

# Microreactor Technology: A Revolution for the Fine Chemical and Pharmaceutical Industries?

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50 % of reactions in the fine chemical/pharmaceutical industry could benefit from a continuous process based mainly on microreactor technology. However, the frequent presence of a solid phase still hinders the widespread application of such a technology as a multi-purpose solution. For small scale and pilot productions, speed in process R&D, as well as the avoidance of scale-up issues, are the main drivers. On the other hand, for large scale productions, a gain in yield and safety are the main motivations for the use of microreactor technology. The gain in yield must be significant in order to cope with the increase in capital expenditure associated with the development of a new technology.

## 1 Introduction

In the fine chemical and pharmaceutical industry, production generally relies on batch or semi-batch processes. They are managed in so-called production campaigns, and are typically operated on a train/stream approach where a solid key reagent is introduced and a crystalline product is obtained [1]. Reaction and work-up steps are fundamental unit operations of such processes. Two major advantages are associated with batch or semi-batch processes over the continuous counterpart, namely flexibility and versatility of the equipment. A reaction vessel is flexible because it can easily accommodate miscellaneous reaction kinetics. In a semi-batch operation the dosage time is usually rate limiting, while in batch operation the reaction time can be adjusted as a function of the kinetics. Various reaction phases (solid-liquid-gas), as well as various downstream operations such as distillation, liquid-liquid extraction, and crystallization can also be accommodated in a versatile reaction vessel.

Based on the analysis of twenty-two large scale processes performed at Lonza Exclusive Synthesis (see Tab. 1), a typical campaign lasts for 4–8 weeks. The characteristic daily productivity is around 1.5 tons, which is low compared to the bulk chemical industry. Once a campaign is completed, a rigorous and intensive cleaning procedure is performed to prepare the train for the next production (2–3 weeks). To optimize the number of downstream operations, consecutive reactions without intermediate work-up or isolation are favored as long as the product quality remains high. Even under such conditions, the average number of work-up unit operations is slightly higher than the number of reaction unit operations (2.7 versus 2.1). The downstream operations being a direct consequence of the reaction steps, a better selectivity would mean fewer side products and a less demanding work-up. Although the average isolated yield of 77 % (often including consecutive reactions) could possibly be further improved, we believe that process opti-

mization has an intrinsic limit and that only an innovative technology might allow drastic process and cost improvements.

For the production of bulk chemicals, dedicated continuous plants have long proved most economical. In the pharmaceutical and agro business, however, given the relatively low volumes, and often short life-time of most products, multi-purpose plants are generally required in order to limit the investment costs. So far, multi-purpose has meant batch reactors (*vide supra*). A multi-purpose plant based on continuous technology could, however, be advantageous for the fine chemical and pharmaceutical industry. Such equipment could combine the efficiency of continuous production as established in the bulk chemical industry, with the flexibility and versatility required in the fine chemical area. The purpose of this study was to determine which percentage of the current processes run at Lonza could benefit from a continuous production process. Additionally, the type of continuous reactor required is also discussed. In particular, low flow microreactors appear well suited for the relatively low tonnage of the pharmaceutical industry. Finally, a cost analysis of continuous versus batch production is presented.

