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Concept Articles

Microreactor Technology and Continuous Processes in the Fine Chemical and Pharmaceutical Industry: Is the Revolution Underway?

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Abstract:

Microreactors have shown their ability to improve chemical processes and routes; however, their integration into chemical production processes depends not only on technical advances. Cost issues and productions logistics play a crucial role, too, and are highlighted with two different case studies. Economical drivers for the pharmaceutical industry are described with emphasis on future development of microprocess engineering.

Introduction

The use of microreactor and continuous processes is gaining in popularity for industrial production of fine chemicals. Some companies have already successfully developed continuous commercial-scale processes such as SK Chemicals, Ampac Fine Chemicals, and Phoenix Chemicals. SK-Chemicals has chosen a global approach through technology fusion including catalysis, microreaction technology, simulated moving bed, etc.[1] Ampac Fine Chemicals works on a technology platform around hazardous energetic chemistries,[2] while Phoenix Chemicals has developed a continuous commercial process using diazomethane.[3] Meanwhile, established players such as DSM and Lonza have also stepped in by demonstrating the applicability of microreactor technology for large-scale production of chemicals.[4,5] In addition, multinational companies in material sciences (Corning),[6] and engineering services (Alfa Laval[7] and Bayer Technology Services)[8] have launched new microreactor designs and systems, showing that the traditional startup-driven technological development is shifting to larger corporations with added capital.

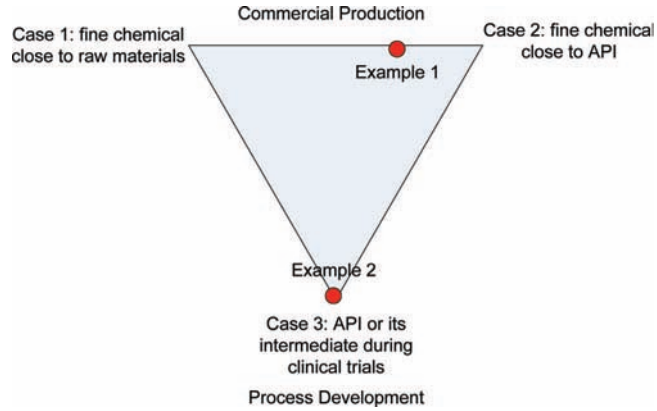

Figure 1. **Three economical cases and two examples within commercial production and process development.**

Is the revolution underway? To answer this question, we share additional results over the past three years of industrial experiences and carry on with a continuity paper to the one that we published in 2005,[9] a paper that was well received by the scientific and industrial community. In this paper we present two examples of commercial projects and locate these examples in their business and economical context. This understanding is of prime importance to reveal the needs of R&D to successfully implement continuous processes in general and microreactor technology in particular.

Three Economical Cases. We will illustrate two examples in this work, but it is important to understand that three main economical cases prevail in the fine chemical and pharmaceutical industry as depicted in Figure 1. Two of these cases relate to commercial productions once an active pharmaceutical ingredient (API) has been approved by the authority. On one

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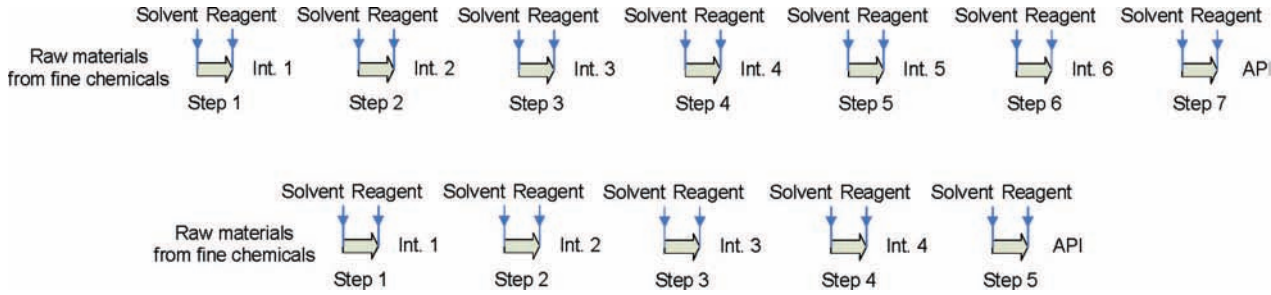

