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Conference Report

12. Freiburger Symposium 2015: Smart Solutions in the Chemical Process & Product Development – Case Studies from the Chemical Industry

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Introduction

Am 23. und 24. April 2015 fand das 12. Freiburger Symposium – organisiert von der Division für Industrielle und Angewandte Chemie der SCG – an der Hochschule für Technik und Architektur in Freiburg statt. Die Veranstaltung wurde unter dem Thema 'Smart Solutions in the Chemical Process and Product Development – Case Studies from the Chemical Industry' ausgerichtet und zeigte in insgesamt 13 Vorträgen das breite Spektrum der chemischen industriellen Entwicklung und Produktion. Einen Schwerpunkt des Programms bildeten Themen aus dem Bereich des Downstream Processing wie z. B. Milling und die Rückgewinnung von Brom als Abfallstrom. Als besondere Highlights konnten die Sandmeyer Award Lectures der Preisträger von 2014 und 2015 sowie eine Key Note Lecture von Lonza-CEO Richard Ridinger zur Entwicklung der chemischen Industrie in der Schweiz präsentiert werden. Insgesamt war die Veranstaltung ein voller Erfolg. Wir bedanken uns ganz herzlich bei unseren Referenten und präsentieren Ihnen hiermit die Abstracts der Vorträge des diesjährigen Symposiums.

The 12th Freiburger Symposium organized by the Division of Industrial and Applied Chemistry of the Swiss Chemical Society took place on April 23rd and 24th 2015 at the School of Engineering and Architecture in Fribourg, Switzerland. The event was held on the topic 'Smart Solutions in the Chemical Process and Product Development – Case Studies from the Chemical Industry' and demonstrated with overall 13 lectures the broad spectra of chemical industrial development and production. Especially the area of downstream processing, a focus topic within the program, was presented impressively by lectures about milling technologies or bromine waste recycling. Special highlights were the two Sandmeyer Award lectures from 2014 and 2015 and the key note lecture of Lonza's CEO Richard Ridinger who presented his thoughts about the future of the chemical industry in Switzerland. Overall, the symposium was a great success and we would like to thank all lecturers sincerely for their contribution to this event. Therefore, we are now presenting the abstracts of the symposium's lectures of 2015.

1. Route Development and Pilot Plant Production of Novel Bacterial Topoisomerase Inhibitors

Dr. Stefan Abele, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland

Several routes for the manufacture of novel bacterial topoisomerase inhibitors (**1**, **2**)[1] at Actelion Pharmaceuticals Ltd are presented (Fig. 1). Whereas Route 1, comprising more than 30 chemical steps, was developed to rapidly manufacture the Active Pharmaceutical Ingredients (API) for first clinical studies, Route 2 was designed and developed to cut the cost of goods and remove severe impediments for larger scales.[2] The penultimate common intermediate, homobenzyl alcohol **3**, features a heterocyclic structure with three stereocenters and was built from fluoro-naphthyridines and a chiral tetrahydropyran. The two hetaryl carbaldehydes **4** and **5**, both manufactured in 5–7 steps, were introduced in the final step.

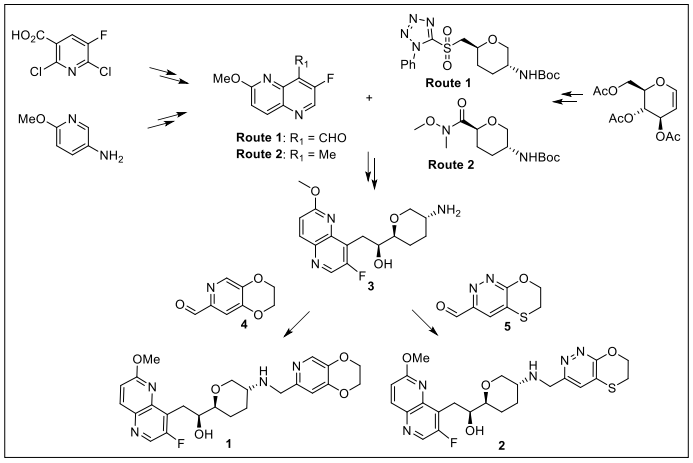


Fig. 1. Synopsis of the two routes to homobenzyl alcohol **3**, the pivotal intermediate for the manufacturing of the topoisomerase inhibitors **1** and **2**.

