough walls, b) tubular microreactor with smooth walls, c) teardrop micromixer and d) swirl micromixer

Table 1. Some advantages and disadvantages of microreactor

Advantages	*Fast mixing and mass transfer*	• diffusion limitations are minimised • no concentration gradient • mixing takes place by molecular diffusion
	High surface-to-volume ratio	• from 10,000 to 50,000 m^2/m^3 • efficient energy, mass and moment transfer
	Laminar flow	• better control of reaction conditions • favours modelling of reactions • provides high surface to volume ratio and interface area • eliminates back-mixing
	Small substrate volume	• significant cost savings • a lot of information about the process can be collected with small inlet volumes
	Environmentally friendly	• small substrate input and small product output • reduction in waste stream and total amount of waste • small energy consumption
	Safe reaction conditions	• small volumes, extensive heat transfer and variety of materials for production that can adapt to extreme reaction conditions (high pressure and temperature, explosive reaction etc.)
	Selectivity	• formation of purer products in shorter residence time
	Rapid reactions rate	• due to combination of previous mentioned advantages, reaction rates are faster on macro scale • higher space-time yield/productivities
	Numbering-up	• simple construction • uninterrupted continuous operation since a broken unit can be easily replaced without disturbing other units • chemistry performance of single unit is replicated on all other
	Easy to manipulate (Fig. 4)	• like LEGO system, microreactors can be easily assemble
Disadvantages	*Clogging* (Fig. 5)	• demands careful preparation of substrates (usually filtration before usage) • limits the usage of substrates
	Production price	• production of microreactor can significantly increase in cost depending on used material, production technique, complexity of the reactor • additional equipment (pumps, sensors etc.) also increase overall cost
	Handling the formation of solids	• if the product of the reaction is a solid, particles aggregate and cause blockage of the channel
	Significant effect of surface (microchannel wall)	• when working on a small scale surface roughness plays important role on the process
	Chemical adsorption on microchannel wall	• chemicals in solution adsorb on the channel walls thereby resulting in a loss of chemical concentration
	Industrial application	• still difficult to find general industrial application due to the production volumes

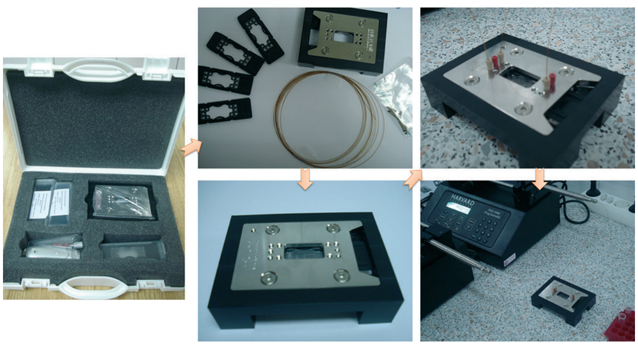

Fig. 4. Steps to assemble a microreactor (from a suitcase to a functional reactor system)

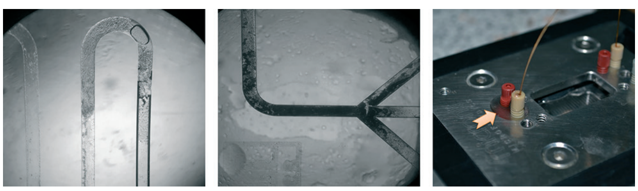

Fig. 5. Formation of clogging and leaking in a microreactor

2. Microreactor types

It is hard to make one uniform classification for different microreactor types. Usually the classification depends upon the aspect (microreactor physical characteristics, application or fabrication method etc.) from which the reactors are observed. According to the one classification [4], microreactors can be divided into two large groups: chip- type microreactors and microcapillary microreactors.

Chip-types are most often used. They offer better process control and easier integration in comparison to microcapillary microreactors. Microcapillary microreactors are usually produced from polymers like fluoropolymer microcapillary film (MCF) and they consist of larger number of parallel capillary channels with mean hydraulic diameters typically between 150 and 400 µm. Example of microcapillary microreactor are microcapillary flow discs used in chemical synthesis [5].

On the other hand, when scoping the literature or searching on the internet, terms like microreactor for chemical reactions, photocatalytic microreactors or enzymatic microreactors can be found. Consequently, most common classification is based on application of microreactors. Another classification of microreactors is based on production material so there are glass microreactors, stainless steel microreactors, polymer microreactors etc. Further classification is based on the shape of channel itself or upon different structures added in to the channel. In that case most common type of microreactors are microreactors with micromixers, zigzag microreactors, microreactors with nozzle injections etc.