Figure 2. **Seven- or five-step chemical synthesis of an active pharmaceutical ingredient (API) from raw materials.**

hand, Case 1 represents the situation when an intermediate is produced close to the raw materials, namely at the beginning of the synthetic sequence. On the other hand, Case 2 represents the situation when the intermediate is close to the API and generally produced under GMP conditions. Example 1 will be a case-study of a commercial product (intermediate) that is located more closely to the API although not yet a GMP step. Example 2 refers directly to Case 3, a product or intermediate within process development. By process development it is meant an API or its intermediate during clinical trials. In this particular case the main driver is usually "speed".

Drivers for Commercial Productions. It takes an average of eight synthetic steps to produce an API from raw materials of the fine chemical industry.[10] Figure 2 depicts schematically a linear seven-step chemical synthesis, where up to six intermediate isolations take place; each intermediate becomes the key reactant of the subsequent step. Under such conditions, the first cost driver is of course the chemical route itself.[11] In a rough estimation the decrease of manufacturing costs is proportional to the reduction of the number of synthetic steps. For example, Figure 2 shows the hypothetical reduction of the synthetic route to five chemical steps where protection/deprotection reactions would have been omitted through a more selective reaction enabled by a new technology. In this perspective microreactor technology may have a significant impact by allowing the use of unstable intermediates by safely performing hazardous reactions. The aim is to develop new chemistry to truncate traditional chemical routes. The economical impact is, however, difficult to quantify and will not be developed further in this work. Readers are referred to a recent review.[12]

The second economical driver is logically the overall yield. However, it is important to point out that an increase of yield for one individual step has not the same impact if the step is located close to the API or at the beginning of the synthetic route.[11] An increase of 10% yield at step 7 (Figure 2) means also as increase of yield with the same order of magnitude for all preceding steps (at step 6, step 5, and so forth). In fact, it is not surprising to observe higher dilution of reaction conditions the closer the step is to the API. Higher dilution relaxes reaction conditions and often favours selectivity and yield over throughput.

Conversely, at the beginning of the synthetic route generally the costs of chemicals are low, and the throughput/productivity

