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Process Development and Production Concepts for the Manufacturing of Organic Fine Chemicals at LONZA

Golo Heckmann, Felix Previdoli, Thomas Riedel, David Ruppen, Dario Veghini*, and Uwe Zacher

Abstract: The constant improvement of efficiency in project development and manufacturing is an essential issue for companies operating in the organic fine chemicals field. Our strategy is based on the following concepts: (i) use of the whole high-technology portfolio available within the company, (ii) organisation of the process development in a process-oriented way, (iii) acceleration of the process transfer from laboratory to manufacturing scale by omitting intermediate piloting stages and (iv) maximisation of productivity by a flexible organisation of production units. How these concepts were implemented and which distribution of competencies within the R&D is needed, will be discussed in more detail in our contribution.

Keywords: Asynchronous production · Custom synthesis · Fine organic chemicals · Piloting · Reactive distillation

1. Introduction

The growing interest in process chemistry is well reflected by the large number of reports recently published. This interdisciplinary field of chemistry offers several challenges for both academia and industry. If process chemistry is the chemistry related to the process, then a chemist would interpret it as the efficient production of complex molecules in an industrial environment. On the other hand a colleague with a more engineering background would define it as the chemistry needed to generate an efficient production process. The truth is probably a combination of both points of view, with 'Efficiency' as the common denominator [1–5].

A CAS search of the item 'process chemistry' gave more than 180 hits, with about 100 of them being related to publications in the last six years. Most of these reports describe the need of increasing efficiency within the pharmaceutical industry, either by using technologies to improve process development, or by introducing novel production concepts. Examples are the use of microreactors [6–8] or the transfer of a process from a batch to a continuous operation mode [9].

The ISO-regulated environment, in which our Organic Fine Chemicals division is active, suffered the competition from low-cost countries earlier than the pharmaceutical industry. Notably, our market sector is dominated by the product price, and therefore production costs are the most important issue (at equal quality and reliability level, which are assumed to be given). The companies facing this challenging situation reacted with strategies based on offering a high-technology and large technological portfolio. This must be combined with higher efficiency during the whole project.

The process development approach we implemented is based on three fundamental concepts:

(i) the process research and development (PR&D) activity is organised in a technical-chemical integrated way, thus the team operates process-oriented rather than chemistry-oriented;
(ii) intermediate scale-up stages (piloting) are omitted, therefore the process fine-tuning is directly performed in the plant, and
(iii) production units are built and structured in a non-conventional way to maximise productivity.

In the following we cover these three issues in more detail.

2. Integrated Technical-Chemical Approach

The older colleagues in our department recall the way how a chemist used to transfer a process to chemical engineers: "…give me a laboratory procedure to produce 100 g and I'll scale it up to 100 t". At that time the chemist had to develop a laboratory procedure and after that supply a research report to the development unit. This unit would then transform the laboratory procedure into a production process. About 15 years ago this approach started to change. Nowadays an interdisciplinary team, working with a strong focus on the process rather than on the chemistry, accompanies the process development until the first production campaign.

An example of the relative distribution of work forces along the different phases of a project recently developed is shown in Fig. 1. The development costs over time are depicted for the four classes of competences: synthetic chemistry, process engineering (reaction technology, separation process engineering), project engineering (plant adaptation) and analytical chemistry. The technical evaluation of the project was based on a laboratory-scale technology package, which was provided by the customer. The task was to transfer the seven chemical steps (>40 unit operations) to the

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**Correspondence*: D. Veghini
New Business Development
Organic Fine Chemicals
LONZA AG
CH-3930 Visp
Tel: +41 27 948 6448
Fax: +41 27 947 6448
E-Mail: dario.veghini@lonza.com

suitable production units within fourteen months. Production scale was a few tens of tons.

The process fit to the production units started just after a three months technical evaluation phase. The required plant adaptations were implemented after eight months, while the first production batch of the first step was completed after twelve months. In the evaluation phase synthetic chemists and project engineers were equally involved, while the activity of process engineering became important from the very beginning of the project. It is noticeable that the chemists' activity is very well balanced with process engineers' along the whole project.

