

Continuous flow (micro-)reactors for heterogeneously catalyzed reactions: main design and modelling issues

Ilenia Rossetti*

Chemical Plants and Industrial Chemistry Group, Dip. Chimica, Università degli Studi di Milano,
CNR-ISTM and INSTM Unit Milano-Università, via C. Golgi 19, 20133 Milano, Italy

ABSTRACT

Continuous flow chemistry is a rapidly developing branch in organic and drugs synthesis, whereas it is common practice in heterogeneous catalysis for base chemicals production. Heterogeneously catalysed synthetic protocols are being developed and can take advantage of the reaction and reactor engineering experience at the macro-scale, provided that suitable models are applied to the micro- and meso-reactors in use. The main process parameters that define possible mass, heat and momentum transport limitations in heterogeneous catalytic reactors are reviewed. Specific models applying such concepts to microreactors are proposed. Finally, examples are reported of heterogeneously catalysed reactions carried out in microreactors for different applications.

Keywords: Flow chemistry; Microreactors; Multiphase reactors; Heterogeneously catalysed reactions; Process intensification; Heat and mass transfer; CFD modelling.

1 - INTRODUCTION

Reactions in continuous mode constitute a well consolidated approach when dealing with heterogeneous catalysis in the petrochemical/refinery/energy field. By contrast, fine chemicals and, more in general, organic synthesis, typically rely on a batch reaction mode. However, in the recent past, continuous flow synthesis raised the attention also in the drug and fine chemicals synthesis,

* Corresponding author: fax +39-02-50314300; email ilenia.rossetti@unimi.it

especially thanks to the development of meso- and micro-reactors. The latter are increasingly available as modules with different sizes and complexity, which have been scaled up or numbered up to an industrially relevant scale. Many very interesting reviews cover widely different applications and reaction classes, such as [1–9].

The advantages of continuous flow organic synthesis are very broad and vary from selectivity or yield improvement to safety issues. Batch processes are advantageous due to their versatility, flexibility and traceability, but scale up is sometimes hard when important heat and mass transfer issues may severely limit productivity, selectivity or safety.

Continuous processes are often more efficient and demand lower manpower due to highly automatized procedures. Furthermore, they are typically characterised by lower costs, reduced wastes, with an improved environmental footprint, decreased time-to-market for new drugs and products [10,11].

Safety improvement is also widely reported. Due to the small size and very efficient and fast mixing, transport limitations are limited with respect to batch reactors. Therefore, very fast and exothermal reactions can be better carried out in microreactors in a much more controlled way. Intrinsically safer conditions are also guaranteed by the very small reactants/intermediates amount circulating in the system. This broadens the choice of reactions to give the desired product or intermediate to options that would not be selected in a bigger apparatus due to toxicity, instability, etc. Sometimes those options may lead to improved yield or lower environmental impact than conventional routes.

Improved mass transfer brings about advantages also from the point of view of selectivity and yield [12].

Very comprehensive reviews have been published, which include numerous examples of organic reactions in continuous mode. However, some asynchrony has been recently evidenced in this field [7,13]. On one hand, there is an explosive interest on continuous flow synthesis using micro- or meso-reactors, with focus on the synthetic details. On the other hand, only in some, very inspiring cases,

the chemical reaction engineering, reactor engineering and transport phenomena issues are taken into account. This mismatch seems critical for scale up, optimisation and technology transfer.

When heterogeneous catalytic reactions are taken into account additional criticisms arise, because heat, mass and momentum transfer can play a predominant role and all these features should be correctly tackled for proper reactor and industrial process sizing. Additionally, while industrial catalytic packed bed reactors can take advantage of a known dependence of performance on size and shaping of the catalyst particles, in microreactors porous monoliths or powdered beds are used, which introduce new problems when defining fluid dynamics and transport phenomena.

More in general, a cultural mismatch seems evident. When micro or mesoreactors are used for base chemicals production, for environmental remediation or in the energy field, the typical concepts of industrial heterogeneous catalysis (*e.g.* heat transport across the catalytic bed, pressure drop estimation, intra- and extra-particle mass transfer issues) are appropriately transferred to the desired scale. In many cases, specific correlations are used or developed to estimate the required parameters, as will be exemplified in the following. On the contrary, when heterogeneous catalysis is applied with success to drugs, intermediates or fine chemicals synthesis, these points are often missing, leading to a description which is mainly phenomenological, thus limiting technology transfer or scale up possibilities to experimental optimisation. Thus, the study from a chemical engineering point of view of all these new reacting systems should be tackled carefully, opening a very promising, multidisciplinary field of study. The topic is further complicated by the fact that multiphase systems are intrinsically present (gas/solid, liquid/solid and even gas/liquid/solid) and that the catalytic action can take place only after adsorption of the reactants and includes safe desorption of products on/from the active sites over catalyst surface. Hence, appropriate mass transfer and kinetic models have to be applied.

On this basis, this review points out some engineering milestones that should be considered during the design of heterogeneously catalysed organic synthesis in continuous mode. Particular attention

will be focused on modelling the relevant transport phenomena and catalytic (micro-/meso-)reactors. Applicative examples will be discussed across the text.

2 - Heterogeneous catalytic microreactors

Heterogeneous catalytic reactors can be classified into three main types: i) packed bed, ii) wall coated and iii) micro-monolithic [14] (Fig. 1).

They can usefully find application in the case of very slow or very fast kinetics. For instance, Grignard reactions can generate a very intense hot spot which limits the yield, besides inducing safety issues. The efficient heat transfer and the possibility to design multi-injection systems lead to better temperature control in microreactors. Intrinsically safer operation is also guaranteed, such as in the case of acetone cyanohydrin synthesis, used as source of HCN [15].

Packed bed microreactors are among the most used, due to easy assembly, high possible catalyst loading. Nevertheless, heat and mass transport limitations can easily occur and significant pressure drop can arise [14,16].

Preliminary calculations, paying attention to transport phenomena, can be used in order to ensure the operability of the reactors. Appropriate description of mixing, residence time distribution and heat/mass transfer is needed for scale up and optimisation. Plug flow behaviour and short mixing times could be confirmed for all investigated flow reactors. Furthermore, interactions of reaction kinetics and the formation of hot spots in the reactor channel should be investigated.

2.1 – Modelling transport phenomena in heterogeneous catalytic reactors

2.1.1 – Mass transfer

Mass and heat transfer must be computed at the surface and in the catalyst particle. In microreactors, the reduction of size can modify the transport rate, and thus its effect on the apparent kinetics has to be checked. An additional question also arises, whether the correlations developed for classic reactors are also applicable to microreactors.

Mass transport includes the diffusion of the reactants/products across the surface layer of fluid around the catalyst particle, as well as, through the porous network of the catalyst. The former is called external or extra-particle diffusion, the latter internal or intra-particle.

2.1.1.a – External mass transfer

External mass transport rate is proportional to the difference between the reactant concentration in the bulk of the fluid and on the surface of the catalyst particle (more in general on the interphase).

$$N_A = k_g(C_A - C_{As}) \quad (E1)$$

where N_A is the molar flowrate of reactant A (kmol/m² s), k_g is the mass transfer coefficient and C_A/C_{As} are reactant concentrations in the bulk of the fluid and on catalyst particle surface.

The reaction rate depends on the concentration of the reactant available on catalyst surface sites, so that, under steady state conditions, the reaction is either limited by the reaction rate itself, or by the reactant refill rate to the surface (e.g. at high temperature or with anyway fast reactions). The two resistances can be considered in series to give the following equation in the simpler first order reactions case:

$$r_A = \left(\frac{1}{k_g} + \frac{1}{k_r} \right)^{-1} C_A \quad (E2)$$

where r_A is the observed reaction rate and k_r the intrinsic kinetic constant (for 1st order reactions).

Two dimensionless numbers are defined to account for the effect of external mass transport, the first (Da_I) and second (Da_{II}) Damköhler numbers:

$$Da_I = k_r C_0^{n-1} \tau \quad (E3)$$

$$Da_{II} = \frac{k_r C_0^{n-1}}{k_g S_a} \quad (E4)$$

where C_0 is the initial concentration, n is the reaction order, τ the contact time and S_a the specific surface area. Dimensionless numbers are useful to define correlations between the characteristic parameters that define a certain phenomenon, which depends on many variables. Grouping them into dimensionless groups allows to decrease the number of independent correlations to be established

among parameters. Furthermore, the correlations are typically independent from the size of the system. This is a huge advantage, since it allows to derive models on a small scale, to be applied to a full scale plant. The approach is powerful and it is based on different methods that allow the determination of the number and the form of the groups that fully describe the system. The correlation between the dimensionless groups is derived from the fit of experimental data. However, caution is needed in the selection of the model, because its mathematical form is based on the correlation of data, thus it is strictly valid only in the range of values used during the experimentation. Extrapolation outside these limits is particularly not recommended.