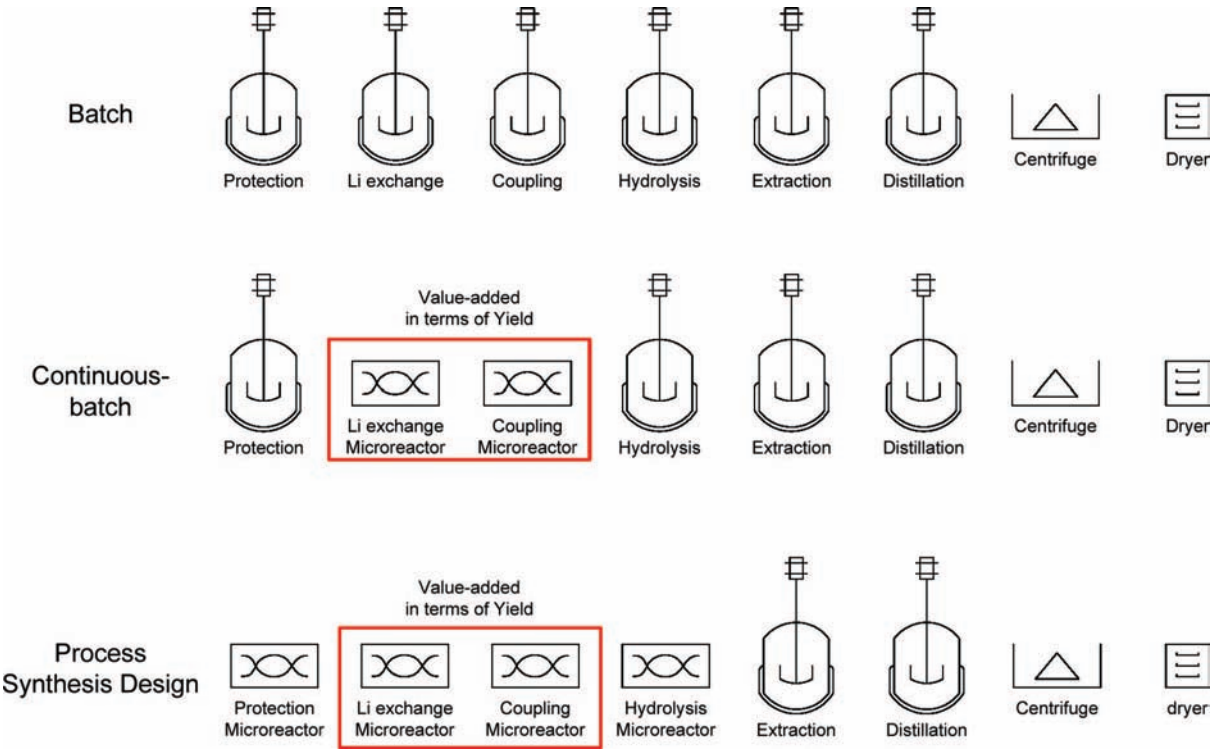

Figure 3. **Three different scenarios of commercial production where the economical benefit is calculated.**

Table 1. **Overview of assumptions and economical gain for the three scenarios in commercial production[a]**

	batch	continuous batch	process synthesis design
campaign size (tons)	5	5	5
batch assets	six 6-m^3 reactors	five 6-m^3 reactors	two 6-m^3 reactors
MR CAPEX[b]	0 Mio $	less than 1 Mio $	more than 1 Mio $
operators	3.5	2.8	2.0
throughput[c] (kg/min)	1.7	2.1	2.1
bottleneck	coupling	distillation	distillation
gain in yield (%)	0	+5	+5
economical gain (%)	**0**	**+10**	**+16**

[a] Cost distribution: starting materials (intermediate, solvent, and reagents) 76%, energy 2%, manufacturing 16%, and change-over 6%. [b] Depreciation over 5 years with 80% plant utilization. [c] Overall throughput at coupling reaction including product and solvent.

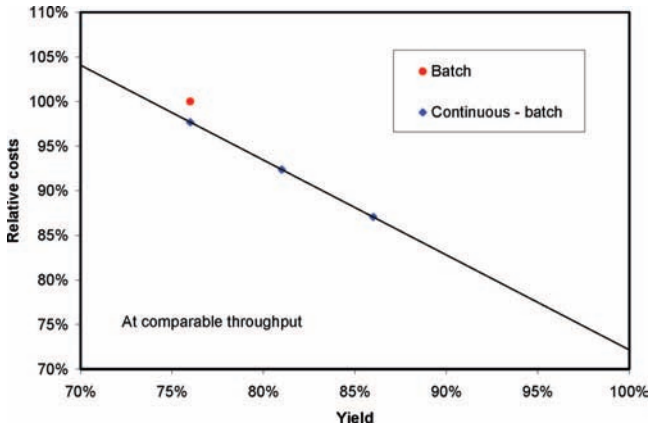

Figure 4. **Influence of yield on the relative production costs.**

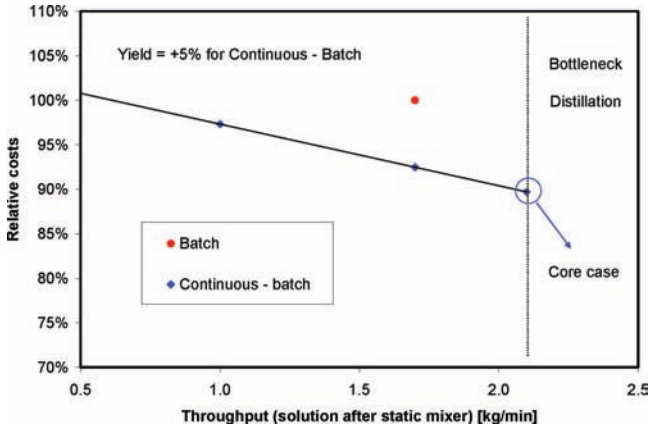

Figure 5. **Influence of throughput on the relative production costs.**

becomes the driving force. Thus, this third cost driver is related to the intense labour costs of this industry as many steps/procedures are performed manually by workers.[9] Thus, a continuous process has the advantage to performing these tasks (steps/procedures) in an automated manner using advanced process control and appropriate modules (dedicated equipment/unit operations), thus reducing the labour costs. The development of an appropriate and versatile toolbox based on micro-

