Continuous Micro-Flow for Pharmaceutical Production

by Volker Hessel

The pre-Socratic philosophers made the first honest attempt, at least in the western world, to describe natural phenomena in a rudimentary scientific manner and to exploit those for technological application [1]. Pythagoras of Samos (570–495 BC) was an Ionian Greek philosopher and the first to actually call himself a “philosopher”. He was credited with many mathematical and scientific discoveries, including the Pythagorean theorem, Pythagorean tuning, the five regular solids, the theory of proportions, and the sphericity of the Earth. The Pythagorean triple is also well-known. Heraclitus of Ephesus (535–475 BC) was famous for his insistence on ever-present change as the fundamental essence of the universe, as stated in the famous saying “panta rhei”—everything flows.

Like the pre-Socratics, continuous micro-flow is the first of its kind, being very different from any other micro-systems technology. It found its way to serious scientific and technological use from a beginning as a spectacular, revolutionary item. A major quality of continuous micro-flow is its ‘ever-present change’, that is, its ongoing transformation towards new applications and towards a constant re-definition of the whole approach itself. One could say that micro-flow is continuously flowing to new directions.

Microreaction technology—a branch from the micro-systems technology tree

Microstructured fluidic devices were developed in the 1990s and tested for chemical reaction engineering after micromechanical systems were developed in the 1980s for a manifold of applications in the field of actuators, sensing, optics, pumping/fluid transfer, dispensing, and more [2]. With the emergence of the micro total analysis system or, as it was later called, the “lab-on-a-chip”, the door was opened to bioanalysis, biochemical, chemical analysis, and environmental analysis. The next logical step was to extend this approach to chemistry [3].

A founding initiative was needed to provide a platform to embrace the scattered activities in this new field and to unite researchers and institutions in a combined force. This was done by PNNL, AIChE, Dechema, and the Institut für Mikrotechnik Mainz in late 1995, manifested in a discussion paper, “Micro reaction technology”, in 1996. This in turn led to the foundation of the International Conference of Microreaction Technology (IMRET) as a platform for the nascent community, as well as a new topic, coined Microreaction Technology.

The first wave: bulk chem—the right solution for industrial problems, but on the wrong scale

Initially, chemical engineers took the lead in the new field, referring to their efforts as microreaction engineering [4]. The first issues they approached were process scenarios that stopped industrial process development, such as those requiring highly exothermic reactions, the handling and generation of toxic or hazardous materials, or operation in formerly explosive regimes. The fluorination of aromatics [5] and phosgene manufacture [6] have all of those characteristics. In these scenarios, the superior heat exchange achieved with microreactors is their winning point. This has been termed transfer intensification [7]. The pull from global chemical players, such as Dow, DuPont, and BASF, directed microreactor applications in the bulk-chemical direction [8]. “Think Big” was the directive, and this culminated in the realization of the ca. 6 m long DEMiS ‘microreactor’ [9]. But the technology was not mature enough to cope with the needs of the first ‘industrial wave’. Still, hope came from optimistic market studies, which were seen more frequently at this time than ever again [10].

The second wave: fine-chem—the right scale searching for the right problems

By around 2001, several fine-chemical pilot plants were reported in very short time, giving microreactor development a needed push [11]. Most of these plants were developed in Japan through a public-private partnership. The reactions were fast and, thus, needed even faster operating process equipment. Consequently, almost all of these plants relied on micromixers and, where needed, added micro- and milli-capillaries as residence time loops to complete the reactions. Virtually hundreds of different micromixers were developed [12]. Selectivity control was the main issue. Another chapter of transfer intensification was opened [7].

Yet, this ‘second industrial wave’ could not provide cost arguments which were game-changing, although...
many benefits from an engineering and chemistry point of view were shown. Despite this, the developments achieved during this time made the move to a larger productivity scale and up to production scale not only a possible, but a routine event. This prepared the field for the ‘third wave’—the real industrial move towards microreactors.

By that time, the focus of research was much more on liquid organic than on gas phase chemistry. Organic chemists who were open-minded about innovative process chemistry tested the new microreactors and found that they were too expensive, too complicated to operate, and insufficiently flexible for the chemist’s needs. To address these shortcomings, they invented “flow chemistry” [13].