In this specific case, Da_I is useful for appropriate calculation of kinetic parameters, which are determined within 10% error due to external mass transfer limitations if $Da_I < 0.1$. By contrast, Da_{II} compares the numerator, which depends on reaction rate, with the transport rate at denominator. High values of Da_{II} denote a reaction which is limited by external mass transfer.

k_g can be calculated from the experimental correlation of dimensionless numbers according to Satterfield [17,18]. Three dimensionless numbers are defined, namely Reynolds (Re), Schmidt (Sc) and Sherwood (Sh) and the latter is correlated to the former two by fitting experimental data.

$$Sh = \frac{k_c D_p}{D_{AB}} \quad (E5)$$

$$Sc = \frac{\mu}{\rho D_{AB}} \quad (E6)$$

$$Re = \frac{D_p \rho u_s}{\mu} \quad (E7)$$

where D_p is the diameter of the catalyst particle, D_{AB} is the diffusion coefficient of reactant A in the reaction medium B, while ρ and μ are the fluid density and viscosity, respectively. Furthermore, u_s is defined as superficial velocity of the fluid, a virtual fluid velocity value to be calculated as the volumetric flowrate and the reactor section as it would be empty (given that the real free cross section available for the motion of the fluid is not known).

Various empirical correlations have been derived, with the general formulation:

$$Sh = f(Re, Sc) \quad (E8)$$

so that for a given fluid, particle and fluid dynamic regime, these equations allow to calculate the external mass transfer coefficient. It should be remarked that Sc accounts for all the fluid properties that affect mass transport, whereas Re define the fluid dynamic regime of the fluid around the catalyst particle. From a practical point of view, it is suggested to improve mass transport by achieving a turbulent flow regime whenever possible, so to drive the reaction under kinetic control, rather than diffusional.

Most important, as mentioned above, the correlations between dimensionless groups are based on experimental data. Thus, they are strictly correct for use with similar systems, only, and in comparable operating conditions window. This is the reason why reasonable doubts arise when conventional correlations, derived for macroscopic reactors, are applied to microreacting systems, apparently without an adequate check.

2.1.1.b – Internal mass transfer

Additional limitations to reaction rate arise from the diffusion of the reactants and products inside the catalyst pores (internal diffusion). This is particularly relevant in the case of very thin pores (e.g. when using carbon supported catalysts, as in many heterogeneously catalysed organic reactions) or sterically hindered reactants. More in general, this phenomenon can limit significantly kinetics in the case of shaped particles with relatively high D_p , whereas it is often negligible with powdered catalysts used in bench scale testing.

An effective diffusivity (D_e) can be calculated, by summing the possible resistances to internal diffusion, i.e. bulk and Knudsen diffusion coefficients (D_b and D_k) [17,18].

$$\frac{1}{D_e} = \frac{1}{D_b} + \frac{1}{D_k} \quad (E9)$$

Indeed, when a reactant diffuses into the pores, two extreme behaviours may be evident: either the molecule is much smaller than the pore, so that the collision with other molecules is more frequent than with pore walls, or it has comparable size with the pore diameter. In the latter case, diffusional limitations arise from the more frequent collisions of the molecule with the pore walls. Both diffusion

coefficients depend on the porosity (θ) and the pore tortuosity factor (τ), given that high porosity should favour mass transfer, while tortuosity hinders molecule transport inside the pores.

$$D_b = \frac{D_{AB}\theta}{\tau} \quad (\text{E10})$$

$$D_k = 1.9 \times 10^4 \frac{\theta^2}{\tau S_A \rho_p} \sqrt{\frac{T}{M}} \quad (\text{E11})$$

Where ρ_p is particle density, T the temperature and M the molecular mass of the diffusing molecule. The rigorous solution of the problem is found by coupling the mass and heat balances to an infinitesimal volume of catalyst particle. The two balances should be considered at once, because both the concentration and the temperature affect the reaction rate and, thus, they mutually interfere. However, from the practical point of view, the solution implies the definition of the effectiveness factor (η), which is the ratio between the real rate of reaction (i.e. limited by internal diffusional limitations) and the theoretical rate if the whole particle would be uniformly exposed to the same surface concentration (i.e. no internal diffusional limitations). The effectiveness factor is either graphically or analytically correlated to the Thiele modulus (Φ), which compares a numerator depending on the reaction rate and a denominator which depends on the effective diffusivity, i.e. on how fast is the internal diffusion rate. This ratio is weighted according to a characteristic length L, which represents the particle volume/exposed area and reduces to the particle diameter in the case of spherical particles.

$$\Phi = L \sqrt{\frac{k C_{As}^{n-1}}{D_e}} \quad (\text{E12})$$

when diffusion is faster than reaction rate and/or the particle characteristic length is small (i.e. small particle size), Φ is <1 , corresponding to an intrinsic kinetic regime without internal diffusional limitations. In this case the effectiveness factor is 1. By contrast, when the reaction is intrinsically faster than internal diffusion, or when the diffusion path is long, the Thiele modulus becomes great and the effectiveness factor significantly decrease. Overall, the effectiveness factor should be used to compute the real reaction rate as follows (always for 1st order reactions):

$$r_A = \eta k_r C_A \quad (\text{E13})$$

The possible decrease of reaction rate ($\eta < 1$) is taken into account to correctly size the process. However, it should be remarked that in case of endothermal reactions η is always ≤ 1 , whereas for exothermal reactions, in case of significant thermal excursion across the particle (hot spots), solutions with $\eta > 1$, often multiple solutions, are also possible. The correlation between η and Φ depends, among other factors, on the particle shape. For instance, in the case of spherical particles and first order reactions the analytical solution is

$$\eta = \frac{3}{\Phi} \left[\frac{1}{\tanh(\Phi)} - \frac{1}{\Phi} \right] \quad (\text{E14})$$

Different models were derived. A comprehensive description of the different geometry cases is presented by Green and Perry [19], while a good discussion on the case of structured and monolithic reactors is proposed by Cybulski and Moulijn [20].

2.1.2 – Heat transfer

The heat transport is qualitatively addressed in the same way as mass transfer. The interphase heat transport under steady state conditions prescribes that the heat absorbed/released from the catalyst particle due to the reaction is furnished/released by convection through the following equation:

$$(-\Delta H_{reaction})r_A = ha(T_s - T) \quad (\text{E15})$$

where h is the liminar coefficient (describing convective heat transport), while a is the exposed area per unit volume of the catalyst particles. Also in this case h can be obtained by proper definition of dimensionless numbers and correlation of experimental data. In this case the relevant numbers are the Nusselt (Nu) and Prantl numbers (Pr):

$$Nu = \frac{hD_p}{\lambda} \quad (\text{E16})$$

$$Pr = \frac{\mu c_p}{\lambda} \quad (\text{E17})$$

Where λ is the thermal conductivity and c_p the heat capacity.

Correlations of the general type below reported are available for different reactors and conditions, which enclose the dependence of h from the fluid properties (Pr number) and from the fluid dynamic regime (Re number):

$$Nu = f(Re, Pr) \quad (E18)$$

Exactly as in the case of mass transfer these are strictly empirical correlations, valid only for the specific case they refer to and in the operating limits for which they were derived. Thus, also in this case, appropriate models should be derived for micro- and meso-reactors.

Finally, the mechanism of heat and mass transport are very similar in nature, so that correlations exist between the different dimensionless numbers. For instance, the Chilton Colburn analogy was introduced [21], of which one of the proposed forms is:

$$Nu = Sh \left(\frac{Pr}{Sc} \right)^{1/3} \quad (E19)$$

2.1.3 – Friction losses

Additionally, attrition within the fluid and with the channel/reactor walls brings about energy dissipation, which results in pressure decrease. Pressure drops in fixed bed catalytic reactors are typically computed using the Ergun equation, for which a conventional formulation is:

$$\frac{\Delta P}{L} = 150 \frac{\mu u_s (1-\varepsilon)^2}{D_p'^2 \varepsilon^3} + 1.75 \frac{\rho_f u_s^2 (1-\varepsilon)}{D_p' \varepsilon^3} \quad (E20)$$

where L is the packed bed length and D_p' is an equivalent spherical particle diameter of the catalyst and ε the porosity of the catalyst bed, defined as the void fraction with respect to the total volume of the catalyst bed.