Table 2. **Toolbox concept where the batch procedures/steps are replaced by continuous operated modules**

batch-procedures/steps	continuous-modules
charging	dosage system (pumps)
heating and cooling	micro heat exchangers
reaction semibatch type A[a]	reactor and manifold
reaction semibatch type B[a]	reactor with adjustable dimensions
reaction batch type C[a]	static mixer and conventional HEX[b]
aging	residence time
distillation, liquid−liquid extraction...	under construction...

[a] Type A, B, and C reactions are defined in ref 9. [b] HEX: heat exchanger.

structure components is of fundamental importance to achieving these goals (vide infra). In addition, continuous processes also stabilize quality and reduce the incidence of failed batches. Here too, the pharmaceutical industry has a very poor track record when compared to other industries.[13]

Example 1 in Commercial Production. The first example presented in this work is illustrated in Figure 3 where three different scenarios are calculated and compared for a campaign producing 5 tons of an isolated intermediate through a multistage organometallic reaction (four chemical reactions). The first scenario depicts the standard case where the reaction is performed batch-wise. Up to six 6-m^3 reaction vessels are immobilized to perform an efficient commercial synthesis of the product. Each of the reaction vessels performs cascade-wise a specific task such as Li-exchange, hydrolysis, and distillation (Figure 3). Once a reaction vessel is emptied, the vessel can be reused for the next batch. In such a scenario the slowest step becomes the bottleneck. In this batch case the bottleneck is the coupling reaction, as this reaction is slower and is operated under cryogenic temperatures to avoid side-product formation (over-cooking).

The second scenario (called continuous batch) depicts the case where the Li exchange and coupling reactions are replaced by a microreactor continuous-flow system to increase reaction temperature and to avoid long residence time. In this particular case the yield is also increased by 5% from the results obtained in the batch process (assessed experimentally). The coupling reaction is no longer the bottleneck as the space-time yield of the coupling reaction is now dramatically increased from the higher temperature of the reaction. Under these modified conditions distillation is bottleneck. Thus, the overall solution throughput (product and solvent) for the coupling reaction can be increased from 1.7 to 2.1 kg/min. In all cases the workup operations (extraction, distillation, centrifugation, and drying) are kept constant as calculated in the costs.

Finally the third scenario illustrates the case called process synthesis design (PSD) where all of the reaction steps are transposed into a continuous-flow operation. In this case we assume no gain of yield for the protection and hydrolysis reactions. Such a scenario has the advantage of reducing the batch assets, which is however compensated by the additional investments required by the continuous process (Table 1), even

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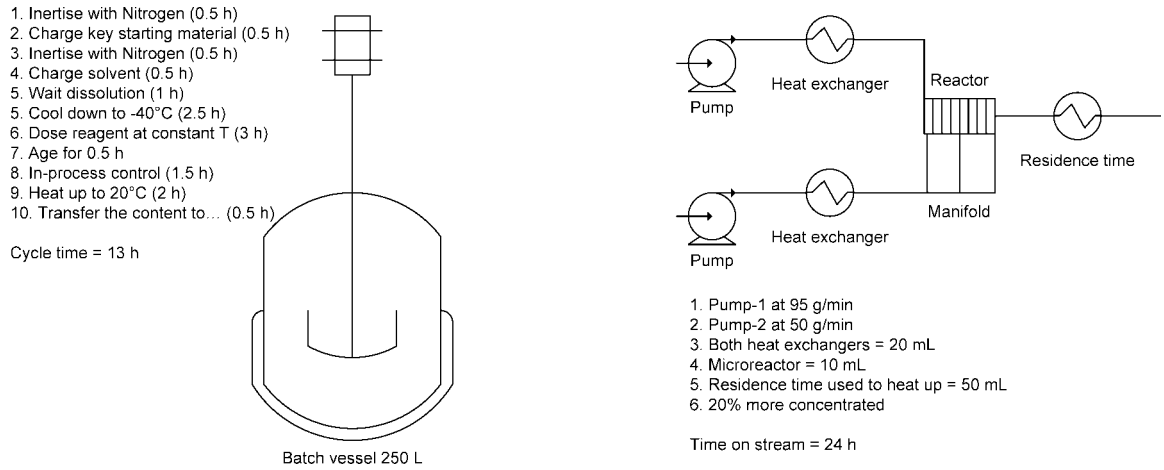

