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Cost Analysis of a Commercial Manufacturing Process of a Fine Chemical using Micro Process Engineering

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Abstract

In the last years micro process engineering was developed rapidly and commercial interest has raised. While process intensification was demonstrated, the question remains if this novel technology can lead to economic profits. In this context, a cost analysis is performed here for an economically conducted fine chemical process of the customised chemical producer AzurChem GmbH, the formation of the 4-cyanophenylboronic acid, using the benefits of micro process technology supplied by IMM GmbH. This process is representative for several other fine and specialty chemical manufacturing processes proprietary to the AzurChem GmbH. This is the first time that a cost analysis is made accessible in open literature for a commercial chemical product made by micro process engineering, i.e. for a real-case scenario with validated data base, i.e. real yields, micro-chemical plant, chemical and operator costs. The conclusions from the particular case given here are extended to more general statements on the micro processing of the whole class of high-value fine chemicals. This is achieved via some potential case scenarios of conceivable improvements by means of capacity or selectivity increases and a comparison with a traditional manufacturing method based on batch processing. In this way, some fundamental issues on the suitability of this novel technology are revealed, i.e. how process intensification translates into business drivers.

Keywords

Cost analysis, microstructured reactor, micro reactor, micro process engineering, 4-cyanophenylboronic acid
1. Introduction

There is now overwhelming evidence that microstructured reactors and micro process engineering are highly promising valuable novel tools and processing approaches to enable process intensification, shared with further reactor and process engineering advantages such as process safety, legislation, or modularity. Industry currently implements these new ideas into business. Most industrial studies, if being published at all, relate to pilot studies, touching upon the engineering applicability of micro process engineering. Recent statements of industrial leaders and magazine reviews leave hardly any doubt anymore that the technology is going to be used [1,2]. This intrinsically implies that there are business drivers for doing so and that cost analyses were performed internally in the chemical industry. With two exceptions, however, such knowledge is not disclosed. One of these is a study from the fine chemical and pharmaceutical company Lonza, Visp/Switzerland detailing on capital (CAPEX) and operational (OPEX) costs for several pilot micro-chemical processes [3]. No advantages for the CAPEX costs were determined, because the microstructured reactors were as or more costly than the equipment routinely used, which are glass-lined vessels with impellers. In turn, the OPEX costs were significantly improved and this was specified to the different portions such as labour, plant costs, QA/QC, waste treatment, transport & logistics, and change over & cleaning. Overall, it is stated that the OPEX improvement outpaced the additional CAPEX costs, but the ratio between the gains and additional costs was not given and thus no net profit can be deduced [3]. Merck Company, Darmstadt/Germany made together with Technical University Clausthal a four-staged potential analysis, which started with a technological evaluation (theoretical and technical potential) to come finally to a business view (material and economical potential) [4]. For the latter, data on profitability and amortisation time were given. A conclusion, if the micro-chemical process is better than conventional routes and if it will be applied is not given. The chemical process investigated was the nitration to the 3-
methyl-4-amido-5-nitro benzoic acid ester. Besides these two reports, a German project (µVTGuide, funded by BMBF, [5]) has been started where the chemistry organisation Dechema and the chemical company BASF are going to evaluate the potential of chemical micro process engineering based on BASF’s widely developed eco-efficiency analysis [6]. Jena University has applied life-cycle assessment analysis (LCA, [7]) to a micro-chemical process, the Li-based synthesis of m-anisaldehyde from n-bromoanisole, at laboratory scale [8] and recently reported on the same investigation for the production scale for the same process [9]. Benefits in terms of cumulative energy demand (CED) as well as green house effect, acidity and toxicity potentials were outlined [8]. An exergy analysis (see [10-12]) was made for microstructured fuel processor technology [13] and a generic benchmarking of microstructured catalytic reactors [14] was given, with the catalyst and overall reactor volume as the figures of merit.

Thus, the investigation of the economic potential of chemical micro processing has been started. However, a generic view is still missing, i.e. which type of microstructured reactors and which type of plants are suited for which type of chemical processing and what are the key figures to optimise micro-chemical processes. Since micro process technology is for many reasons still far away from the daily’s experience of industry’s process engineers, the performance of a generic cost analysis at this point of development is not simply the mechanical repetition of the same automatism for conventional chemical processes (see e.g. [15] for the cost analysis method); it rather gives scientific insight how applied developments should orient on in future.