Flow chemistry—continuous micro-flow for the chemist

As chemists developed flow chemistry, small-scale continuous equipment available in most labs, such as that used in HPLC, was reused as heating, cooling, and reaction capillaries [14]. Small tee pieces served for mixing, and back-pressure regulators were used to operate under pressure. This allowed solvents to operate above their boiling points in single phase. The equipment developed is interchangeable, may be of one-way use, and in a way modular. These processes allowed for the investigation of ever more complex chemistries—the new tool was now the enabler of new process paths and even of new chemical products.


New avenues in chemical intensification in continuous micro-flow were explored under the aegis of the ERC Grant “Novel Process Windows—Boosted Micro Process Technology” (project No: 267443).

- New reaction pathways: modern activation principles, such as UV-photo-flow and homogeneous catalysis, open doors to new pathways. With the first, the synthesis of Vitamin-D was intensified, both using commercial and laser light sources [16]. With the second, the direct synthesis of adipic acid from cyclohexene was achieved, replacing a two-step synthesis with a direct route [17]. The use of an alternative reactant provides a third option: using gaseous HCl in place of thionyl chloride enabled a green hydrochlorination [18].

- High-T processing: the result is often a 100–1,000 fold speed-up of reaction time—sometimes even more. The Huisgen dipolar cycloaddition of a dienophile and 1,3-difluoro benzylazide to a rufinamide precursor was accelerated in this way [19].

- High-p processing: high-pressure flow chemistry studies were very rare in 2011, and remain so today. A high-p study on the above-mentioned Huisgen dipolar cycloaddition gave insight into what pressure can do in combination with continuous micro-flow [20].

- High-c processing: flow chemistry typically uses high reactant concentrations. Some continuous-flow reactions were even run solvent-free. For the first time, a complete flow cascade (3-steps) was realized completely solvent-free [21]. This was done for three flow chemistry steps towards the rufinamide precursor, including the mentioned hydrochlorination, an azidation, and the Huisgen cycloaddition reaction. As an alternative to solvent-free processing, organic solvents can be replaced by modern designer solvents. A CO$_2$ converting methoxylation used a supported liquid phase catalyst (SLPC) in supercritical CO$_2$ [22].

- Process simplification: Flow processing enables the direct synthesis of adipic acid from cyclohexene by omitting one process step, while simplifying the other. The corresponding impact was quantified for the first time by sustainability (LCA) and cost/cash-flow analysis [23]. A cost/cash-flow analysis was performed for micro-flow synthesis in modular container production platforms [24].

- Process integration: a 4-step flow cascade to cinnarizine, cyclizine, and buclizine was realized [25]. Synergistic process effects could be shown for a fully-continuous, uninterrupted 3-step flow cascade to rufinamide, resulting in environmental benefits, considering 5 more steps starting from the platform chemical nitrobenzene [26]. Assuming a world-scale (400 kt/a) continuous-flow process for the direct adipic acid synthesis, energy costs can be reduced by classical process optimisation (heat integration, pinch analysis) [27].
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Entirely new process regimes, e.g. with regard to temperature and pressure, were opened and termed novel process windows (NPW) [15]. This allowed to conduct reactions several orders of magnitude faster, and made the factor-1000-acceleration “normal.” NPW achieved the latter through an exploration of unusual and typically harsh process conditions with much enhanced activation. They also provided the chance for different selectivity patterns [15]. Several flow chemistries were developed via high-T, high-p, high-c (solvent-free; alternative solvent) concepts, leading to a boost of reactivity. This is complemented by the implementation of new smart electromagnetic activation modes (photo, ultrasound, plasma, microwave, etc. with their discrete rotational, vibrational, electron levels) as a powerful alternative to temperature activation (Maxwell-Boltzmann theory: collision, momentum, probability). Once the single processing steps are intensified, they can be brought to a higher level of process integration and simplification—process-design intensification [7].