Figure 6. **Batch procedures/steps versus continuous operating modules.**

Figure 7. **Kilogram-laboratory setup showing that the handling of solvent is now the bottleneck under intensified reactor conditions.**

though the main impact is on the number of operators to manage the process. A decrease is observed from 3.5 to 2.8 and 2.0 operators per shift for the batch, continuous-batch, and PSD scenarios, respectively. An overview of the assumption is presented in Table 1.

The economical results show a gain of 10% for the continuous-batch scenario and a further gain of 6% (total 16%) for the PSD option (Table 1). At first glance these results may look meagre, but it must be understood that the reaction cost is mainly driven by yield (intermediate close to the API), and the gain in yield is only 5% for this example. The importance of yield is also appreciated by the large fraction of starting material cost (76%) on the overall cost. Any gain in yield has a direct impact on these costs. Moreover, the results also show that the gain in productivity (higher throughput and less manpower) has an impact on the cost (10% for continuous-batch versus 16% for PSD). Nevertheless, the fine chemical industry relies on complex production processes where downstream operations (workup) also play a critical role on the overall cost.

Figures 4 and 5 show the sensitivity analysis for yield and throughput on the relative production cost. It is observed that yield has a larger effect on cost than throughput (the slope is more pronounced with yield). As mentioned earlier, it is explained by the large cost contribution from the starting material since the intermediate product lies closer to the API than the raw materials. For an intermediate at the beginning of the synthetic sequence, this situation may be reversed, and in such a case throughput, productivity, and concentration would become the critical cost factors of the process. In this particular case, throughput has a physical maximum as distillation is the bottleneck at a certain point. In some cases a higher yield could also mean a less tedious workup procedure that further reduces the costs; however, in this particular case we assumed a constant effect of yield on workup.

Drivers for Process Development. The situation is different in process development as "speed" is now the predominant factor; although factors such as yield and product quality remain

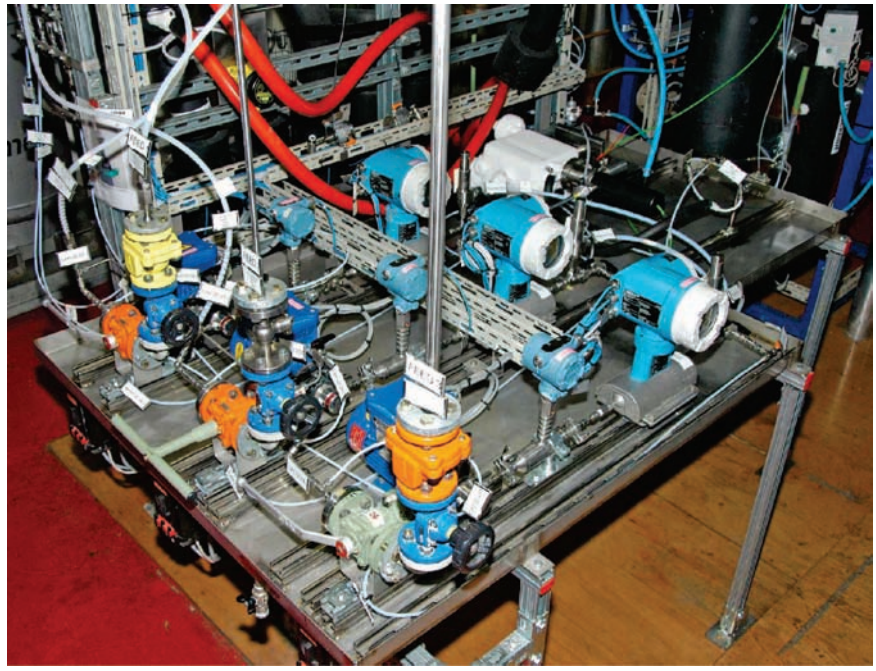

Figure 8. **Lonza new continuous small-scale plant (c-SSP) for the production of fine chemicals in process development.**