Relatively similar expressions can account for microreactors, although, given the very small channel diameters, surface tension effect may influence.

3 – Modelling transport phenomena in microreactors

3.1 – Packed bed microreactors

Specific models for packed bed microreactors have been developed to account for k_c , such as [22,23]:

$$\frac{k_c(D_p+2\delta)}{D_e} = \left\{ 2^{5.8} + \left[0.61 \left(\frac{\varepsilon^{\frac{1}{3}}(D_p+2\delta)^{4/3}}{\nu} \right)^{0.58} \left(\frac{\nu}{D_e} \right)^{1/3} \right]^{5.8} \right\}^{1/5.8} \quad (\text{E21})$$

Where δ is the catalyst shell thickness, ε the power input to the impeller and ν the kinematic viscosity.

As alternative [24]:

$$\varepsilon J_d = \frac{1.043}{Re^{0.82}} + \frac{0.95}{Re^{0.46}} \quad (\text{E22})$$

$$J_d = \frac{k_c}{u} Sc^{2/3} \quad (\text{E23})$$

$$Re = \frac{\rho u(D_p+2\delta)}{\mu \varepsilon} \quad (\text{E24})$$

Where ε , in this case, is the bed porosity. Alternatively, the influence to mass transfer rate of laminar, turbulent and stagnant contributions has been formalised as follows:

$$Sh = \left(1.26 Re^{\frac{1}{3}} Sc^{\frac{1}{3}} \right) + (0.054 Re^{0.8} Sc^{0.4}) + 0.8 Re^{0.2} \quad (\text{E25})$$

Or again [25,26], valid for packed beds with $40 < Re/(1-\varepsilon) < 4000$, $0.25 < \varepsilon < 0.5$:

$$Sh = \frac{(1-\varepsilon)^{0.5}}{\varepsilon} Re^{0.5} Sc^{1/3} \quad (\text{E26})$$

Correlations for heat transport are usually more complex and rely of two different approaches. On one hand the liminar coefficient is calculated as the sum of a flow dependent and a stagnant contribution. Correlations relying on Nu, Re and Pr numbers are used also in this case. Following a different approach, the Biot number is defined and correlated with Re and with the relevant parameters for each case. Examples for the interested reader are reported in ref. [27,28].

To compute pressure drop, the Ergun equation seems appropriate also in the case of packed bed microreactors.

3.2 – Wall coated microreactors

Wall coated microreactors are used to avoid excessive pressure drop, which sometimes prohibits the use of packed bed microreactors. The set up of such systems is more complex than packed bed, since a uniform, thin coating should be achieved on the microchannel(s). Lower catalyst loading is typically allowed in this configuration. In this application, the definition of reactants convection and diffusion across and along the channel is compulsory, to understand the concentration profiles and to calculate the reactants concentration on the active catalyst layer on the wall.

Wall coated reactors can be constituted by single channels or multichannel systems with various shapes [29], such as honeycomb monoliths. Radial mass transport limitations on the conversion have been studied by comparing a wall coated with a fixed bed microchannel reactor [30,31]. To limit radial diffusion and achieve a quasi-plug flow regime, the empty space in the microchannel was filled with large particles $D_p/D_{\text{tube}}=0.4$ (Fig. 2).

In this configurations the modelling of kinetic + transport becomes a must to predict reactor behaviour. 2D models are needed to cope with the axial and radial concentration profiles in the channel. Moreover, kinetics should be appropriately described making a distinction between homogeneous kinetics (pseudo-homogeneous models, which consider apparent kinetic terms and neglect surface adsorption and reaction) or the often most appropriate heterogeneous models, which consider different concentrations in the fluid bulk phase and on the catalyst surface. Depending on the reaction rate and/or on its exothermicity pseudo-homogeneous models may be insufficiently accurate. On the other hand, the numerical solution of these problems is based on the definition of a grid and on the approximation of the differential equations which describe kinetics, mass, heat and momentum transport in a finite differences scheme. This implies that heterogeneous models substantially double the variables and hence prohibitively increase the computational demand for a reliable solution in complex kinetic schemes.

The logical frame of the problem is reported in Fig. 3 and examples of concentration and thermal profiles in the case of wall coated channels are reported in Fig. 4. The latter refer to a first order reaction occurring on a catalytic wall at constant inlet conditions. The Figure evidences the effect of

the kinetic constant (rate of reaction) on the radial and axial profile of the reactant concentration, as well as the effect of channel radius [I. Rossetti, unpublished results].

The main design parameters for microchannel reactors [32] have been expressed as 4 dimensionless numbers: the Graetz number, the inlet Da_{II} , the diffusion ratio and a parameter related to catalyst geometry. Specific correlations to compute k_g are available for microchannel reactors, such as:

$$k_g = 1.66Re^{0.49}Sc^{0.33}\frac{D_{AB}}{b} \quad (E27)$$

where b is defined as a boundary layer thickness. Catalyst effectiveness has been also correlated to the Thiele modulus as described in [33,34], while correlations for Nu are reported in [35]:

$$Nu = \left\{ 3.66^3 + 0.7^3 + \left[1.65 \left(\frac{RePrDh}{2} \right)^{1/3} - 0.7 \right]^3 + \left[\left(\frac{2}{1+22Pr} \right)^{1/6} \sqrt{\frac{RePrDh}{L}} \right]^3 \right\} \quad (E28)$$

with Dh the hydrodynamic diameter of the channel.

Considerable efforts have been focused on the description of honeycomb monoliths, which can be regarded as arrays of microchannels. Nice examples for Sh correlations are reported in the literature, e.g. [25,36–38], whereas for Nu [39]:

$$Nu = 2.9 \left(1 + 0.09RePr \left(\frac{d}{L} \right) \right)^{0.45} \quad (E29)$$

Pressure drop correlations should account for wall friction, acceleration in the gas phase, orifice effects at the inlet and the contribution of the gas-liquid distributor. A summary of models has been reported in [40].

The friction factor can be calculated as [41]:

$$f = \frac{14.23}{\varepsilon Re} \quad (E30)$$

$$\frac{\Delta P}{L} = \left(2 \frac{f}{d} \right) \rho u^2 \quad (E31)$$

Alternatively [25]:

$$f = \frac{13}{\varepsilon Re} \quad \text{for } \frac{Re}{\varepsilon} < 1000 \quad (E32)$$

$$f = \frac{0.03}{\varepsilon^{1.88} Re^{0.12}} \quad \text{for } \frac{Re}{\varepsilon} > 1000 \quad (E33)$$

3.3 – Micromonolithic reactors

Finally, micromonolithic reactors are used, that may be generated inside pipes, channels or columns e.g. by polymerisation of a porous network, onto which the active phase may be immobilised. This field is on one hand in very rapid expansion, due to the huge interest and spread in organic flow synthesis, but modelling studies are very rare. In part this is due to the very irregular structure of the matrix, but also to lacking kinetic data and to a descriptive approach which is often predominantly phenomenological.

A simplified structure of the pores network was proposed for foams [41], with the following correlations for Sh and Nu:

$$Sh = 1.1Re^{0.43}Sc^{\frac{1}{3}} \quad (E34)$$

$$Nu = 0.9Re^{0.4}Pr^{\frac{1}{3}} \quad 10 < Re < 100 \quad (E35)$$

This approach seems interesting and rational, so it is highly recommended to adapt it to newly developing micromonolithic reactors. In any case, suitable models to describe the performance of these reactors are substantially lacking, thus it is an almost virgin field of investigation.

3.4 – Scaling-up or numbering-up

Increase of capacity in microreactors is feasible by coupling different strategies. At first microreactors size can be increased and operating conditions optimised up to the meso-scale. The flowrate per channel at this level can range from 10 to 1000 L/h. Additional capacity is hardly achieved without loosing the important features of these systems, e.g. mass and heat transfer enhancement, safety, etc. In order to further improve productivity to the desired pilot or commercial level such systems are “numbered-up”, by connecting modular units (5-6) [42].

4 – Modelling the flowpatterns in microreactors

Computational Fluid Dynamics (CFD) is a computational approach which allows the accurate description of flow patterns inside the microreactor, as well as concentration and temperature profiles. Clearly, this is an important information in light of optimising the performance of these systems. Some nice examples of application of CFD to microfluidic systems are reported in the literature, in order to demonstrate the effect of channel sizes and geometry to improve mixing or heat transport (see e.g. [43–50]). The application to reacting systems is less frequent and rarely applied to organic synthesis, likely due to lacking details on kinetics.