In our projects we observe an averaged ratio of work forces of 45:40:15 for synthetic chemists, process engineers and analytical chemists. Notably this distribution only slightly depends on the technical information available at the beginning of the project, while the absolute effort is directly proportional to the information initially available.

We believe that this is an important point: when process chemistry is approached in a production-oriented way, then the composition of the team needed for PR&D is independent of the development stage of the process. For this reason our R&D department itself has the analogous distribution of competencies that we need in our projects, *i.e.* 2:2:1 (for synthetic chemists, process and project engineers and analytical chemists). This strong presence of engineering competence is necessary to find the best fit between synthetic pathways and available plants.

In such an integrated approach the chemical steps are replaced by unit operations. Hence, a process is treated like a sequence of unit operations rather than a sequence of chemical steps. Therefore, from the point of view of a 'process designer', the filtration of a very fine ruthenium oxide powder at elevated temperatures receives the same degree of attention in a given development phase as the improvement of the reaction yield.

Two examples for production-oriented process development from our recent activities are given here below.

2.1. *Development of a Reaction Concept Using DSC: Synthesis of Quats*

Quaternary ammonium salts like $[NMe_3(CH_2Ph)]Cl$ are well-established biocides produced in thousands of tons per year. They are usually prepared by the interaction of trimethylamine with alkylhalides (benzylchloride in this case) at moderate temperatures in a batch process. At high temperatures these reactions are fast enough to make a continuous operation mode attractive. However, under these conditions the product starts to decompose.

In course of a process improvement program we recently reviewed the efficiency of this process for a series of products. The current processes for more than 20 products take place in a multi-product plant environment using small to moderately sized batch vessels. A batch operation mode has usually higher personnel costs and, particularly in large batch vessels, less efficient heat transfer than a continuous process. On the other hand it guarantees the flexibility for product switch and a better control of product quality. The goal of the project was to increase the production capacity, either by using larger vessels than the ones currently used or by transferring the batch processes into a continuous operation.

The efficiency of a continuous process is very much related to its kinetic and thermodynamic properties. Our approach to evaluate the best operation mode for the benzylammonium salt was first to measure kinetics by DSC and then to calculate the necessary hold-up volume needed. Since literature data were available only for analogous systems, the data required had to be first estimated and then measured experimentally.

From analogous literature data we estimated a reaction enthalpy of –120 kJ/mol, an adiabatic temperature increase of 60 °C and a reaction rate constant of $6.1 \cdot 10^{-03}$ l/(mol.s) at $T_R = 95$ °C. On the basis of these values one can estimate a hold-up volume of 13.6 m^3 [10].

A DSC-experiment was performed using 10.66 mg of a starting material mix heated up with a constant rate of 4 °C/min (range 0–400 °C), while the heat flow over time *vs.* temperature was measured. The resulting curve is shown in Fig. 2.

The exothermic peak around +80 °C represents the quaternisation reaction to full conversion while the second peak centred at +340 °C indicates the decomposition of the product. The measured reaction enthalpy was in line with the estimated value (110 *vs.* 120 kJ/mol).

As the volume related heat flow q_v at a given time respectively temperature can be described with

$$q_v (t) = k(t) \cdot c(t)_{Amine} \cdot c(t)_{Educt2} \cdot \Delta H_R$$

the rate constant k could be calculated.

The conversion could be determined by integrating the heat release, with the full area corresponding to 100% conversion. An Arrhenius plot (ln k over 1/T) was generated by using a set of values. For a reaction temperature of 95 °C a rate constant of $1.14 \cdot E^{-02}$ l/(mol.s) was obtained (*cfr.* with estimated $6.10 \cdot E^{-03}$ l/(mol.s)). For a continuous production of this slow process we calculated that a reactor volume of 7.3 m^3 would be required.