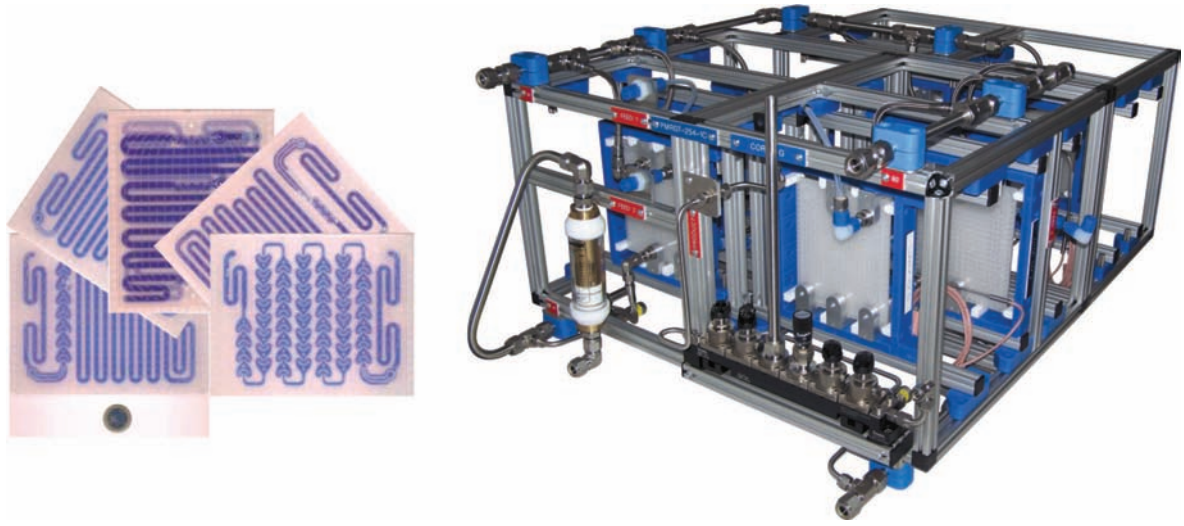

Figure 9. **Corning individual glass microstructures and reactor setup containing three reactor modules to perform reactions in series in the context of pilot to industrial production in process development.**[6]

important. Microreactor technology and continuous processes however play a vital role on three main features of speed namely:

(a) It accelerates laboratory process development as flow systems behave as a high throughput screening apparatus.[7]

(b) It allows the development of scalable processes in the laboratory so that common scale-up issues are avoided.

(c) It allows an expeditious change-over and technology transfer to the plant.

In this context the use of a toolbox concept is of fundamental importance as it is not practical to develop specific microreactors for specific reactions.[14] From the rather low flow rate in process development (for example around 100 g/min) the toolbox will be predominantly based on microstructured elements.[15] Although the reaction is easily studied in a laboratory environment with a low flow rate, the accumulated quantity is important when operated over 24 h and can fulfill most of the needs in process development.[5] The development of this toolbox is schematised in Table 2 where one observes that the common batch procedure/steps are replaced by various modules in a continuous process. The microreactors for the different reaction types[9] are important, but one needs also to consider other modules such as the pumps, micro heat exchangers, and eventually the workup units.

Example 2 in Process Development. The three main advantages of speed in process development are well understood when located in their context through a real case example as depicted in Figure 6 for an organometallic reaction similar to the one previously presented. On the left-hand side of Figure 6 one observes the typical procedures/steps of a cryogenic 250 L

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reactor leading to a cycle time of 13 h. On the right-hand side one observes the typical modules that replace these procedures/steps such as the pumps, the micro and conventional heat exchangers, the reactor, and the manifold. By operating at a flow rate of 150 g/min in the microreactor over 24 h, it is possible to cope with the throughput of a 250 L batch reactor. The bottleneck in this case is the workup step so that the flow rate can be adjusted properly. In addition, this flow rate of 150 g/min is easily studied in the laboratory for a short period of time so that the scale-up impact can be assessed before any process transfer to the plant.