## 2 Analysis of Reactions in the Fine Chemical and Pharmaceutical Industry

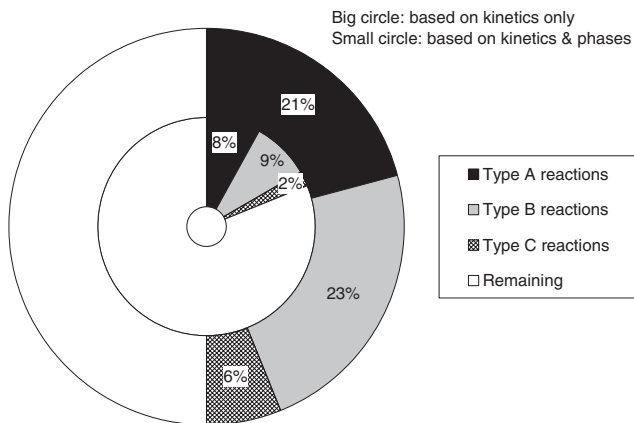
According to a detailed analysis [2], reactions in the fine chemical and pharmaceutical industry can be divided into three classes, depending on their kinetics. One of the striking observations was that more than 70 % of these reactions are currently performed in a semi-batch manner. These reactions are controlled by one reagent dosage, with the consequence that the reaction vessel is oversized in terms of active volume. Under such circumstances, the space-time yield is low. A continuously operated reactor would, in principal, be better suited to such reaction kinetics.

These published results [2] were reanalyzed in the context of continuous processes (see Fig. 1). Three reaction types

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**Table 1.** Average characteristics of twenty-two different processes in the fine chemical/pharmaceutical industry, which refer to large scale production campaigns.

Production [t/a]	Duration	Productivity [t/d]	Yield [%]	Unit operations reaction	Unit operations work-up
44	4–8 weeks	1.5	77	2.1	2.7



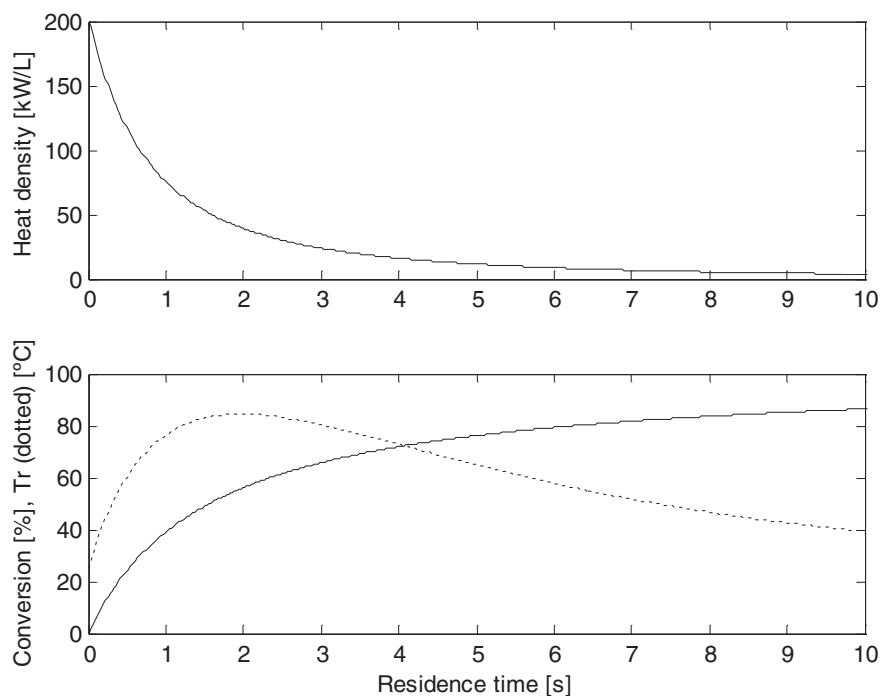
**Figure 1.** According to our classification of eighty-six different reactions carried out at Lonza, 50 % would benefit from a continuous process (Type A, B, and C), but 63 % of those reactions cannot currently be carried out in a micro-reactor due to the presence of a solid.

were identified, for which a continuous production process would be advantageous:

- **Type A** reactions are very fast with a reaction half life of less than 1 s. Such reactions take place mainly in the mixing zone and are controlled by the mixing process (micromixing domain) [3]. The flow rate and the mixer type play a significant role. A microstructure is required to control local temperature gradients. Type A reactions involve reactive species such as chlorine, bromide, amines, and acid chlorides, and are often performed at around 0 °C. Organometallic reactions (lithium- and Grignard-type chemistry) also fall into this category and usually require cryogenic temperatures.
- **Type B** reactions are rapid reactions, occurring between 1 s and 10 min. They are predominantly kinetically controlled. Nevertheless, these reactions would benefit from a microstructure in order to better control the heat flow and thus the reaction temperature. With a conventional system, such as shell and tube heat exchangers,

high temperature gradients are generally obtained resulting in reduced selectivity (see Fig. 2). The mixing is not so critical for such reactions, and the pressure drop can be minimized to allow the use of a residence time module to complete the reaction. Scale-up issues are avoided if the same area to volume ratio is maintained.

- **Type C** reactions are slow reactions (> 10 min) which, based on their kinetics, suit batch processes, but where a continuous process would bring a safety or quality advantage. Indeed, carrying out reactions with thermal hazard and/or autocatalytic behavior in a continuous way means that the reactive volume and thus the potential danger are significantly reduced. Processes requiring short exposure to high temperatures or pressures would also benefit from a continuous technology since this is difficult to realize batchwise. In terms of equipment, large residence time modules are needed and conventional tech-



**Figure 2.** The heat density of a real case acetoacetylation of an aromatic amine with diketene in a tube reactor was calculated by computer simulation and reported as a function of residence time and conversion. The half life of the reaction is around 1.5 s, so the reaction is mostly located in the kinetic regime (Type B). A second order reaction implies that most of the heat density is located at the start of the reaction. Under such conditions, the small conventional tube (diameter 3 mm) cannot sufficiently extract the heat and a temperature gradient builds up between the process fluid (Tr) and the heat transfer fluid. The reaction needs a microreactor at the beginning, but can be completed with a conventional (not micro) residence time unit once the initial heat density is consumed (99 % conversion after 154 s). The following parameters were used for the simulation: heat transfer coefficient 500 W/m<sup>2</sup>/K, fluid heat capacity 2.0 kJ/kg/K, second order kinetic constant 0.363 L/mol/s, enthalpy 180 kJ/mol, diketene and amine concentration 15 %, respectively, heat transfer fluid at a constant temperature of 25 °C, activation energy is not considered.

nology such as static mixers and shell and tube heat exchangers are sufficient. The use of a microreactor is only required in case of sudden heat generation (autocatalysis).

For Type A and B reactions, a microreactor would be needed for an efficient continuous production (at least those with a sizeable adiabatic temperature rise). Indeed, one of the main drivers for the use of microreactors is the strong localized heat generation, or, in other words, the strong heat density (W/L, Watts per Liter, Fig. 2). A high local heat density in a batch vessel translates into local temperature gradients, which generally reduce selectivity [4]. A microreactor with an integrated heat exchange capability is a technical answer to this problem.

Besides reaction kinetics, another factor to take into account for a continuous process is the different phases involved (solid-liquid-gas). In more than 60 % of the reactions studied [2], a solid was present, whether as reactant, catalyst, or product. From our experience, the microreactors currently available can only handle solids very poorly. Although a reaction in microreactors involving solids was reported [5], this example can not be generalized and easily applied to other reactions. The multi-purpose use of microreactors is, so far, limited to homogeneous reactions and, to some extent, to gas-liquid and liquid-liquid reactions. The consequences of this statement are important for the wide application of microreactor devices. When taking into account the various phases and removing the reactions involving solids, the number of possible candidates for microreactor technology shrinks significantly (see Fig. 1). The versatility associated with the reaction vessel is thus still an important advantage favoring batch production. A further technological development will be needed to develop modular microreactors capable of handling solids. A step in that direction is, for example, the Micro Jet Mixer from Ehrfeld Mikro-technik BTS.