An example of the potentials of the CFD approach in catalytic microreactors is proposed by studying a microcombustor, which catalytically converts H_2 over a Pt based catalyst [49]. Catalytic microcombustors extend the flammability region, can lead to more stable operation than homogeneous devices and allow process intensification with more tunable and controllable output, to be designed for tailored applications. Actually, they exceed the energy density of traditional lithium batteries for portable energy generators. A microcombustor channel is modelled, including homogeneous ignition near the catalytic wall and flame propagation towards the channel axis. Despite the small channel size, considerable mass transfer limitation is evident and it must be addressed with improved design, due to the extremely fast hydrogen oxidation over Pt. The thermal uniformity and heat losses depend on the combustor material (thermal conductivity), feed composition and flow rate, as exemplified in Fig. 5 and 6 [49].

The oxidation of volatile organic compounds, with propane as reference, was modelled by CFD in a multichannel microreactor with different size and geometry. The application of microreactors to exothermal and fast reactions such as combustion, allows also for this application better control of the system and thus higher efficiency. The flow uneven distribution in the inlet, channels and outlet induce different conversion levels, but also possible risks for runaway. At first, the fluid dynamics has been described for cold flow, to understand which geometry and size could lead to even flow distribution [44]. In case flow non-uniformities can generate a local hot spot and consecutive thermal

runaway of the reactor, a conservative definition of the flow uneven distribution should include minimum and maximum values with respect to the nominal flow rate as follows.

$$\text{Uneven Distribution (\%)} = \frac{\max(F) - \min(F)}{\max(F)} \times 100 \quad (\text{E36})$$

Where F is the vector describing flowrate through the n microchannels. Otherwise the standard deviation with respect to the average flow (\bar{F}) can be set as descriptor:

$$\text{Standard deviation} = \sqrt{\frac{\sum_{i=1}^n (F - \bar{F})^2}{n-1}} \times 100 \quad (\text{E37})$$

The deviation steeply increases with channel number and depends on the shape, more than the size of the distributor and outlet chamber. A 3D reacting model was then developed, considering the kinetics of propane oxidation and assuming channels geometry as wall coated cylinders with a thin layer of Cr/Al₂O₃ catalyst.

5 - Case histories of heterogeneously catalysed microreactors

5.1 – Multistep integrated modules

Several examples of continuous flow multistep reactions, often catalytically mediated, have been recently reviewed [8,51]. Very versatile configurations of micromixers, microreactors, heaters, pumps, membrane separators, etc. were connected in parallel or in series to illustrate the production of a variety of compounds [52,53], among which many different Active Pharmaceutical ingredients (APIs). Particularly interesting examples are the routes to Ibuprofen and Artemisinin, an antimalarial drug because such reactions were object of detailed process simulation and scale up studies [10,54]. A compact but yet comprehensive description of multistep units is discussed by K. Jensen [9]. In that review the author very well highlights the evolution of microreacting systems from pioneering systems including only micromixers and very basic microreactors, to the present highly automated units for industrial scale production of drugs. Appropriate materials for piping and reactors are now employed to improve resistance to organic solvents and avoid fouling (e.g. Teflon pipes), with

optimised size and geometry to achieve appropriate dispersion and phase mixing. Separation and work up modules are connected with the reacting system, with preferable use of liquid-liquid extraction, which is less energy demanding than distillation. Automated, small scale, gravity based separation units are available. Membrane separation is efficiently employed to favour separations between aqueous and organic phases, while some limits are evidenced for solid separation units. The things become more difficult in the case of heterogeneously catalysed reactors, due to the need of multiphase characterisation of flow and to the much larger influence of surface tension, which enhances the possible liquid hold up (if relevant) with respect to macrosized systems. Automated operation and optimisation algorithms are also discussed [9], which however should rely on accurate and fast analytical tools, e.g. UV-Vis, FT-IR spectroscopy and very fast HPLC, mass spectrometers and NMR tools. Versatile, fully automated systems are finally described, such as a modular unit “Pharmacy on-demand”, that produces 100 doses/day of diphenhydramine hydrochloride, lidocaine hydrochloride, diazepam (Valium®) and fluoxetine hydrochloride (Prozac®).

Nice examples of multistep synthesis of various classes of drugs have been reviewed [55] with emphasis of the control logic. Integrated systems allow the one-step (“telescopic”) production of complex molecules by sequential addition of reactants without need of intermediate separation. In many other cases separation units are needed, e.g. to separate the desired phase or isomer, to change solvent or to eliminate interfering byproducts. Integrated modules can be used, where automation can belong to any of the following complexity level. At first, in line systems of analysis permit to monitor reactants, products and process conditions (temperature, pressure, pH, etc.). A second level is optimisation, to improve the yield of the desired product, which may be achieved following a Design of Experiments (DoE) approach. The system follows appropriate algorithms to select the optimal conditions, but the application of this tools to multistep processes is often too complex. Even in single step systems, if the number of experiments exceeds 20-25, separate kinetic modelling is preferable, followed by optimisation [56]. The third level of automation complexity is likely the most important for the industrial scale up and includes a control logic extended to the whole system. This aims to

keep the plant under steady state conditions and to predict its evolution following possible perturbation. It is very important not only to guarantee reproducible productivity, but also for safety reasons. Dynamic simulation is a fundamental tool to this aim. A fundamental step is the selection of the appropriate control variable and the design of the control logic of the system. Comprehensive examples for the production of many drugs are discussed in [55]. One example is the synthesis of olanzapine, a drug for bipolar disorder and schizophrenia, which include 4 reactors, inline extraction and filtration [57] (Fig. 7). Accordingly, the synthesis of (\pm)-Oxomaritidine is described and a series of fixed bed reactors optimised accordingly [55,58] (Fig. 8).

5.2 – Organometallic and enzyme-catalysed reactions in organic synthesis

Enzymes are very active and selective as catalysts, but hardly usable in batch reactors due to recovery and recycle problems. Immobilisation strategies should be proposed and one straightforward example has been introduced by loading α -transaminases on silica monoliths, with very high void fraction to minimise pressure drop, to be loaded in microreactors. The choice of silica is appropriate being a non toxic compound, inert, quite inexpensive and highly surface functionalised, so to allow enzyme anchoring. The monoliths were used for the production of chiral amines as precursors for drugs [59]. 50% product yield was achieved by packing 8 monoliths in series. The absence of diffusional limitations has been checked by the authors and enantioselectivity was retained after grafting on the support.

The enzyme-catalysed synthesis of biodiesel has been also reported in microreactors [42]. Here two points are of major concern, i.e. the immobilisation of the enzyme and the promotion of an intimate contact between the oil and methanol, that can be achieved in such devices thanks to efficient mixing. Different examples are reported which confirm the validity of the approach in the case of the alkali catalysed reaction. For instance, 98% soybean conversion was achieved at 60°C with contact time 180 s [60]. This result was further improved to 99.5% conversion at 56°C and 28 s contact time by improving the microreactor configuration, with zig-zag channels and optimised micromixers [61].

Less positive results were reported for the lipase promoted process [62,63]. Conversion was limited to 67%, likely due to accumulation of glycerol which inactivated the lipase. Connecting three microreactors in series the conversion increased only up to 85%. A detailed economic assessment of the enzymatic biodiesel production is also reported [42], which evidenced as expected the excessive impact of the enzyme cost and of its immobilisation.

One of the key points is the selection of a suitable substrate for the enzyme, with suitable porosity to limit the pressure drop and appropriate surface functions (e.g. diols) to graft the enzyme. A nice example of a bio-microreactor with an organic polymer monolith is reported in [64]. The supporting polymer was prepared from glycidyl methacrylate, glyceryl monomethacrylate and acrylamide monomers, using the diethylene glycol dimethacrylate as crosslinker and the 1-propanol as porogen solvent. The immobilisation procedure of trypsin and test reactions are also reported.

Au nanoparticles are active for many important redox reactions and their use is possible by immobilisation over supports. Nanoparticles incorporation into protein cages allows their full accessibility, while the surface functional groups of the protein permit stable anchoring in microreactors channels. Testing has been carried out for the reduction of nitroarenes to amines as a proof of concept [65].

The main problems in the use of homogeneous catalysts immobilised over supports are metal leaching, swelling of the polymer supports (when relevant) and the progressive decrease of catalyst performance due to deactivation. This may lead to insufficient life of the cartridges with consequent ruling out of the process for economic reasons, since most of these reactions are carried out over noble metal based catalysts [66]. Moreover, linking the organometallic catalysts or enzymes to a solid support often results in decreased catalytic activity. In order to avoid such phenomenon, the separation of homogeneous catalysts from the products stream can be done by nanofiltration membranes. To do so, sterically hindered metal ligands are selected, so to increase catalyst size and allow sharper separation [67,68]. Also in the case of metal-catalysed reactions, metal leaching can

occur, especially when the catalytic cycle involves oxidative- reductive reactions as for Pd catalysed coupling [69].