An optimized sequence of steps starting from tri-O-acetyl-D-glucal afforded the required tetrahydropyran building blocks. To mitigate the quality and safety risks of a high-temperature Overman rearrangement, a continuous flow application was developed and successfully used at 100-kg scale.

The fluoro-naphthyridines were either manufactured by starting from a fluorinated building block (Route 1) or by fluorinating an advanced intermediate (Route 2). More and more methods are emerging for the late-stage introduction of fluorine. However, once a route has to meet the stringent requirements for scale-up, the range of technologies is still restricted to fluorinations that have proven viable on very large scale, for example for the manufacturing of fluorinated heterocycles as raw materials in the fine chemicals or agrochemical industry. Amongst these, a modified Balz-Schiemann protocol and an unprecedented selective fluorination with fluorine gas have been most successful.

A major challenge was the synthesis of the homobenzylic alcohol **3** with full control of the stereochemistry. Route 1 features a Julia-Kocienski olefination followed by an asymmetric Sharpless

dihydroxylation to build up the homobenzylic chiral center. This approach was flawed by the use of toxic osmium, the need to remove the unnecessary benzylic hydroxyl group, and an overall unfavorable Process Mass Intensity (PMI). To prepare for larger scales, a diastereospecific reduction of the homobenzyl ketone precursor was chosen amongst many conceivable approaches: reduction with diisobutylaluminium hydride (DiBALH), used on ton scale as catalyst in the polyolefin industry gave rise to a surprisingly high diastereoselectivity.

[1] J.-P. Surivet, C. Zumbrunn, G. Rueedi, D. Bur, T. Bruyère, H. Locher, D. Ritz, P. Seiler, C. Kohl, E. A. Ertel, P. Hess, J.-C. Gauvin, A. Mirre, V. Kaegi, M. Dos Santos, S. Kraemer, M. Gaertner, J. Delers, M. Enderlin-Paput, M. Weiss, R. Sube, H. Hadana, W. Keck, C. Hubschwerlen, *J. Med. Chem.* **2015**, *58*, 927.
[2] a) WO/2013/118086; b) WO/2013/160875; c) WO/2012/164498; d) WO/2013/038374.

2. Continuous Improvement and Process Re-Design for Large-scale Insecticide Production

Dr. Anne-Laure Dessimoz, Syngenta Crop Protection Monthey SA, Monthey, Switzerland

Syngenta is a world-leading agri-business with more than 28,000 employees in some 90 countries. Monthey is one of the largest production sites worldwide. The site produces herbicides, fungicides and insecticides for the protection of the most important crops such as cotton, rice and corn.

CCT is the key intermediate in the synthesis of Syngenta's most important insecticide. The production process is based on the reaction between i-TCN and a chlorinating agent. In the old production process, the chlorination reaction was done with SO_2Cl_2 in a solvent.

A significant amount of laboratory & production optimization work was performed to improve this several thousand ton process in terms of:

Change of the synthetic route to a solvent-free process

The chemical process was intensified by performing the reaction with Cl_2 solvent free. This process redesign allowed an increase of the capacity and a decrease of the production costs. However, since the implementation of the new process, CCT quality is more difficult to control and maintain within specification. New by-products were detected in the final CCT that have a negative influence on the yield of the process.

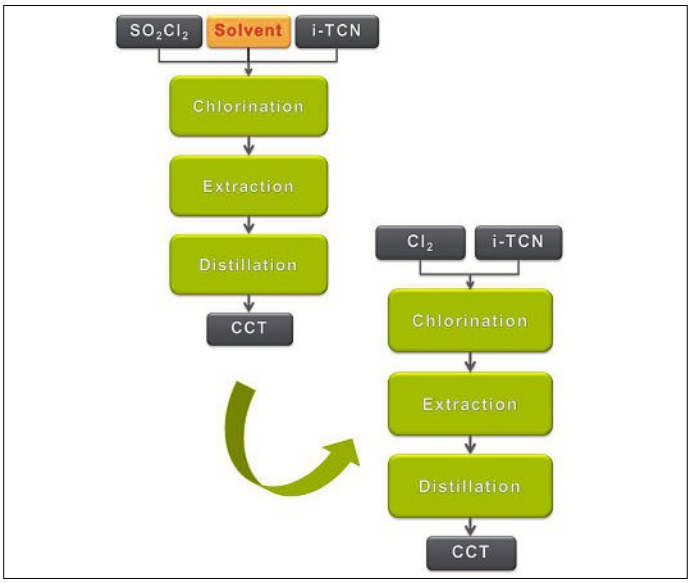


Fig. 1. Intensification of the chemical process.