In conclusion to this section, the multi-purpose use of microreactors is believed to be a condition to the success of this technology in the fine chemical and pharmaceutical industry. In this field, one cannot develop a specific reactor for a specific reaction: the number of reactions studied is large and the resources limited. As already proposed [6–8], a toolbox concept is necessary. A few modular microreactors should be developed for the various physico-chemical characteristics of the reactions. They could then be flexibly used in a multi-purpose continuous plant depending on the reaction type. By developing the right device for a specific reaction type, one will fit a production unit to a chemical process and not fit a chemical process in a production unit. The present development of material science and process instrumentation should allow for the efficient implementation of continuous processes and the wide range application of microreactor technology.

### 3 Economical Analysis of Batch versus Continuous Production

When specifically considering pharma and agro productions, different cases should be distinguished depending on the life cycle of the products:

- **Small scale production** to supply the pre-clinical and clinical phase I studies: during the pre-clinical and early clinical studies, speed is the most important factor. Currently, the delivery time for kilogram quantities of a three–four steps project is in the order of 4–6 months. A highly automated laboratory microreactor system would have the advantage of speeding up R&D process by favoring high throughput experiments. Process R&D being the most important operating cost expenditure at that stage, a faster process development would simultaneously result in a significant cost reduction as well as an increase in speed.
- **Pilot production** to generate clinical phase II and III material: here, the main focus is on quality. The use of a device which suits the reaction kinetics should, especially for Type A reactions, allow a quality improvement. Moreover, essentially no scale-up issues are expected for continuous small scale productions based on microreactors. The advantage of avoiding scale-up difficulties by a parallelization approach is a strong incentive for the use of microreactors in terms of time, quality, and cost.
- Finally, **commercial production** after the product launch: once the supply chain and quality are established, the production cost is the key driver. Overall, the commercial phase is the most important one since this is the one where profits can be realized. A continuous process based on microreactor technology must thus have a clear added value in order to compete with the currently used batch technology. A cost advantage can occur from a reduction in capital expenditure (CAPEX) and/or a reduction in operating costs (OPEX). The next sections present a cost analysis of both expenditures for large scale pharmaceutical productions.

#### 3.1 CAPEX Analysis

A multi-purpose batch train consists of various types of equipment. In decreasing order of equipment cost, the following trend is observed: filter drier > vacuum pumps > reactor > dosage cabine with aeration > head tanks > scrubber. It is noteworthy that the reactor is not the most expensive piece of equipment. Besides the central jacketed vessel, other equipment pieces, such as sealed stirrer, heating and cooling system, sampling loop, charging unit, and condenser are necessary. But even with this equipment and the additional costs arising for montage, piping, electric, process control, engineering, and commissioning, one batch reactor accounts for only ca. 15 % of the total cost.