Moreover, a cost analysis for micro chemical processing is performed here for the first time based on a commercial process and product, while the above mentioned studies refer to pilot processes under further optimisation, as far as information is disclosed. The enterprise AzurChem GmbH, a spin-off of the Institut für Mikrotechnik Mainz GmbH (IMM), produces
and sells fine and specialty chemicals, manufactured with own and IMM hardware, for researchers, developers and producers in chemistry and biotechnology.

In the following, a cost analysis was done regarding a real existing process and the results were then compared with some scenarios which base on different and partly virtual assumptions.

2. Cost Calculation Methodology, Chemical Process, and Case Studies

2.1. Cost calculation data base and shares considered

Significant revenue shares for fine-chemical plants refer to raw-material supply, waste disposal, operator salaries, and finally the investment of the plant itself. Accordingly, the cost analysis includes both fixed costs and variable costs, roughly corresponding to the CAPEX and OPEX costs, respectively.

2.1.1. Variable costs

The variable costs include costs for reagents, the operator's salary, energy consumption, and disposal. The cost figures for the reactant, the metallisation agent, the borate, the solvent and some adjuvant used as input for the calculation comply with the purchase prices of AzurChem GmbH for one production period, in which 10 kg 4-cyanophenylboronic acid are manufactured. For some scenarios these costs were adapted as described there.

For the calculation of the operator's salary it is assumed that the supervision of the continuous working reaction plant can be done in parallel to the purification steps of the crude 4-cyanophenylboronic acid that takes place batch-wise. In the case of the existing process the overall time allocation for plant operation is obtained from AzurChem GmbH, in the other cases it is following industrial practise as far as known from discussion with industrial processing and cost analysis experts via personal communications [16]. The salary used for the calculations is based on costs for skilled German personnel. Due to the small dimensions
the micro reaction plant can be started up and shut down in a short time. A daily working time of 8 hours, 5 days a week and 50 weeks per year is the base of the calculation.

The energy costs are mainly limited to the electric power consumption of the thermostats and the pumps. Average energy costs of 0.25 €/kWh are used in the cost analysis. Disposal costs for the waste, especially for the halogen containing solvent, base on the amount specific costs AzurChem GmbH has to pay. In a second step all the determined variable costs were related to 1 kg of the purified and saleable product.

2.1.2. **Fixed Costs**

The method used is a simplified analysis of fixed costs absorption.

**Product Related Fixed Costs**

The equipment costs encompass both the existing micro reaction plant according to figure 1, including 3 microstructured reactors, 4 pumps, valves and piping, measurement and control technology, cryostat and installation costs and the necessary devices for the purification, e.g. a distillation unit. These costs had to be divided by the depreciable life and then are summarised with the annual maintenance costs and the annual costs for premises. Based on the fact that premises costs only have a marginal effect on the product related fixed costs they were obtained from estimated costs of 300 € for a laboratory per year and square meter multiplied with the required 3 m² floor space for micro reactor processing.

In accordance with AzurChem GmbH's practice an amortisation period of 5 years was assumed.

**Remaining Fixed Costs**
Including of the remaining fixed costs is necessary to cover costs which arise for a company independent from the relation to a specific product. The remaining fixed costs include administration costs, costs for offices and sales activities, for instance. In the case considered here such costs are unknown in detail, but as a realistic approach an overhead in terms of 50% of the variable and product related fixed costs was added.

2.2. Chemical reaction investigated

Boronic acids are used as intermediates for the synthesis of pharmaceuticals and fine chemicals, e.g. for Suzuki couplings. High-value boronic acids are within the product portfolio of AzurChem GmbH besides other precious fine chemicals. As representative of this class of chemical intermediates, the manufacturing process of the 4-cyanophenylboronic acid (1) was chosen to be investigated.

\[
\text{Reactant + metallisation agent + } R-O \quad B-O-R \rightarrow \quad \text{HO-B} \quad \text{HO-N}
\]

One key feature of reaction (1) is the high price of the raw materials and respectively of the chemical product 4-cyanophenylboronic acid; therefore the process is characterised in the following as dominated by the high-value raw materials.
2.3. Process Flow and Plant

Fig. 1: Simplified flow sheet of the reaction plant

Figure 1 shows a basic flow sheet of the investigated synthesis process and the used continuous working micro reaction plant. Four pumps deliver the three reactants and the quenching substance. The main reactant is primarily solved in a certain amount of a solvent and reacts with a metallisation agent in microstructured reactor A. Afterwards the resulting product reacts with a borate in microstructured reactor B mainly to the final product 4-cyanophenylboronic acid. Both reactors are immersed in a thermostatic bath. In a last step the reaction is quenched by hydrolysis in micro reactor C. The subsequent purification steps like distillation are performed batch-wise.