Pd-catalysed allylic substitution reactions are used to build C–C, C–N, C–S, and C–O bonds with high chemo-, regio- and stereoselectivities [70–72]. An example is the Tsuji–Trost reaction to add functional groups in allylic position with high regioselectivity at the less-hindered carbon atom. The reaction conditions have been optimised for the conversion of cinnamyl acetate and dibenzylamine in ethanol with Pd/C, 10 wt.% as catalyst and triphenylphosphine. Various substituents have been also tested under the optimised conditions, with high yield and mostly total selectivity to the desired linear product [73].

C-C bond formation through cross coupling is often catalysed by Pd. Examples of Suzuki-Miyaura reactions are reported in [74], which consist in coupling organoboron compounds with aryl, alkenyl and alkynyl halides. Typically, a homogeneous approach is used, but heterogeneously catalysed reactions were recently proposed [75]. The generally accepted mechanism implies that Pd(II), formed by leaching of the heterogeneous catalyst, is the active species, through a quasi-homogeneous mechanism. The reaction has been carried out both in homogeneous and heterogeneous mode in continuous flow. Heterogeneous Pd-based catalysts are also commercially available for this reaction (e.g. Pd/C), but leaching remains the major point. A library of reactions and products has been recently proposed [76], as exemplified e.g. in Fig. 9.

5.3 – *H-transfer and hydrogenation reactions*

Hydrogen transfer reduction reactions have been tested by using a Pd/C catalyst [77]. This avoids the presence of H₂ tanks to the in situ generation of gaseous hydrogen, which anyway results in a multiphase system. Pd-based catalysts are very often used for reduction of various organic substrates. A review of different types of catalysts for various applications is reported in [78].

Sugar alcohols are emerging interesting materials both for the food industry due to lower impact on health than conventional sugars [79]. Their production is commonly based on hydrogenation of the

corresponding carbohydrates by enzymatic catalysis or heterogeneous catalysts. A comparison between batch and continuous reactors has been proposed using molybdenum based and phosphomolybdic acid catalysts in acidic form or as Ag or Cs salts. The heteropolyacid catalyst performed better in the epimerisation of glucose to mannose with respect to bulk molybdenum oxide, though Mo loss was a major issue in both cases. Different hydrogenation functions were also added for alcohols production.

Selective hydrogenation reactions are becoming increasingly important to exploit biomass derived raw materials. As an example, 5-hydroxymethyl furfural (HMF) is an important intermediate from glucose or fructose derived from lignocellulosic biomass. It can be converted by hydrogenation to different compounds useful as building blocks for polymers, such as 2,5-dihydroxymethylfuran (DHMF) and 2,5-bis(hydroxymethyl)tetrahydrofuran (DHMTHF). Various heterogeneous catalysts have been tested, including Ni and Cu Raney[®] [80]. High conversion (94%) and selectivity to DHMF (84%) was obtained with Cu Raney[®] as a first reactions step at 90°C, 90 bar, 24 h-on-stream. The second step conversion of DHMF to DHMTHF was performed over Ni Raney[®] but deactivation was evident, though no significant leaching occurred.

Ni as active phase was loaded over magnetic magnetite particles and applied in a microreactor for the reduction of 4-nitrophenol [81]. The application of an external rotating magnetic field induced a very efficient local stirring and can be also used for particles recovery after the reaction.

5.4 – Oxidation reactions

The control of exothermal reactions such as oxidations is compulsory to improve selectivity in case of partial oxidation products. Many different examples have been reviewed recently by Pennemann et al. [82]. For instance, decreasing channel size and adopting a catalytic wall configuration is the key to improve heat removal. A first example is the continuous production of H₂O₂ from H₂ and O₂ catalysed by Pt or Pt/Au supported over TiO₂. Interesting applications are described for the on demand production of 10% solutions of hydrogen peroxide [83]. The synthesis of ethylene oxide was

modelled in a silver plate microreactor [84] and the hydroxylation of phenol to hydroquinone and catechol was carried out in liquid phase by using titanium silicalite (TS-1) and H₂O₂ [85]. The authors observed catalyst deactivation operating with a microfixed bed, which was negligible when using wall coated channels. Very high yields (89-99%) of benzylic, allylic and aliphatic aldehydes from the corresponding alcohols was obtained over gold coated microreactor walls in a multiphase microreactor under mild conditions and very short residence time [86].

6 - Conclusions

Heterogeneous catalysed reactions in continuous flow are a mature technology in the fields of base chemicals/refinery/energy, whereas the description of the continuous flow synthesis of fine chemicals and drugs is often based on phenomenological description and experimental optimisation. Specific models are needed to account for transport phenomena in microreactors and their role in defining productivity and/or safety. Starting from consolidated approaches used for macro-scale reactors, appropriate models have been developed in some important cases. Nevertheless, stronger efforts should be put in the definition of experimental correlations for a wider applications window.

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Figure captions

Fig. 1: Classification of heterogeneously catalysed microreactors: a) fixed bed; b) micromonoliths; c) wall coated microchannels.

Fig. 2: Effect of fillers on fluid flow and concentration profiles for microchannel reactors.

Fig. 3: Scheme of the main mass transport issues in microchannel wall coated reactors.

Fig. 4: Example of 2D concentration profile of a reactant, fed in a wall coated microchannel with variable r (1,5,10 mm, top three figures) or kinetic constant ($k= 0.001, 0.01, 0.1$ or 1 s^{-1}). The first order reaction occurs at channel wall with a first order kinetics. The system has been numerically solved considering a backward finite differences scheme, with 20 grid points in the radial direction and 50 points in the axial one [I. Rossetti, unpublished results].

Fig. 5: Contour plots of the temperature and water mass fraction for the catalytic combustion of hydrogen-air mixtures. The parameters used are $u_{in} = 0.8 \text{ m/s}$, $\lambda_s = 0.8 \text{ W/(m}\cdot\text{K)}$, $h_o = 20 \text{ W/(m}^2\cdot\text{K)}$, and a stoichiometric feed. Reproduced from [49] under the terms of the Creative Commons Attribution License.

Fig. 6: Temperature and conversion profiles along the wall and axis for the catalytic combustion of hydrogen-air mixtures. Reproduced from [49] under the terms of the Creative Commons Attribution License.

Fig. 7: Multistep synthesis of olanzapine [57]. A) Reactions scheme and B) process layout and control logic for the continuous plant [55]. Dotted reactors represent fixed bed catalytic steps, open rectangles are homogeneous reaction steps. Reproduced from [55] under the terms of the Creative Commons Attribution License.

Fig. 8: Multistep synthesis of (\pm)-Oxomaritidine [58]. A) Reactions scheme and B) process layout and control logic for the continuous plant [55]. Dotted reactors represent fixed bed catalytic steps, open rectangles are homogeneous reaction steps. Reproduced from [55] under the terms of the Creative Commons Attribution License.

Fig. 9: Suzuki–Miyaura cross coupling scheme in a flow system using H-Cube[®], as summarised by Len et al. [74]. Reproduced from [74] under the terms of the Creative Commons Attribution License.