Taking into consideration the frequent products change-over, such a large hold-up volume is not at all convenient (more than 20 analogous products are produced in the plant). For this reason the continuous operation model was disregarded in favour

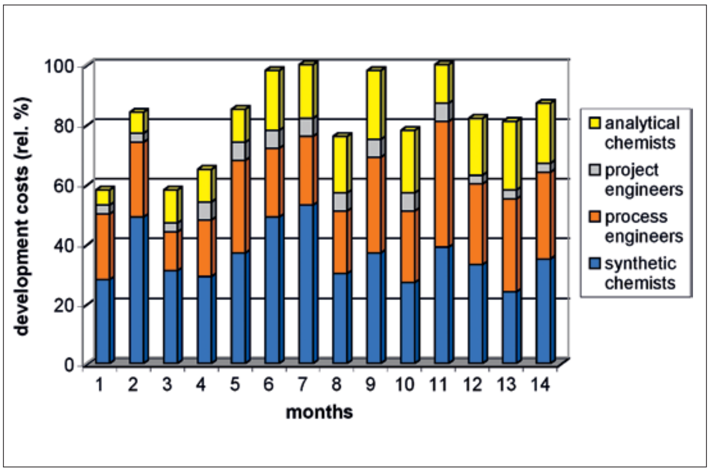


Fig. 1. Typical distribution of work forces up to the first production campaign

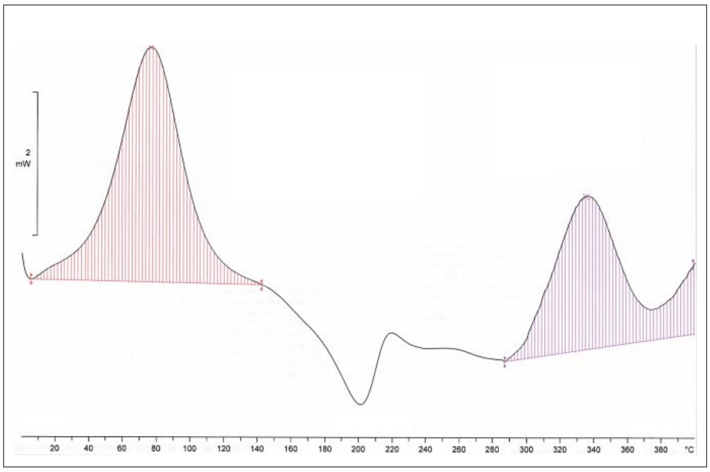
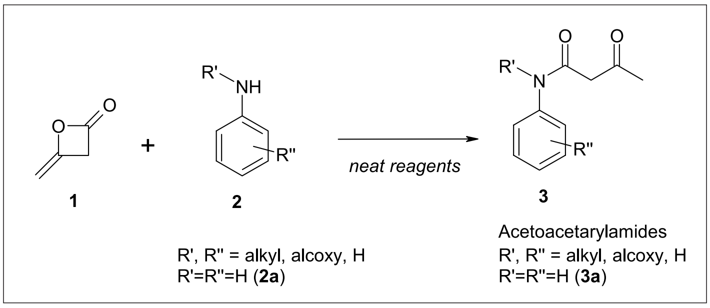


Fig. 2. DSC-dagram for the quaternistion reaction of trimethylamine with benzylchloride

of a large vessel batch concept. The moderate enthalpy values related to this process, together with the slow kinetics, show that thermal control in a large vessels batch process is definitely possible.

2.2. *Development of a Novel Continuous Process for Acetoacetarylamides*

Acetoacetarylamides of the general formula **3** are important starting materials for the preparation of coloured pigments and agrochemicals. They are manufactured in thousands of tons worldwide by reacting diketene with aromatic amines in a variety of solvents. The down-stream processing includes completely batchwise operated crystallization, solid–liquid separation and drying (Scheme).



Scheme. Preparation of acetoacetarylamides

Due to the strong exothermic reaction, diketene (**1**) has to be slowly added to a solution of aniline (**2a**) in an appropriate solvent. Batch cycle times of several hours are required to crystallize the product **3a**, separate the crystalline material from mother liquor by centrifugation and remove residual solvent by vacuum drying. The analysis of the process costs distribution revealed that major improvements could be achieved by reducing the unit operations and improving productivity. This was realised by switching the operation mode from batch to continuous by a Loop Reactor and a Reactive Distillation Technology [11–12].