2.4. Choice of case studies

Microstructured reactors may improve selectivity and in this way reduce the costs for chemical starting materials, waste disposal, and energy [17]. This sometimes can be achieved by simply transferring a batch protocol into a continuous-flow micro reactor operation with increased mass and heat transfer and kinetically-derived (shorter) residence times. The latter may also impact the operator costs. In many other cases, however, the simple repetition of batch processing protocols is not enough, but rather process intensification demands for new
tailored protocols for chemical micro process engineering, termed ‘novel chemistry’ [18]. Both cases are considered here.

A virtual case for achieving higher selectivity was added. An improvement gap of 20% was added, based on reported selectivity achievements of Clariant [19] and Merck [20] Companies for organometallic reactions.

One prominent scale-out concept for microstructured reactors is ‘numbering-up’ (see e.g. [17]). Here, the concept of external numbering-up of 10 microdevices in parallel was considered, being a realistic number based on our expertise. Therefore, such virtual case was added to the cost analysis.

Another scale-out concept is the ‘smart dimensioning’, i.e. a small increase in characteristic internal dimensions without loosing performance [21]. This is practised especially for mixer-reactors using many grouped-class devices, dedicated to IMM’s chemical processing concepts. The same, however, can be done by process intensification via ‘novel chemistry’ [18]). In this way, order-of-magnitude changes in productivity are achieved (see reported examples, e.g., in [17, 18, 22-25]) which, respectively, also may decrease the plant size per given production rate, targeting the operator salaries and the plant investments. This is achieved by not only exploiting the engineering potential of microstructured reactors, but by using the latter to utilize essentially ‘novel organic chemistry’ – e.g. at high temperatures combined with high pressures combined with very short residence times [18]. Again, such virtual case was considered in two variants, assuming 5- and 10-fold increases in productivity.

3. Results and Discussion

3.1. Cost Analysis of the Existing Micro-chemical Process

These calculations base on an average yield of the process of 75% which could be achieved, including not only the reaction yield but also the loss of the product within the purification process.
3.1.1. Cost Allocation of the Manufacturing Costs

Figure 2: Cost allocation of the existing process

Figure 2 emphasises the large share of variable costs amounting to 63% compared with the product related fixed costs which amount only 4%. This is caused by the use of high-value fine chemical raw materials and by the large share of operator costs for any chemical process (at least when based on German salary standards, as done here). The investment costs for micro process equipment thus cannot be a major decision driver in this case, whereas the importance of suitable micro process engineering (also for future process optimisation) is evident, affecting directly the variable costs. This is in accordance to other fine-chemical studies done by some of the investigators, used for internal purposes or to be published (see [26]), and thus seems to be general for fine-chemical syntheses with microstructured reactors. These studies also demonstrate that the costs of the microstructured reactors usually amount to less than 10% of the overall plant-related costs (not published here, see [26]), which go along with the costs of conventional plant engineering. Therefore, the microstructured reactor costs have nearly no relevance for the overall decision for or against this new technology, but rather their performance and reliability are main drivers (future studies may consider plant
breakdown). In this context, it has to be mentioned that the costs of today’s microstructured reactors and their plants may vary largely, as off-the-shelf devices encompassed within conventional balance-of-plant equipment to give retrofitted plants are opposed to customised, complex (e.g. highly integrated) devices within specialised peripherals and own-developed plant interconnection. The prices may vary by factor of ten and shift in this direction the product-related costs. The fraction of the remaining fixed costs here comprises one third of the total costs, which however is given by definition (see 2.2.2).