FIGURES

Fig. 1

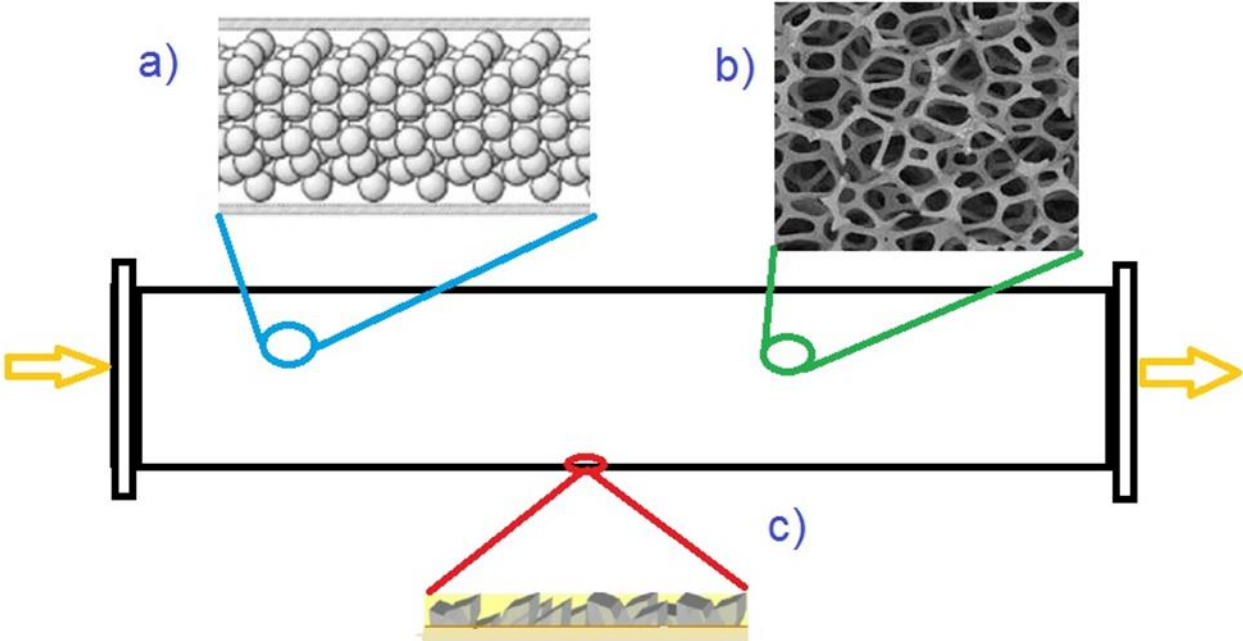


Fig. 2

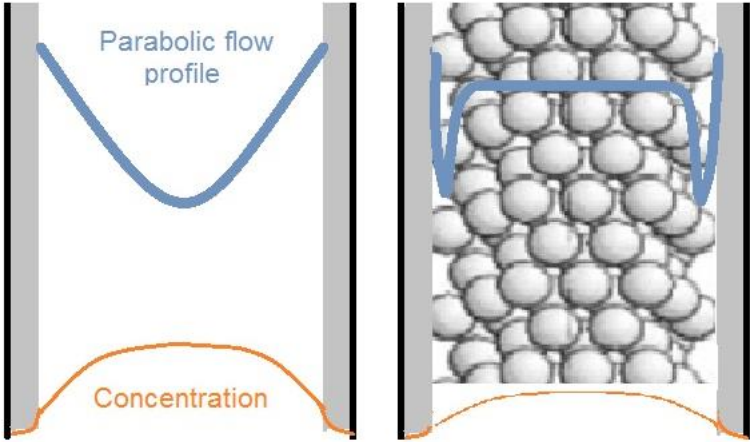


Fig. 3

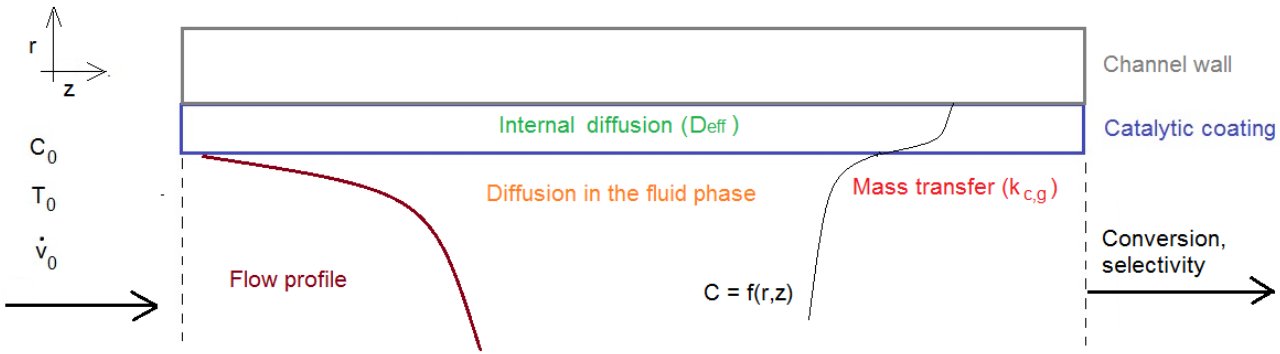


Fig. 4

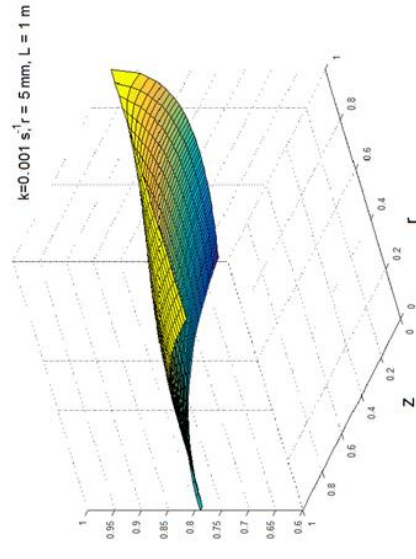
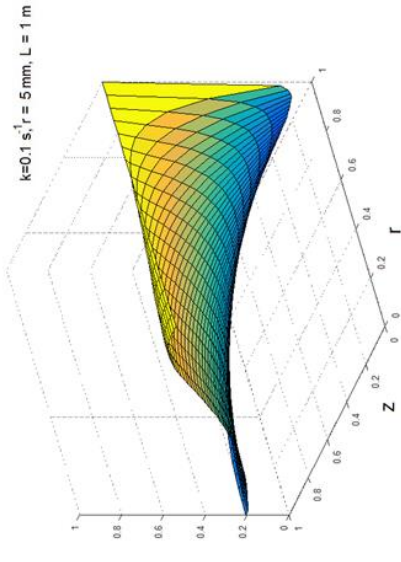
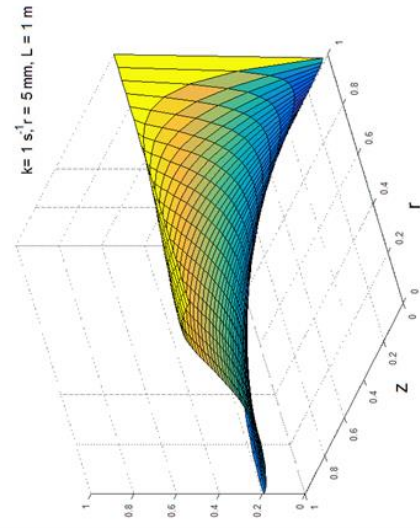
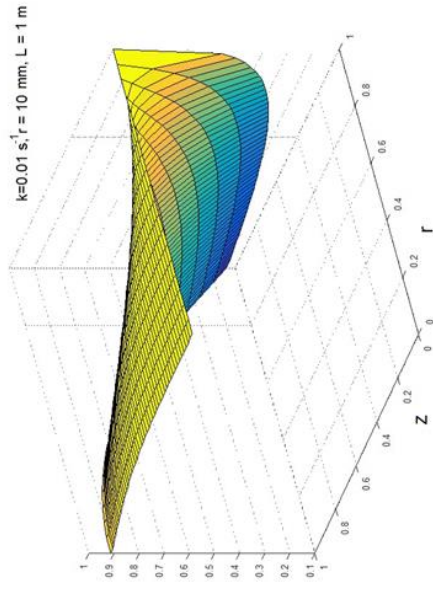
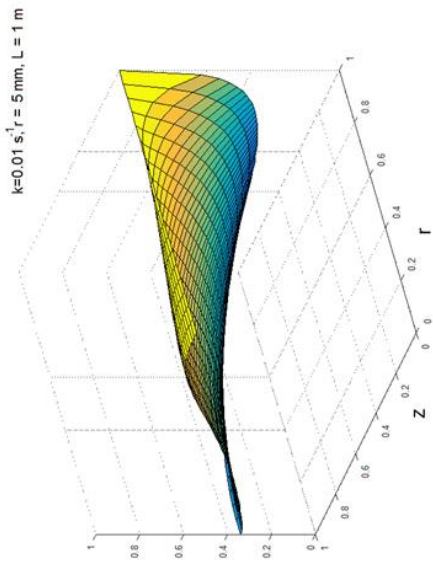
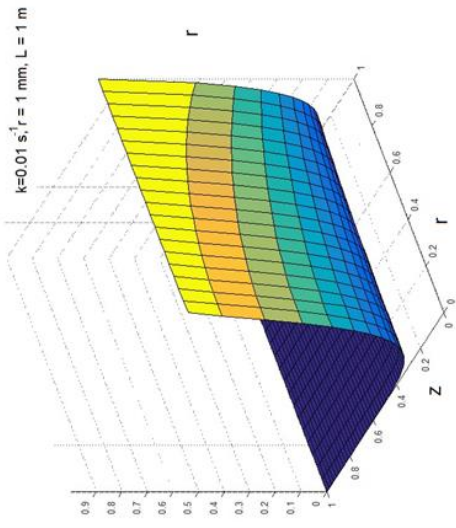
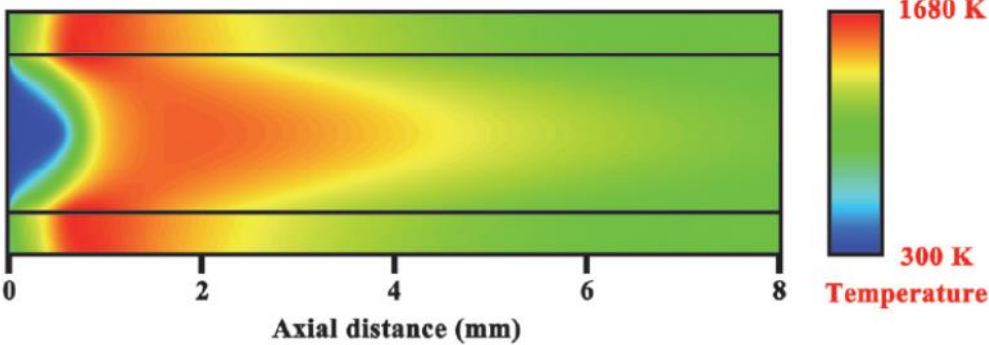
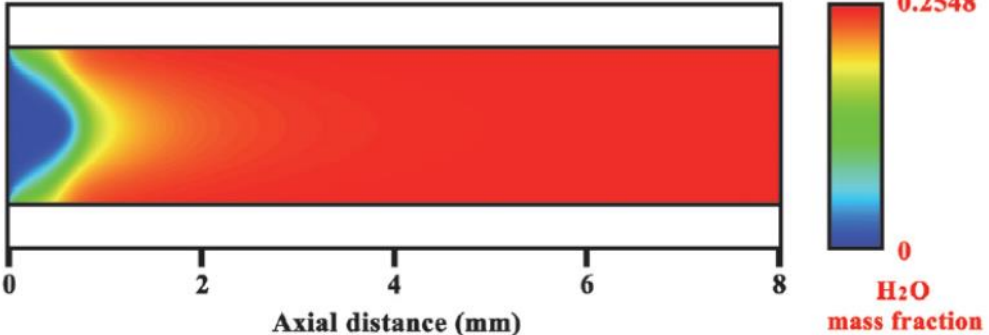