The third wave: flow chemistry and pharma-chem—a perfect fit

As the success of medicinal syntheses attracted the pharmaceutical industry, flow chemistry was able to fill the gaps left by industrial process development, e.g. as for too large exotherms, for highly hazardous materials, and in cases with the potential danger of explosions. As a consequence, all major pharmaceutical companies engaged in flow chemistry [28] and the first business cases were reported and representatives of the pharmaceutical industry engaged with the ACS Institute Green Chemistry Roundtable [29]. They listed their top 10 priorities for new technologies: (small-scale) continuous processing received the highest score. Just five years later, the FDA declared the batch-to-continuous transition to be the new standard in pharmaceutical manufacturing [30]. This gave Johnson & Johnson’s Janssen drug unit the thumbs up for the continuous manufacturing process for the production of HIV drug Prezista on a line at its plant in Gurabo, Puerto Rico [31].

Such end-to-end processing requires automated operation. Behind superb process control that ensures pharma’s process analytical technology (PAT) and process quality standards, the new fully automated flow machines prepare us for another chemical revolution [32]. This so-called ‘Chemical Nespresso Machine’ can do much more than gather automated synthesis [33]. Flow machines can be controlled and operated at very different and distant sites of the world and even communicate with and learn from each other. This variant of the Chemical Internet of Things is the “All-Around-The-World-Synthesis” or the “March of the Machines” [34]. The potential is even greater—fully automated, self-developing multi-step synthesis by virtue of artificial intelligence and 3D-printed flow reactors [33-35].

The Flow Chemistry Society was founded as a platform for the flow chemists, creating a journal for flow chemistry and organizing many conferences on the topic. As the formation of the IMRET conferences did for microreactors about 15 years prior, this provided a major push for the popularity of the topic.

![Fig. 1: Proposed designer solvent system which acts as fluidic ‘reactor-separator’ for the flow cascade to (1R,3S)-1-(3-chlorophenyl)butane-1,3-diol.](image-url)
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**Future systemic innovations for continuous pharmaceutical manufacturing**

Two current topics on the application of continuous micro-flow for pharmaceutical synthesis are important for future exploration. One is the exploration of new ‘factory’ concepts to handle the complexity of multi-step synthesis, purification, and formulation (with the pill as the final product). The other topic of relevance is ensuring quality control in a highly legislated production environment.

Two future approaches of the author’s research are presented here as an outlook to this feature.

**ONE-FLOW**

The FET-Open project ONE-FLOW translates the ‘vertical hierarchy’ of chemical multistep synthesis, with its complex machinery, into the self-organising ‘horizontal hierarchy’ of a compartmentalized flow reactor system—a biomimetic digital flow cascade machinery with just one reactor passage [36]. To keep horizontal hierarchy manageable, orthogonality needs to be increased among the different consecutive reactions. Luckily, nature has already invented catalytic cascades. ONE-FLOW builds on this by enabling the best bio- and chemocatalysts working door by door: four synthetic flow reaction networks (‘metabolic pathways’) and one flow cascade driven by automated intelligence (‘signaling pathway’) will be developed, producing 4 Top-list 2020 drugs.

A functional solvents system serves as an integrated reactor-separator for the 3-step flow cascade to (1R,3S)-1-(3-chlorophenyl)butane-1,3-diol. The ethoxylated ionic liquid Among 110TM acts as a phase separator for the biocatalyst alcohol dehydrogenase while also increasing its activity and stability. The system water/acetoephonone/Ammoneng 110TM gives up to 5 metastable phases. The large diversity of ILs (>10 exp 6) and conventional solvents (> 7000) opens up the possibility for solvent modelling via the COSMO-RS method. Cost/LCA assessment and experimental screening will then guide users to the final solvents of the “Multi-Step-Solvent-Factory.”

**On-line PAT quality control**

A very fast flow chemistry reaction—the photo-Claisen rearrangement of allyl phenol—has been combined with a modified ultra-high-performance liquid chromatography (UHPLC) system, allowing for very fast lowest-volume sampling and analysis [37]. With the applied online sampling system, it is possible to perform a full factorial analysis of all relevant reaction conditions (243 experiments) almost unattended, while using 12 times less sampling volume, all in just three days. Assuming a systematic difference compared to manual sampling and dilution of 0.5 % ± 1.4, online sampling avoids random errors due to automation. The reproducibility and robustness of the sampling were tested as well.

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![Fig. 2: Process sequence in UHPLC analysis with online and offline sampling for the photo Claisen rearrangement of allyl phenol.](#)
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References


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