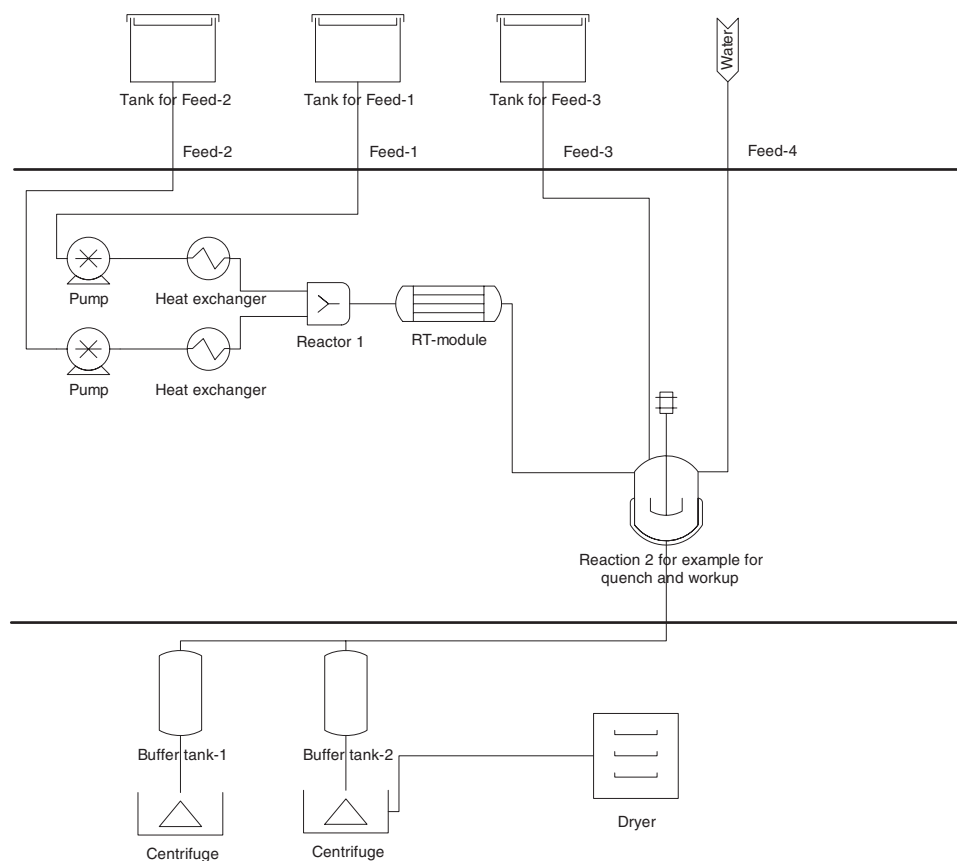
Although the construction of a multi-purpose production plant relying fully on continuous technology is conceivable, we believe that a stepwise approach is currently more pragmatic. The integration of a continuous process into a train can indeed be realized by replacing one batch reactor by a continuous reactor (e.g., a microreactor), while retaining a classical batch equipment for the work-up (see Fig. 3).

With this configuration, a microreactor unit (comprising pumps, flow controllers, valves, etc.) would, based on our estimation, not be cheaper than a batch reactor. A similar capital expenditure can be expected for a small scale unit. For a large-scale unit, the CAPEX for a microreactor system would be even higher than that of a batch vessel. Indeed, a plot of the hardware costs as a function of the reactor size (see Fig. 4) shows that a quite low scale-up coefficient is obtained in the case of batch equipment ( $n = 0.3$ ). Such a low scale-up coefficient has major implications. Firstly, it shows that the volume and the area obtained by increasing the reactor size are not associated with large cost increases. Consequently, an analysis in terms of higher space-time yield is not a strong argument in favor of a continuous process. Secondly, it gives pressure to the numbering-up approach of microreactors where such a low coefficient can hardly be expected in the near future given the present state of technology.

### 3.2 OPEX Analysis of Large Scale Productions

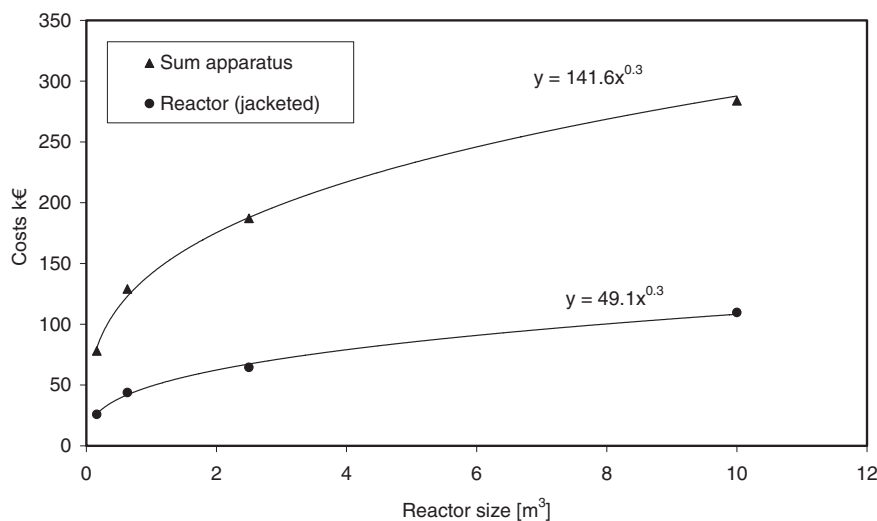
In a production campaign, the raw material costs account for 30%–80% of the operating costs, depending on how close the product is to the API. The raw materials include here the starting material or intermediates, reagents and solvents. The complexity and the cost of the intermediates logically grow along the way to the API. Yield and quality improvements thus have a major effect on the production costs. This represents the main cost saving potential for microreactors, as well as the main challenge.

