ABSTRACT

Flow chemistry is gaining increasing attention as a mean to achieve process intensification in the fine chemicals synthesis field. Furthermore, it can overcome heat and mass transfer limitations thanks to more efficient mixing, allowing applications characterised by insufficient yield or safety issues, when carried out in the traditional batch mode. Despite their spreading use, micro- and meso-reactors are complex systems that require some detailed modelling in order to achieve the desired process intensification effect. In this review, some examples will be provided dealing with three main modelling items. On one hand, kinetic modelling is needed in order to correctly size the reactor and to estimate its productivity with time-on-stream under different conditions. Then, fluid dynamics issues have to be carefully modelled to predict heat and mass transport properties, which are ultimately related to fluid flow inside micromixers and microreactors. All these topics will be discussed, to review the current developments in continuous microreactors modelling and design, together some examples of process simulation.

Keywords: Microreactors; Flow chemistry; Process intensification; Process simulation; Kinetic modelling; Computational fluid dynamics.

1 - Introduction

Batch processes are the preferred choice in fine, specialty and pharmaceutical chemistry because they offer sufficient versatility and flexibility. However, they pose scale-up issues due to important heat and mass transfer limitations. Flow chemistry is increasingly addressed in the fine and pharmaceutical chemistry fields as a way to modify traditional batch processes, by transformation into continuous flow mode (1-6). Typically, this is achieved by using micro- or meso-reactors.

Continuous processes are usually designed with smaller equipment volumes, need lower maintenance and operating personnel, ultimately leading to limited costs with respect to batch analogues. Additionally, the possibility of continuous operation allows reduced wastes, better atom economy and, in general, decreased time-to-market for new products than batch processes. It has been reported that continuous flow reactors can deliver significantly higher yields, while solvent and energy wastes can be decreased up to 90% (7). Different commercial units for continuous manufacturing are already available on the market (8). A very compact system for the continuous flow production of active pharmaceutical ingredients has been recently described by Adamo et al. (9). It included the whole steps from synthesis, to purification and even dosage for

* Corresponding author: fax +39-02-50314300, ilenia.rossetti@unimi.it
the final formulation. The authors described the flexible possibility to obtain different products, such as Diazepam, fluoxetine hydrochloride, lidocaine hydrochloride and diphenhydramine hydrochloride with a compact and integrated continuous process.

A general improvement of safety and sustainability of the fine-chemicals and pharma industries is also envisaged through a progressive transition to flow processes. Indeed, if intrinsically safer production processes may be developed, synthetic routes characterized by much lower E-factor (i.e. kg of waste per kg of product, typically higher than 25 for the fine chemistry/pharmaceutical fields) can be developed (10,11). Process intensification is a further improvement, achievable by broadening the process conditions window and by better integrating different process steps (12).

All these points, however, need a careful process design. The use of modelling techniques for the correct description of flow reactors (either micro- or meso-) is at the basis of this transition from batch to continuous production. Some examples of computational fluid dynamic studies, kinetic modelling and process simulation are discussed in the following, to highlight the main issues to be addressed during the design of continuous flow processes. The importance of modelling prior to experimentation and scale-up, especially in terms of economics, is thus strongly stressed.

2 – Computational Fluid Dynamics (CFD) to model flow reactors

Most microreactors are specifically designed with appropriate channels size and shape, so to improve mass and heat transfer. This is commonly achieved by appropriate mixing and ultimately relates to the fluid dynamic regime achieved inside the reactor. Fluid flow in the reactor channels can be effectively studied by using computational fluid dynamics (CFD) methods. Different examples of application of this strategy to micro- and meso-reactors are reported in the literature. For instance, velocity profiles inside a heat exchanger reactor are discussed as a function of channels geometry (13). The main application is in the field of intensification of very exothermal reactions.

Fluid dynamic descriptors are proposed by Nagy et al. (14) to model mixing in microfluidic systems. Different flow regimes can be identified, such as slug, parallel, drop and dispersed flow. Accordingly, reactor performance was described on the bases of the two Damköhler dimensionless numbers (see (14,15) and references therein). The description of different micromixers is also proposed in the same paper.