3.1.2. Variable Costs

![Variable Costs Pie Chart]

**Fig. 3: Breakdown of the variable costs of the existing process**

There are only two major constituents of the variable costs which represent together almost 98% (see Figure 3). The costs of the starting substances comprise 65.8% and the salary for the operator is 32.1%. This as a net result, as mentioned above, is in accordance with results of other cost analyses we carried out before [26]. However, the ratio between both cost portions is specific for the case considered here. Compared to the prior studies with average-priced fine chemicals this ratio was rather inverted owing to the processing of precious materials. Indeed, the manufacturing of high-value chemicals in relatively small amounts
requires a relevant operation effort. This also points out that it is economical to produce such materials with micro process technology even in countries with a high wage level. The small fractions of energy consumption and disposal costs show that the use of the micro reaction technology leads to a relatively low environmental impact.

As the cost analysis of the existing manufacturing process of the 4-cyanophenylboronic acid points out, this can be done with an earning when using a continuous working micro reaction plant.

3.2. Cost Analysis of a Virtual Batch Process

A direct comparison with a real existing batch process is not possible, since the synthesis route used in the micro reaction plant is not feasible in a batch reactor. For this reason a virtual batch reaction process was investigated using the same substances but with some reasonable assumed changes with respect to the micro-chemical process.

3.2.1. Cost Allocation of a Virtual Batch Process

![Cost Allocation](image)

![Variable Costs](image)

Fig. 4: Total cost allocation of a virtual batch process and shares of variable costs.

To produce the same amount of a product in a certain time a batch process needs larger equipment compared with a continuous one. The reason is that such a process usually
needs at least some hours and the reactor, feed vessels and receivers must be suited to contain the necessary amounts. A significant higher amount (calculated with factor two) of the solvent was assumed to be necessary to dissipate the reaction heat. As results the product related fixed costs fraction is in the factor of 1.5 higher compared with the existing micro-chemical process (see Figure 4).

3.2.2. Variable Costs

The higher necessary amounts of solvent lead to a doubling of the disposal costs fraction (see Figure 4). Furthermore, a batch process normally requires more attention of the operator, respectively more costly process control equipment. In the calculation used here this leads to manufacturing costs even a bit higher than the sales price AzurChem GmbH could get for its product.

3.3. Case Scenarios of Possibly Improvements and their Influence of the Manufacturing Costs

The motivation for selection of this and the following virtual case studies are given in 3.5 (see above). At first, capacity increase is considered. This can be reached by the so-called "external numbering-up", which means a multiplication of the microdevices themselves as well as by an enlargement of the internal dimensions in a certain range. Concerning the latter, IMM has developed families of microstructured devices by scaling up and down the internal dimensions and has established some correlations on their performance, e.g. concerning the mixing times (see e.g. [27] for the StarLam mixer series). Here, micron-sized dimensions are given within the microstructured reactors (‘micro-inside’), while the outer dimensions range from fist- to shoebox-size (and even approach the meter-scale in near future).
3.4. Microstructured Reactors with a Fivefold Higher Throughput

Fig. 5: Total cost allocation for 5-fold capacity and share of variable costs.

This scenario assumes an averaged 20% reduction of the purchase prices of the reagents, if a microstructured reactor with fivefold capacity would be used. Compared with the existing process no notable differences in the allocation of the manufacturing costs can be observed, which as to be expected due to very low contribution of the costs of equipment in general. However, regarding to the variable costs, changes in the ratio between the several portions are noted. While the operator's salary portion decreases from 32.1% to 19.5%, an increase of the portion of the reagent costs is given and correlated with this of the disposal costs as well.

3.5. Microstructured Reactors with a Tenfold Higher Throughput

Fig. 6: Total cost allocation with 10-fold capacity and variable costs.
In this case the reagents costs were calculated with an averaged reduction of 25% when converting a tenfold amount. A modification in the range of 2% lower product related fixed costs and higher variable costs owe to a further decrease of the operator's salary portion down to 12.6%. Conversely, the fractions of reagent costs and waste disposal rise to 81.1% and 6%, respectively.

3.6. Ten Microstructured Reactor Lines in Parallel

![Cost Allocation and Variable Costs](image)

**Fig. 7:** Total cost allocation for 10 microstructured reactor lines and variable costs.

The assumptions regarding to the reagent costs are the same as in the case of a tenfold reactor capacity. Since the tenfold multiplication of the micro reactor costs leads to significant higher investment costs it is not surprising to get a doubled factor of the product related fixed costs fraction compared with the existing plant. Assumed that the handling of ten reactor lines in parallel is about 30% more time-consuming than for a single one, the portion of the operator's salary is almost 3% higher compared with the tenfold capacity of only one micro reactor line.
3.7. Optimised Process with Higher Yield

**Fig. 8: Influence of the yield to costs and earnings**

The relevance of selectivity increase (to give higher yield) as one main motivation in process optimisation studies is investigated for the case studied here. In many practical cases, however, the manufacturing process for a product which is produced temporarily and in relative small amounts is only optimised to a certain extent for economic reasons. Further investigations thus depend on the trade-off between higher earnings and the costs of such investigations.