Further classification can be based on microchannel properties, type of flow, number of phases etc. Some of them are listed in Table 2.

Table 2. Different microreactor types based on specific characteristics

Characteristics:	**Microreactor types:**
Flow type	• laminar flow microreactors • segmented flow microreactors
Design complexity	• basic (i.e. single tubular microreactor) microreactors • complex (i.e. μ- Total Analysis System) microreactors
Channel wall surface roughness	• smooth (relative roughness around 1%) microreactors • rough (relative roughness around 10%) microreactors
Shape of the inlet	• T microreactors • Y microreactors • ψ microreactors
Number of reaction phases	• single-phase microreactors • multi-phase microreactors
Durability	• disposable microreactors • reusable microreactors
Phase type	• liquid-phase microreactors • gas-phase microreactors
Application	• microreactors for (bio)chemical synthesis • microreactors for polymer synthesis • microreactors for process analysis • microreactors for material analysis
Fabrication material	• glass microreactors • ceramics microreactors • silicon microreactors • polymer microreactors • steel microreactors • perfluoroalkoxy (PFA) microreactors
Product type	• T, Y or ψ microreactors • falling fil microreactors
Mixing	• round bottom flask microreactor • jacketed microreactor • asia microreactor

3. Application of microreactors – bridging the gap between laboratory and industry

For many years now microreactor technology has been reserved mainly for laboratory research. Main focus in research was to collect as much as possible information about: (*i*) the transferring the process from batch regime to continuously operating regime, (*ii*) process optimization, (*iii*) production, (*iv*) kinetic measurements, (*v*) separation, (*vi*) discovering new production routes, etc. The biggest progress was made in chemistry especially in organic or polymer synthesis of a variety of products [6,7]. During the organic synthesis main challenges are usage of toxic chemicals and extreme conditions like high pressure and temperature. Microreactors present advantage by carrying such reactions in much safer environment [8]. In polymer synthesis it was reported that narrow particle size and molecular weight distribution was achieved in microreactor due to good efficient mass transfer and good heat removal [9]. Photochemical application of microreactors was also studied [10]. By combining the benefits of micro-scale with continuous-flow mode, microstructured reactors enable, when compared to conventional photochemical equipment, higher conversions and selectivities while reducing irradiation time. Additional benefit is more efficient light penetration, minimization of side reactions, easy control or irradiation time and safer conditions. Synthesis of nanoparticles in microreactors was demonstrated as potential alternative for large scale production of nanoparticles. Most progress was made on synthesis of inorganic and metal nanoparticles [11].

Of all the fields, biochemical and pharmaceutical application of microreactors is the last explored. Enzymatic microreactors for biochemical and pharmaceutical application can be roughly divided in to two groups, one includes biosynthesis and biochemical processes and second, screening, protein folding, enzyme kinetic estimation and analytical assays [3]. Enzymes as key element can be used in immobilized or in suspended form. Different approaches can be applied to immobilize enzyme in to microreactor. Most common are covalent immobilization, adsorption and co-polymerization [4]. The main problem in this field is that many microreactors that are well established for chemical productions can not be used for biochemical reactions. The first problem is residence time distribution since enzymatic reactions are usually slower then chemical. This leads to development of new microreactors that will satisfy demand for longer residence times. The second problem is catalyst lifetime because in comparison to chemical catalyst, enzymatic catalysts have shorter lifetime. As a solution, immobilization and development of new reactor systems that will enhance enzyme stability and activity are proposed. The third problem is cascade catalysis where one has to adapt different reaction conditions for different enzymes. As a solution, compartmentalization of microreactors is proposed [4].

Besides laboratory research, lately the interest is slowly shifting towards development of modular systems that should be the next step that is necessary if microreactors will be implemented in to the industry. Main idea is that these modular systems include all production steps – from substrate preparation to clean product ant the end of the process. Some systems presented by Corning and Chemtrix B.V. are already present on the market but there are still several disadvantages to overcome like numbering up, production costs, flow stability etc.

4. Microreactor technology in Croatia

As mentioned, microreactor technology is known and implemented in science for more than 40 years. The first reaction in the microchannels done by Croatian scientists was performed in the laboratory of Faculty of Chemistry and Chemical Technology, University of Ljubljana in Microprocess Engineering Research Group by prof. Tišma [12]. Laccase-catalyzed L-DOPA oxidation in an oxygen-saturated water solution was studied in a Y-shaped microreactor at different residence times.

