

## Flow Chemistry: New Concepts from Batch to Continuous Organic Chemistry

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Flow chemistry and microreactors technology are situated at the intersection between Industrial Chemistry, Chemical Engineering, Organic Synthetic Chemistry and Green Chemistry.

Batch processes are usually found in fine, specialty and pharmaceutical industry due to their versatility and suitable costs for small scale production. Nevertheless, they pose scale-up issues and non-negligible heat and mass transfer problems. Continuous processes typically require smaller equipment size than batch ones. The possibility of continuous operations offers many advantages also for the pharmaceutical industry, such as lower costs, reduced waste production, decreased time-to-market for new drugs, raising more and more the interest towards process reconversion to continuous mode, or construction of new continuous systems from the grass route. Continuous flow reactors can deliver significantly higher yields, while solvent and energy waste can be decreased up to 90% [1]. The increasing importance of flow chemistry has been recently reviewed by many different authors [2-7].

Continuous processes for fine chemicals and drugs are based on a relatively new concept of microreactors. Continuous operation in micro-devices has been suggested to improve the safety and sustainability of the fine-chemicals and pharma industries [8], which until now have very important environmental footprint. New synthetic routes can be indeed proposed, characterized by lower E-factor (i.e., kg of waste per kg of product, typically higher than 25 for such applications in traditional batch mode). Furthermore, some new alternatives may become possible using microreactors due to intrinsically safer operation than impracticable options in batch mode due to safety problems [9,10]. Process intensification is another aspect of the problem, achievable by broadening the process conditions window and by better integrating different process steps in flow chemistry [11].

One of the main reasons of microreactors success is the improved heat and mass transfer. Transport limitations are considerably reduced with respect to conventional reactors configurations. This leads to important applications from the point of view of process intensification. It is considered that *ca.* 20% of the organic reactions inventory can effectively take advantage of improved mass and heat transfer in terms of productivity, selectivity and/or safety [12].

Broader operating conditions are also possible in microreacting systems. These include unconventionally high temperature, pressure and the use of high-boiling solvents [4,5,13,14].

Extremely fast reactions are usually carried out under mass and heat transfer control. In such cases, micromixers may improve transport phenomena and thus the overall process rate. The same features allow better reaction control in case of very exothermal reactions, which may raise safety issues. Hazards are also limited due to the low critical mass usually flowing through the device [9,15]. Indeed, microreactors allow safer handling of toxic compounds, either used as reactants or produced as intermediates [12]. In the meantime, the use of relatively high flow rates induces sufficient productivity during continuous operation.

Continuous flow demonstrated appropriate to improve safety with respect to batch in the case of high concern reactions [16]. Grignard reactions were exemplified as very fast and exothermal reactions, which take advantage of the improved heat transport guaranteed by microreactors. Total and selective oxidations, nitrations and organometallic reactions, represent additional examples of exothermal processes with need of careful temperature control and rapid heat removal. Quenching is also easier in microreactors in case of emergency.

Due to these advantages, many applications have been proposed in the fields of fine chemicals and drugs production, as well as for the synthesis of natural products [17].

The industrial synthesis of Boscalid®, an antifungine compound, has been also exemplified in continuous flow mode [18]. The growing importance of microreactors is testified by the availability of commercial, versatile modules for different production scales.

An inventory of Pd-catalysed reactions in microreactors have been described in the recent literature, such as the Heck, Sonogashira, Suzuki, Stille, Negishi, Hiyama, Corriu-Kumada, Tsuji-Trost and Ullmann's reactions [19]. Coupling and cross-coupling reactions are among the most studied examples. Microreactors have been also coupled to unconventional activation systems, such as microwaves [20,21], ultrasounds and UV-Vis irradiation [22]. Indeed, the short life time of radical species in photochemistry and photocatalysis and improved irradiation make microreactors advantageous with respect to batch analogues.

Unconventional application is continuous flow solid synthesis have been also described, e.g., ceramic nanoparticles synthesis by flame pyrolysis [23,24] and mesoporous silica [25,26].

Examples of scale-up philosophy for different pre-clinical trials in drug development have been effectively reported [9].

Heterogeneous photocatalysis has been also proposed in continuous flow, but with significant scale-up problems [22,27]. In general, process design and optimization are still insufficiently applied to photochemical processes.

Summarizing, flow chemistry represents an emerging topic, with very relevant applications, also on industrial scale, in the pharmaceutical field and, broader, for organic synthesis. The key for every improvement observed during transition from batch to continuous processes rely on better heat and mass transfer. Much has to be done to improve the

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applicability of microreactors by addressing the relevant engineering and scale up issues, which are often open questions also when industrial application is just behind the corner [28].

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