Fig. 5



Axial distance (mm)

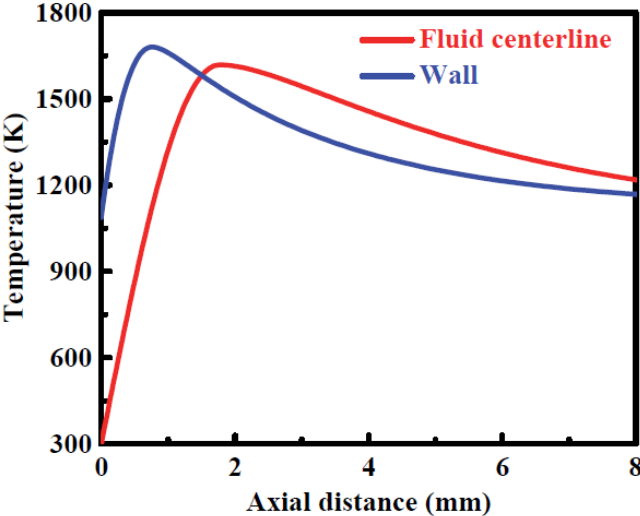
(a) Temperature



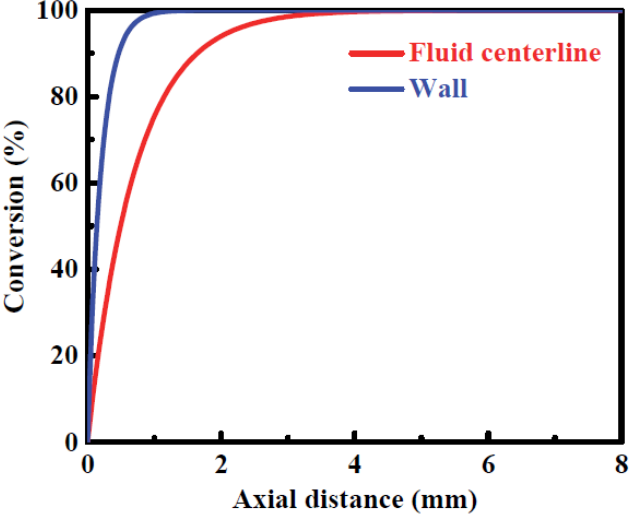
Axial distance (mm)

(b) Water mass fraction

Fig. 6

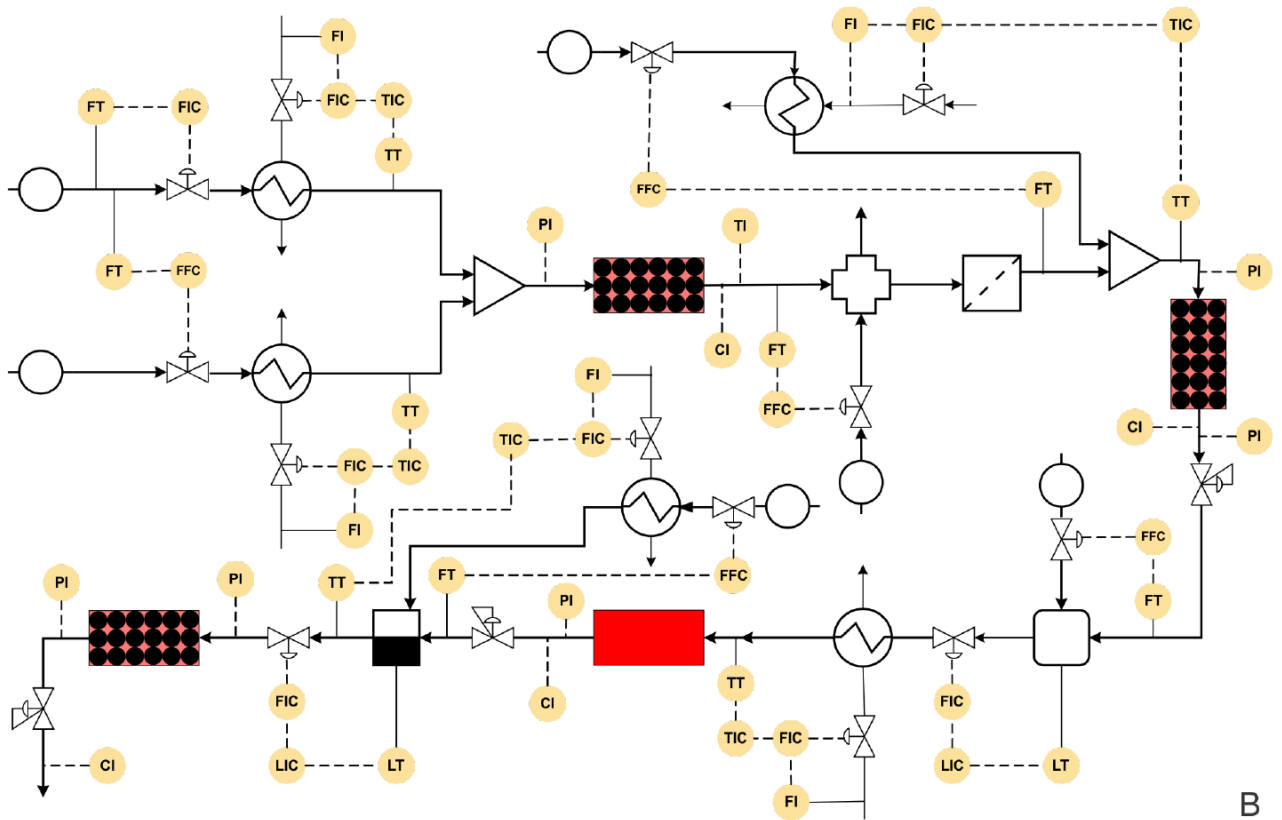
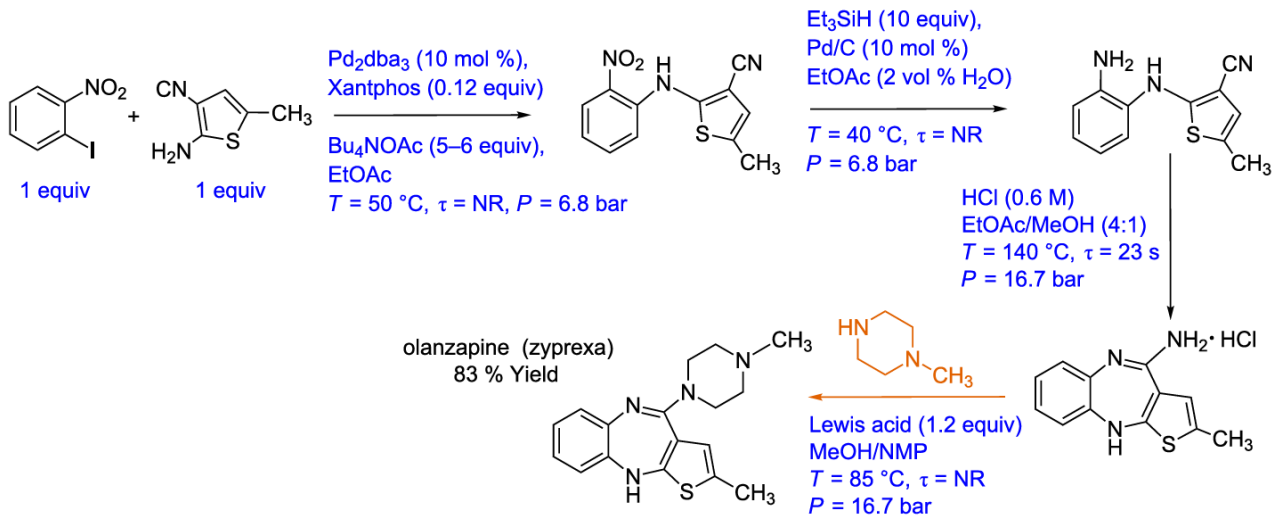