Homogeneous mixing in microfluidic systems is often a very challenging task. Indeed, slow flowrates usually characterize microreactors channels, with the consequence of laminar flow and intrinsically inefficient mixing. Appropriate micromixers designs have been proposed to cope with this problem and to achieve efficient mixing, as reviewed by Nguyen and Wu (15). Complex structures are often involved which induce high realization complexity and therefore high cost. High flow rates should be achieved in mixers, to improve mass transfer. This is usually accompanied by high pressure drop, so that, again, the surveillance on the fluid dynamic regime is a must to optimize system performance (Fig. 1). A Y-shaped, turbulent microfluidic mixer has been designed, achieving a Reynolds number as high as ca. 4423, one of the highest values achieved in a microfluidic channel (16). The turbulence generated allowed to obtain stable emulsions.
Different other examples of flow modelling in microreactors have been developed. A numerical model of a two-phase flow in a plate microreactor has been proposed by Semyonov et al. (17). A cold flow, i.e. a flow without a reaction and a mass transfer was considered in this study. The model was validated by comparing with experimentally measured hydrodynamic parameters: gas holdup and the interfacial area of gas bubbles inside the existing prototype. Particularly valuable was the use of an open source toolbox (OpenFOAM) as alternative to proprietary software.

Furthermore, the optimization of microreactor designs for applications in chemical process engineering usually requires knowledge of the residence time distribution. CFD was used to compute this parameter for different industrial microstructured reactors (18).

3 – Kinetic modelling in microreactors

The development of accurate and reliable kinetic data is at the basis of the description of system performance. It is also at the basis of process simulation, which will be discussed in the next paragraph. Some examples of kinetic analysis and modelling applied to microreactors are reported here below.

A bifurcated flow silicon microreactor was developed to collect kinetic data on catalytic reactions under differential conditions (19). The latter are implemented in form of very low conversion (5-10%), but for very fast reactions this means the need of very short contact time or high space velocity. With packed beds this implies that very high pressure drop arises, especially when small...
particle sizes, around 0.1 mm, are used to limit diffusional limitations inside the catalyst. Therefore, to limit pressure drop a very short bed length should be used. To achieve sufficiently high catalyst loading, the catalyst was placed in to a silicon wafer, which was printed with the desired shape, so to allow 256 microchannels for catalyst loading. The flow pattern was checked with and without the catalyst, observing a negligible increase of pressure drop with catalyst loading. The flow regime was laminar and modelled through a computation fluid dynamics code, revealing uniform profile across the catalyst bed. The test reaction was the catalytic oxidation of CO, which returned kinetic parameters very similar to those obtained with conventional reactors.

A miniaturised plasma reactor was set up for the production of ozone, to be used for water treatment (20). Plasma reactors usually operate under high vacuum and need high voltage. The assembly in micron size device allowed to achieve plasma formation conditions with much lower voltage (ca. 100 V) and required ambient pressure operation, with considerable intensification of the process from both the capital and operation costs. Furthermore, increased productivity was achieved. The detailed microkinetic scheme to describe the reactor is proposed by the authors, who identified two characteristic time regions for ozone formation, as well as the concentration profiles of the reactant and activated intermediates.

The detailed kinetics of the Paal-Knorr reaction of 2,5-hexanediol and ethanolamine in dimethyl sulfoxide has been elaborated in flow mode. A microreactor was modelled as a series of batch reactors, taking advantage of the kinetic analogy between the batch and the plug flow reactors, if ideal reactors are taken into account (21).

The kinetics of epoxidation of propene has been also studied as a mean to better control the reaction when operating under explosive regime (22). Kinetic investigation evidenced the effect of reactants concentration on yield and deactivation of the gold-based catalyst. In particular, the propene concentration did not influence the product formation rate, but higher propene concentration reduced the catalyst deactivation rate.

The detailed kinetics of the synthesis of benzodiazepine has been studied by Grom et al. (23). The authors proposed a detailed mechanism for a multistep synthesis, based on 15 reactions hypothesised based on reasonable reaction mechanisms and FT IR identified products and byproducts.