Figure 7 shows the same process implemented in the laboratory for a long-run study and kg production. The learnings are remarkable: it took 2 days to build the setup (expeditious change-over); the cleaning was performed with standard qualified kg-laboratory methods; the system was operated with a flow rate of up to 440 g/min with a combination of microreactor (first step at 150 g/min) and static mixer (second step at 440 g/min). It took 6 h to fill 6 × 35 L quench vessels in the kg-laboratory (laboratory next door), and 15 kg of isolated product were produced. The single drawback was the experience of plugging that could be managed with appropriate measures. Worth mentioning is the fact that the plugging took place in the second step, namely in the static mixing.

A paradox is clearly emerging from this example and is demystified in Figure 7. On one hand, the setup relies on high-tech reactor technology, while on the other hand, the setup depends on an archaic method to handle solutions and solvents. At this point it must be emphasized that this setup is not appropriate due to safety concerns as this quantity of solvent is in general not acceptable in a laboratory unless very constraining safety measures are employed. Clearly, under these conditions the bottleneck becomes the handling of solutions and solvents as well as the downstream operations (workup) in the kg-laboratory. Thus, intensified continuous processes will lead to a redesign or a new plant strategy in the fine chemical and pharmaceutical industry.

Finally, with modules no bigger than chocolate bars, one realizes the tremendous impact of process intensification and size reduction. This intensification leads directly to a faster change-over, enhanced safety, less demanding cleaning, lower reactor investment, higher flexibility, and less manpower. The aforementioned reaction was run at Lonza in the new continuous small-scale plant (c-SSP,[5] Figure 8) and nearly 700 kg of isolated product was produced using one single microreactor over a period of a few weeks. A gain of 9% manufacturing costs was achieved when compared to the "state of the art" batch process. Notwithstanding the problem associated with plugging, the gain could have been higher, up to 25%. Thus, microreactor technology has become a standard technology capable of producing the required quantity of product in process development at Lonza.

Conclusions

The driving forces for an implementation of continuous processes in the fine chemical and pharmaceutical industry are different, depending where the process is located: in process development, in commercial production driven by yield, and/or in commercial production driven by throughput/productivity (or both of them). This understanding has an impact on the needs of R&D and future technological development.

The necessity to increase throughput/productivity leads to the concept of process synthesis design (PSD). The development of different modules to perform the various batch procedures/steps is required not only for complex chemical reactions and workup/downstream operations but also for simple procedures such as aging and heat exchange. The complete integration of various intensified steps in series will lead to a new concept of the mini-plant where chemical engineering plays a more predominant role.

Production processes driven by yield will lead to the adoption of the "best reactor technology" for the key reaction of the process independent of the use of a microreactor. Examples of these technologies are simple static mixers, microreactors, spinning disk reactors, rotor stators, microwaves, etc. In this case the gain in yield and the resulting decrease in manufacturing cost can be calculated in relation to the capital expenditure for the new technology using net-present-value. The use of continuous processes will allow an easier integration of the best reactor technology and will be the main driving force to implement a new technology.

Continuous processes in process development will direct the design of a new plant concept to allow high flexibility in the context of intensified processes (Figure 9). The development of this plant will rely on microstructures as the typical flow rate through such structures is high and can easily accommodate the requested product quantity in process development. The small liquid holdup will enhance safety in this new plant environment. Initially, most of the effort will be concentrated in process development as the attrition rate is very high at that stage for a pharmaceutical product.

Is the revolution underway? The transformation of the fine chemical and pharmaceutical industry cannot rely solely on a few numbers of industrial players. The adoption needs to be generalized in the pharmaceutical industry, and the big players have to be involved. The recent press release from Novartis announcing a $65 million investment towards a Center for Continuous Manufacturing with MIT is for sure a big step in the right direction.

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