(a) Temperature



(b) Conversion

Fig. 7



B

Fig. 8

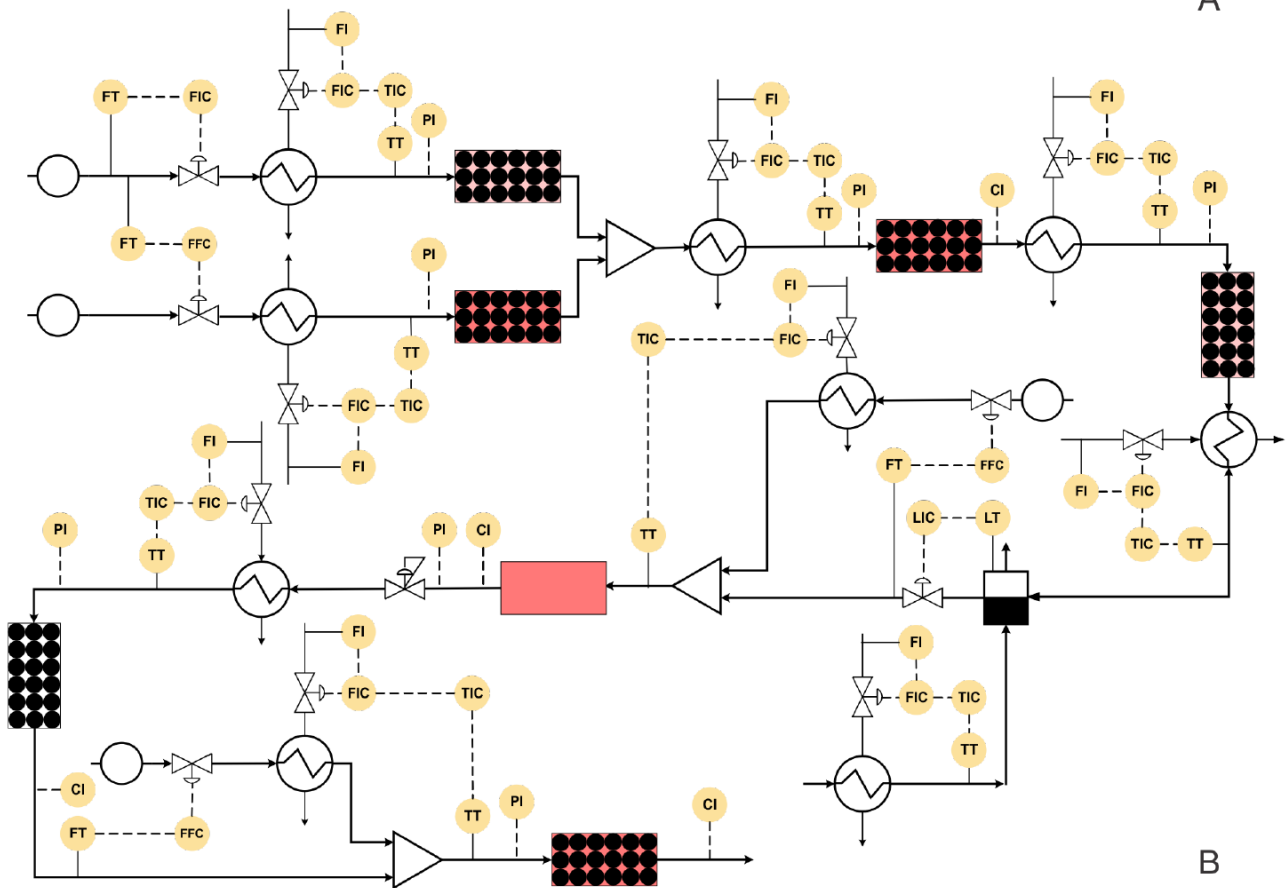
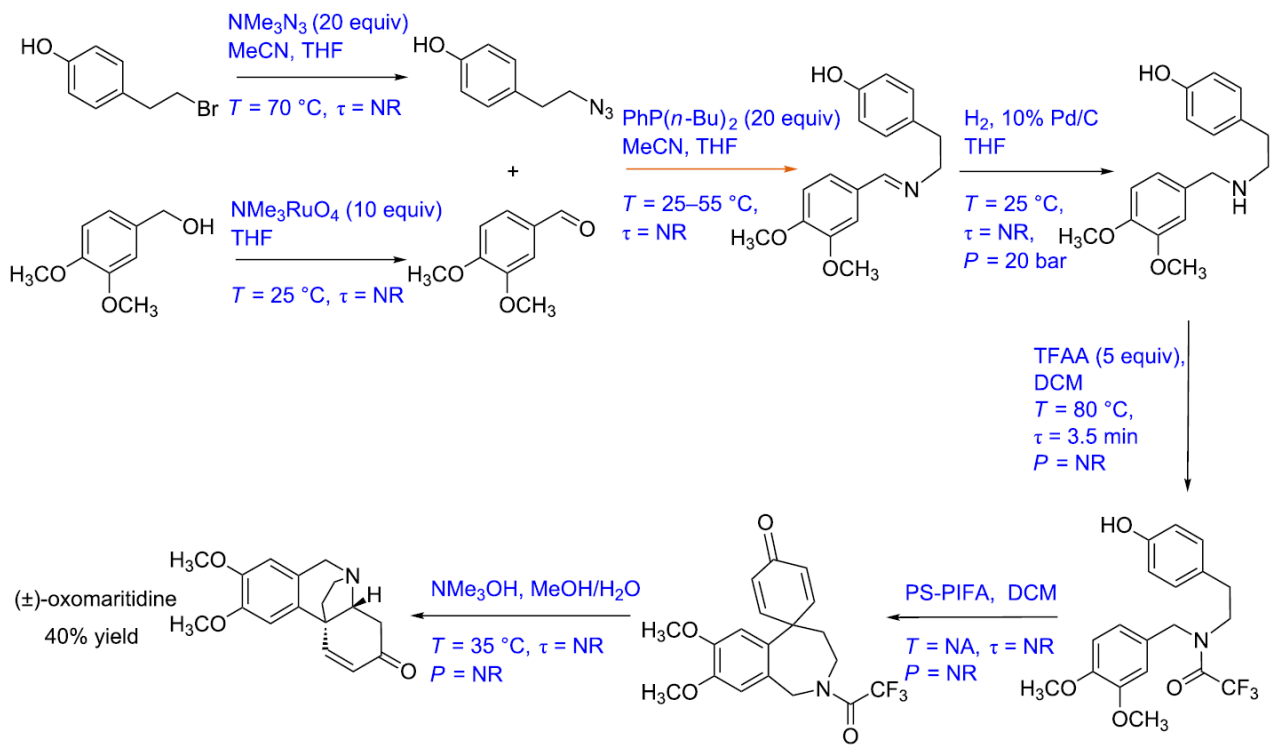


Fig. 9