Both novel continuous technologies offer following advantages:

(i) a reduced number of unit operations (4 *vs.* 6) by removing the crystallisation and the separation steps;
(ii) a higher assets utilisation (20 *vs.* 0.3 $t/m^3/d$) leading to increased capacity and lower investments for a new plant;
(iii) reduced personnel costs due to an automated continuous instead of batchwise operation mode; and
(iv) omitting the use of solvents by performing the reaction in neat reagents.

The two new process technologies are briefly described below.

2.2.1. *Loop Reactor Technology*

Diketene and aniline are simultaneously fed into a loop reactor, in which water circulates at high velocity. In this environment, droplets of diketene and aniline, interacting with each other, behave like well-mixed microreactors. The heat of reaction is efficiently transferred to the surrounding water phase. Under a nearly quantitative conversion, the low boiling impurities are removed from the top of the stripping column and equilibrium is reached in the final separation tank. The high boiling phase containing **3a** is transferred from the bottom of the tank to a cooled steel band where it immediately solidifies to flakes. The aqueous phase is recovered through a heat exchanger into the circulation loop. The simplified process is illustrated in Fig. 3.

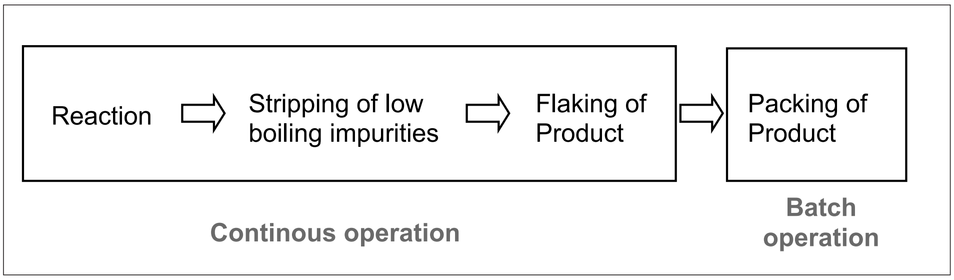


Fig. 3. Process production scheme for **3a**

The quality of the final product depends on the quality of the starting materials, the reaction rate and accurate control of feed rates. An important additional benefit derives from the partial solubility of water in the product melt (~5–15%). This lowers significantly the melting point of the mixture (thus the reaction temperature), inducing less thermal stress on the product and enhancing selectivity.

2.2.2. *Reactive Distillation Technology*

The key issue to be addressed was the removal of the large amount of energy that is generated in the reaction step. This problem was elegantly solved by introducing water into the system. Under these reaction conditions the water evaporates and efficiently removes the reaction heat.

In the set-up depicted in Fig. 4, a tray distillation column is operated under reflux and reduced pressure, while aniline is continuously fed into the column head. Aniline, being the high boiler, migrates down the column interacting with diketene, which is fed a few stages above the bottom. In this configuration, the diketene/water azeotropic mixture migrates towards the top of the column. The reaction of aniline and diketene takes place in the mixing zone, thus in the centre of the column. The high-boiling product **3a** finally leaves from the bottom as a single melt phase. On a flaker it solidifies in analogy to the loop reactor process.

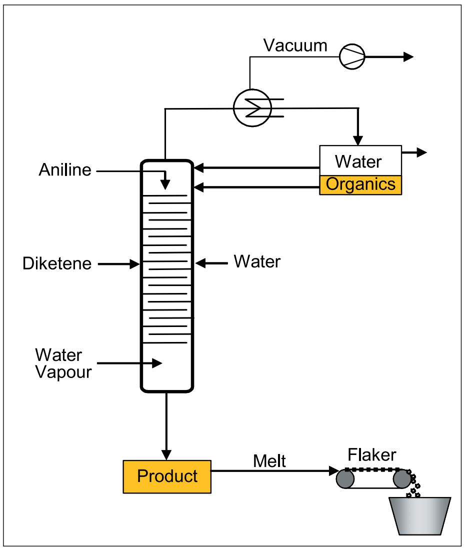


Fig. 4. Manufacturing process for the synthesis of **3a** by reactive distillation

Experiments in a pilot unit generated product with high purity (99.8% in case of **3a**) and excellent starting material balance (<3% loss of diketene by hydrolysis). This reactive distillation technology could be extended with success to other acetoacetarylamides of type **3** under different process conditions.