In Croatia, a decade has passed since the first chips were assembled and tested for different processes. The first one was bought by the Faculty of Chemical Engineering and Technology, University of Zagreb and up to today they were applied mostly in biotransformation processes by group of Prof. Zelić. Main research focus of Prof. Zelić group was related to the production of valuable chemicals such as hexanol [13-15] and hexanoic acid [16], polyphenol oxidation [17,18] and coenzyme regeneration [19-22]. Besides that, application of microseparators for polyphenol extraction in two-phase aqueous systems was analysed [23,24]. Following the world trends, they were uses in the synthesis of different chemical compounds [25] and in photochemical processes. Applications of microreactor for biodiesel production and purification [26,27] as well as expanding the research on photochemical application of microreactors for production of pharmaceutical chemicals were set as future challenges in the same group by dr. Šalić.

The research group of Prof. Vrsaljko from the same Faculty is focused on utilising the 3D-printing technology for microreactor production from different polymers [28]. The combination of microreactors and 3D-printing reactors is also a worldwide growing terrain. Production of cheap but highly efficient reactors is something worth of the attention. Manufacturing of microreactors by 3D-printing technology is performed also in group of Prof. Šercer at Faculty of Mechanical Engineering and Naval Architecture, University of Zagreb.

Two research groups from the Faculty of Food Technology and Biotechnology, University of Zagreb are also implementing microreactor technology in different fields. While group of Prof. Jurinjak Tušek is oriented towards mathematical modelling [29] of microreactor processes, the group of prof. Rezić is focused on dye decolourization processes and microreactor production by PolyJet Matrix Technology.

Recently, the research group from the Josip Juraj Strossmayer University of Osijek, Faculty of Food Technology Osijek, set-up a microreactor system and started with the research in the field of biotransformations of phenolic compounds originated from food industry waste.

5. Future perspective of microreactor technology

Worldwide, there are several key players when it comes to microreactor technology: Soken Chemical & Engineering Co., Ltd., Bronkhorst (UK) Ltd., Chemtrix B.V., Little Things Factory GmbH, Ehrfeld Mikrotechnik BTS GmbH, Micronit Micro Technologies B.V., AM Technology Co., Ltd., Corning Inc. and Vapourtec Ltd. They usually set the trends and these days; they are holding majority of microreactor technology market. There are many different predictions about the future trends of microreactors worldwide. Some estimation says that global microreactor technology market will reach 105 million USD by the end of 2025, and some even triple the mentioned number [30-32]. Although the numbers vary depending on initial parameters, all market researchers predict significant growth in the next five-years period. They estimate that the main focus of technology itself will be in expansion in regions with significant growth potential, such as India and China. Also, reduction of labour costs is expected and connected with high level of plants automatization. The predictions are that the switching from batch to continuous processes, will lead to the increase of labour costs between 10-20%, while the investments will decrease between 5 – 15%. Focus will also be on high speed development and high-performance products (i.e. development of new materials) together with process intensification (performance, stability etc.). It is believed that during process intensification, the yield should grow from 0 – 40% and energy should decrease from 5 – 15% and by shortening the time-to-market aspect development time should be reduced between 10-30%.

As for research area, three areas are marked as spotlights in the next time period: drug development processes, chemical production and biodiesel synthesis.

Chemical production in microreactors is present from the early days of microreactor technology, while drug development processes and biodiesel production drown the attention later on.

Drug development process is still considered as one of the most expensive processes. Because of that pharmaceutical companies are trying to find new development routs that will decrease time-to-market aspect, that will enable new process formation and increase production throughput. Microreactors are considered as good and efficient tools that could meet all those demands [33].

As for biodiesel production, biodiesel as an alternative fuel with low environmental impact become interesting with increasing concerns of global warming. Most common method of biodiesel production is transesterification. Application of microreactors in the production will allow the reaction to be carried out faster and higher gains will be achieved in reasonable period of time [26,34].

At the end, as mentioned before, researches, by developing robust modular systems, are working on how to bridge the distance between laboratory and the industry. It is believed that application of microreactors in the industry will have several advantages in comparison to traditional macro reactors as follows:

1. *technical*, meaning better process control, efficient heat transfer and better performance at extreme conditions
2. *ecological*, meaning safer production of chemical and pharmaceutical products, smaller usage of chemicals and reduction of waste

3. *economical*, meaning reduction of costs by implementing numbering-up instead of scale-up and″integration of different production steps.

Going towards industry is the final challenge that microreactor technology will face in the future.

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