In all these examples, a detailed kinetic scheme is proposed, which is at the basis for the correct estimation of process outcomes. Nevertheless, care should be taken in data interpretation for this kind of experiments. Indeed, typical kinetic experiments in “macro”-reactors are usually anticipated by the verification of the basic hypothesis to operate under an intrinsic kinetic regime. In other words, turbulent flow should be ensured to limit external mass transfer limitations, as well as appropriate heat transport. Some microreactors are appropriately designed in order to improve mixing (micromixing sections are added on purpose), whereas in other applications separated flow is maintained, which may lead to mass transfer limited kinetic results.

The transesterification of vegetable oils with alcohols for the production of biodiesel or in general of esters for the cosmetic industry is a typical example of multiphase reaction where mixing dominates kinetics (24). Further examples come from very fast reactions, such as the one of cyclohexanecarboxylic acid with oleum, which is a fundamental step in the synthesis of ε-caprolactam (25). The reaction time was lower than 1 s, so that the reaction rate was substantially
controlled by mixing. For these kind of applications the use of microreactors can make the difference, improving mixing efficiency by orders of magnitude. However, kinetics is controlled by the fluid dynamic behaviour of the reactor, so that it is strongly recommended to couple kinetic investigation with the detailed description of the fluid dynamic regime.

4 – Process simulation in the field of flow chemistry

Process simulation is an important step for the design of integrated processes. It is commonly used for the development, optimisation, integration and intensification of continuous plants, but it has hardly found application yet in flow chemistry applied to fine chemicals synthesis. Two very straightforward examples are provided by Jolliffe and Gerogiorgis (7,26).

A first, very inspiring example, is the simulation of the continuous manufacturing process of ibuprofen (7). The authors start selecting some possibly interesting cases of APIs (Active Pharmaceutical Ingredients), that have been studied on a lab scale for the transition from batch to microreactors, then continuous production. Ibuprofen has been at first selected due to its wide market significance and the availability of sufficient and reliable data for process modelling. After the definition of a proper flowsheet, including three continuous plug flow reactors (Fig. 2), kinetic parameter estimation is implemented, based on literature data. The product separation section is also described, with suitable attention to the thermodynamic properties of the mixtures of interest and, thus, appropriate selection of the thermodynamic package to be implemented in the process simulator.

Fig. 2: Conceptual flowsheet for the continuous flow production of ibuprofen. Readapted from (7).

Ibuprofen synthesis was considered also by Patel et al. (27), who performed a dynamic optimisation of the whole process. A crude yield of 90% at a residence time of 33 seconds was obtained, without purification of intermediates, thus saving time, energy and wastes.

A similar approach than in ref. (7) was applied by the same authors to the continuous flow synthesis of artemisinin, a promising anti-malarial active principle (26), based on preliminary fundamental studies (28,29). A couple of plug flow continuous reactors are designed. Also in this
case, preliminary regression of kinetic parameters revealed an essential step for the correct description of reactors performance. Proper attention is paid also in this case to the appropriate synthesis of the separation section of the continuous process. The potential for toluene as a solvent, with the simultaneous introduction of an antisolvent intended to replace the batch recrystallisation procedures (based on cyclohexane and ethanol) is systematically investigated (Fig. 3). Also here, the separation is correctly based on a preliminary assessment of the relevant thermodynamics.

![Conceptual scheme of the artemisinin separation and purification procedure.](image)

**Fig. 3:** Conceptual scheme of the artemisinin separation and purification procedure. Readapted from (26).

**CONCLUSIONS**

Continuous flow processes are applied as possible substitutes of batch analogues to various fine chemicals/pharmaceutical products synthesis. This usually allows the intensification of the process, the improvement of efficiency and safety, making possible some process options discouraged in batch mode. Appropriate sizing of the process should be based on three main points: the knowledge of reaction kinetics, the appropriate description of fluid flow inside the reactor (on which most of the positive features of microreactors are based) and finally process simulation, which allows the integration of all the manufacturing operations, including continuous separation of the products, as well as the optimisation of process conditions, cost evaluation, the development of an appropriate control strategy, etc. These aspects are at the moment addressed only for limited cases, while it is strongly recommended to consider them already at an early design stage.

**References and notes**