3. Intermediate Scale-up Stages and Production Concept

3.1. *Omitting Intermediate Scale-up Stages is Possible*

In the ISO-regulated custom manufacturing business it is important to accelerate the transfer of the process from the laboratory to the production units, thus from 1 l to 10'000 l scale. Intermediate scale-up may be useful for improving unit operations, whose sensitivity to a change in the surface/volume ratio cannot be rationalized properly in laboratory experiments. On the other hand the amount of information obtained from piloting campaigns rarely justifies the time and resources needed for this. Therefore, we prefer to study the process sensitivity in laboratory scale intensively enough to be able to omit this intermediate step. It should be noticed that the shift from the lab to the pilot plant (1 l to 600 l = 1:600) is a larger step than going from the pilot plant to the production units (600 l to 10'000 l = 1:15). Within the boundaries defined by the process risk analysis, an efficient batch-to-batch analysis allows parameter optimisation directly on the production unit. The process chemistry necessary for the scale-up transfer must therefore include a robustness study.

3.2. *Non-classical Production Concept for a Multi-purpose Plant*

In order to manage a diversified product portfolio, a multi-purpose plant must have a large degree of flexibility in using its technical competencies. In our recently built multi-purpose plant this is realised by implementation of a number of non-classical production concepts. The first important element is a wide ranging coupling station (Fig. 5), where almost all the equipment (reaction vessels, work-up equipment, and storage tanks) can be connected with each other. Using this set-up the plant equipment can be easily adapted to changing process requirements. A buffer tank volume of 300 m^3 for a total reactor vessel volume of 70 m^3 supports this strategy. This large operational storage tank volume, in combination with the flexible coupling station, allows the asynchronous operation of the different production units. Using this production concept the batch identity is lost, but the throughput for each single unit operation can be optimised efficiently.

A further important element is the fixed lines network concept. The plant is connected by fixed lines to

(i) other plants nearby, allowing the utilisation of additional equipment or special technical competencies (*e.g.* high pressure hydrogenation),
(ii) the waste treatment plants, allowing the direct disposal of gaseous and liquid waste streams and
(iii) logistic facilities.

Fig. 5. Coupling station in the E13 multi purpose plant

Since handling of corrosive media is often required, around half of the equipment is glass-lined.

A plant structured this way allows an effective batch-to-batch optimisation and therefore helps to increase productivity. Further important elements required to reach the target efficiency are on-line data recording and the application of suitable analytical methods. The optimisation of the speed, accuracy and volume of the data analysed help quickly to identify and subsequently eliminate the bottlenecks of the process.

By using the plant and manufacturing concept described, a process originally developed for a total reaction volume of >200 m^3 could be fitted into the 70 m^3 of the multi-purpose plant and operated at the same productivity level.

4. Conclusions

The strong price pressure from low-cost countries in the last decade has induced a series of structural and strategic changes in the development of chemical processes and the manufacturing of the respective products. Nowadays, the key issues for a Western custom manufacturer can be summarised as: process orientation in PR&D, maximisation of productivity in manufacturing and speed. A production-oriented PR&D team consists of engineers, chemists and analytical chemists in a ratio of 2:2:1. This ratio is independent of the initial technical information available. The maximisation of productivity can be obtained in every single production unit using an asynchronous operation mode. In this case the batch identity is lost and the plant efficiency is maximised. Speed means directly transferring the process from laboratory to the manufacturing units taking into consideration all safety issues. An important part of the process optimisation is performed directly batch-to-batch in the production plant.

Although the industrial approach to innovation is necessarily very pragmatic, a few novel technologies show a real industrial potential. Those which we are actively following are the immobilization of homogeneous catalysts in different solution phases or on a solid support, the use of membrane technologies for catalyst/products separations, the use of supercritical fluids as reaction media and the use of microreactors for specific applications. Our innovation strategy relies on the identification of the technology leaders in a specific field of interest. In a closer cooperation the know-how concerning the products is merged with the know-how concerning the technology of the academic or industrial partner. We believe that this approach may bring these technologies out of the 'alternative' into the 'more efficient technology' field.

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