A typical distribution of the remaining operating costs (see Fig. 5) shows no dominant factor, although labor, change-over, and cleaning are the main ones. The labor costs can be reduced by increasing the throughput (productivity). A highly automated continuous process will not only stabilize product quality, thus reducing the QC/QA demand, but will also reduce the number of people needed to operate the process (reduced labor). The change-over and cleaning costs are inherent drawbacks of multi-purpose plants and should not be substantially different in a continuous process compared to batch production. Of course, the yield here also has a direct influence on labor, plant, and waste treatment costs.

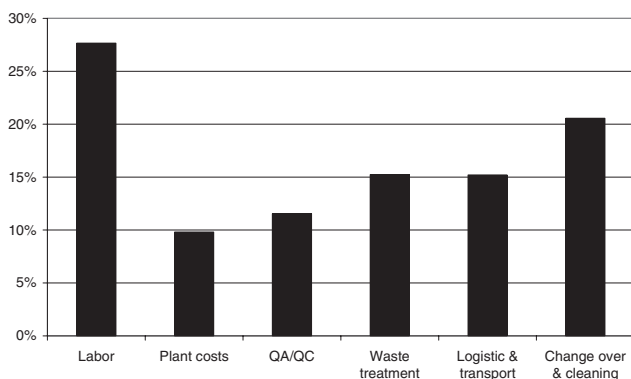


**Figure 3.** Schematic representation of a multi-purpose train used in the fine chemical/pharmaceutical industry with an integrated microreactor unit.

Reactor size [m <sup>3</sup> ]	0.16	0.63	2.5	10
Hardware / apparatus	k€	k€	k€	k€
Reactor (jacketed)	26	44	65	110
Sealed stirrer	6	6	13	26
Heating / cooling system	17	35	61	61
Sampling tool	6	6	6	6
Charging unit	6	10	10	16
Condensator	16	27	33	65
Sum apparatus	78	129	187	284



**Figure 4.** The costs of a batch vessel plotted as a function of the reactor size reveals a low scale-up coefficient.



**Figure 5.** Typical distribution of operating expenditures (OPEX) in a fine chemical plant based on a campaign analysis.

## 4 Conclusions

Based on the study of several exclusive synthesis processes, 50 % of the reactions would benefit from a continuous process. For most of them (44 %) a microreactor would be the preferred reaction device. A large proportion of these reactions, however, can not be performed in a microreactor since the currently available devices can not handle solids, at least not with the flexibility and versatility required by multi-purpose equipment.

The investment costs for a continuous multi-purpose plant were calculated to be as high as or even higher than that of a batch plant. Significant cost saving can be expected either from a yield improvement or from reduced labor costs thanks to higher automation. Additionally, microreactor technology might enable new reaction pathways such as solvent free reactions, hazardous reactions [9,10], and control of particular reactions such as oxidation and fluorination [11], although here the economical gain is difficult to evaluate.

Will microreactors revolutionize the production of fine chemicals and pharmaceuticals? Although it is clearly too early to provide a definitive answer, two conclusions can be drawn from this study: the development of flexible and versatile microreactors capable of handling solids is necessary in order to use them widely in multi-purpose continuous plants, and a yield improvement compared to batch production is also necessary to justify higher investment costs.

Received: December 6, 2004 [CET 7128]

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