Selectivity improvements may result from the reaction itself or from lower loss during the purification. The influence of a 5% yield increase on the relation between costs and earnings is shown in Fig. 8. The change is about 3% which is ‘nice to have’, but normally does not justify cost intensive studies.
3.8. Comparison of Total Costs for all Scenarios - Profitability

**Fig. 9: Comparison of total cost for different case scenarios**

The total costs are highest for the virtual batch and amount to 133%, when levelling the total costs of the real micro-chemical process to 100% (see Figure 9). For the three different scenarios with increased capacity a dramatic decline in costs can be achieved. The total costs are reduced to one third (33%) for the micro-chemical process with fivefold capacity and further decline to 25% in the case of tenfold higher capacity, respectively. It is evident that both process intensification and numbering-up provide a practicable way to further increase profitability.

**Fig. 10: Influence of the plant scenario to costs and earnings**
A similar view is provided by the comparison of the ratios between manufacturing costs and earnings (see Figure 10). For all scenarios considered the theoretically attainable selling price was reduced in the same degree as the purchase prices were assumed. Under more realistic conditions of future competition, the selling price for such relatively large amounts of the product will probably even more fall. Similar to the results given in Figure 9, Figure 10 also highlights possible cost advantages by using microstructured reactors with higher throughput, presumed the produced amounts can be sold on the market.

3.9. Comparison of costs for investments (product related fix costs)

![Comparison of the product related fixed costs for different case scenarios](image)

**Fig. 11:** Comparison of costs for investments (product related fix costs)

The costs for the investments into equipment (microstructured reactors and balance-of-plant equipment) are small as compared to the total costs, as mentioned before. Nonetheless, since the purchase of this equipment is one of the first steps when entering process development and plant installation, the corresponding costs may impact the final decision in favour of or against the micro-chemical process. Figure 11 provides a comparison of the share of the product-related fix costs which relates to the absolute equipment costs. The equipment costs are normalised to the possible earnings and are also given as total costs normalised to 100% for the real-case scenario. It is evident that process intensification (having still only one
microstructured reactor) is a practicable way to reduce equipment costs. The earning-rated contribution declines to 2% and is the best option from the financial side, however, at the expense of further process development. Numbering-up increases equipment costs, but not in the same extent as the number of parallel operated microstructured reactors increase, only from 4% (‘real process’) to 6% (‘ten micro reactor lines in parallel’).

4. Summary and Conclusions

The cost analysis of the commercially applied manufacturing process for the fine chemical 4-cyanophenylboronic acid points out that an optimisation of operational (variable) costs is the key driver to develop a business perspective for micro process engineering. Two major trends are visible. The first relies on the synthesis high-value products from expensive raw materials and the process mentioned above falls into this category. Then, even the high operator costs, which otherwise dominate, are outpaced. The second strategy is based on reducing the operator costs by process intensification through micro process engineering as compared to the batch, which is also practised and will be reported elsewhere.

In both cases, the equipment costs (microstructured reactors and balance-of-plant equipment) have a low share. Thus, finally these costs should have minor impact on the decision to go for the novel technology, but rather the latter has to proof the expected process optimisation and reliability.

Where demanded, an increase of capacity by numbering-up, smart scale-out or further process intensification concepts helps to further reduce the overall costs of the processes (in the case considered here down to about 25%) and increases respectively the earnings. Thus, plants with microstructured reactors are more profitable when operated at larger scale, as their conventional counterparts.
Within the – certainly severe - limits of comparing a real-case micro-chemical and a virtual batch process, the respective cost comparison identified commercial advantages for the continuous synthesis in the micro reaction plant.

Finally, a cost analysis was analysed for a real-case fine chemical process based on micro process technology for the first time. The fact that the results show earnings by the new path and – even more convincing – that the product is actually sold, make evident that micro process engineering is for some cases a commercially viable processing alternative.

Fig. 12: Commercial product of AzurChem GmbH, 4-cyanophenylboronic acid

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