Optimization of the yield through full understanding of the synthetic route to by-products

Laboratory development work was done to understand the complex mechanisms of the CCT process and improve the yield of the synthesis.

Precise scale-down of the synthesis reactor for development work

The study of the mass transfer performance has shown that there is an important difference between the laboratory and production scale, with the plant being approximately 6× higher than the lab.

The laboratory reactor was modified to better represent the full-scale process and support continuous improvement.

3. Opportunities and Challenges in Development and Scale-up of Continuous Chemical Manufacturing Processes at Novartis

Dr. Berthold Schenkel, Novartis Pharma Ltd, CH-4002 Basel, Switzerland

The pharma industry promotes Continuous Manufacturing as a way towards lean production processes, giving access to cheaper chemical synthesis and simultaneously reducing investment costs. New methodologies and technologies have to be developed and implemented in order to unleash the full potential of Continuous Manufacturing (CM). Intense internal and external R&D activities were started in Novartis in 2007 to reach these goals in the development and manufacturing of APIs (small molecules) for clinical and for market supply.

An analysis of the portfolio of chemical synthesis in development and in marketed product phases was performed to evaluate feasibility and benefits of CM. Expected benefits of CM are: improvement of yield and quality, new continuous reactions showing higher safety compared to batch (*e.g.* formation and immediate consumption of energetic intermediates), shorter synthesis routes or alternative synthesis routes with lower raw material costs and/or higher productivity. In the analysis of the portfolio the assumption was made that continuous reactions become feasible if the reaction time is shorter than 2 hours. Reactions containing solids were excluded in the study though technologies are available or in development which can overcome plugging in selected cases. Currently, 50% of the reactions in the portfolio are feasible for CM. 10% of the reactions show benefits in CM which was concluded from ongoing screening for CM opportunities in the portfolio and from experimental results. Advanced reactor and process designs, however, will increase the ratio of feasible reactions. In the same way, new reaction classes and new continuous synthesis strategies will increase the ratio of reactions with economic benefit. An analogous study was performed for the work-up of reaction masses: focusing work-up on standard continuous distillation and extraction processes as a direct replacement of the batch equivalent, a relative high ratio of work-up operations (51%) can be covered. However, only 17% of the entire processes consisted uniquely of these unit operations. Therefore, dedicated continuous work-up processes have to be developed focusing on economic extraction and distillation technologies, avoiding solids and minimizing number of crystallization steps by telescoping synthesis steps.

For the development of continuous processes in Novartis, lab equipment was designed with a broad throughput range of 1.5 to 150 g/h which is used in the development laboratories in early, late phase and life cycle management projects. A tailor-made, multipurpose pilot plant was designed and qualified for GMP

manufacturing of up to 15 t/a of APIs covering a broad range of flow reactors.

Equipment and applied methodologies for CM process development are presented. Key functions of the equipment for successful development in daily operation of flow laboratories are mixing of starting material, plug flow and heat transfer. Methods how to select commercial micro-mixers for fast reactions are described. It is shown how typical flow reactors such as tube reactors have to be operated in the labs to guarantee plug flow conditions for high reaction selectivity. Effects of limited heat transfer in micro-reactors are shown for highly exothermic reactions leading to non-isothermal conditions. In pilot and production scale thermal safety is a key element for the design of flow reactors in case of highly exothermic reactions. A method for the safe design and operation of flow reactors such as multi-tube static mixer reactors (SMRs) in production scale was worked out. The method allows to put together different types of SMR tubes according to the heat release profile of the exothermic reactions and to guarantee thermal robustness and safety according to Semenov and Frank-Kamenetzkii methods.

The drivers for selection and development in CM as well as the benefits are described by applied examples out of early, late phase and life cycle management projects:

In a first case, the large volume production of a highly expensive API was investigated. In particular the alkylation of a primary amine in the API moiety was followed by an undesired consecutive reaction to the corresponding tertiary amine. By-product formation could be suppressed by 10-fold excess of the nucleophile. Continuous manufacturing of the API combined with continuous recycling of the nucleophile in a highly efficient counter-current extraction process with minimal losses of the nucleophile allowed us to significantly reduce the production costs and justify the investment in a new continuous production plant.

Another driver for Continuous Manufacturing involves the poor robustness of a low temperature organolithium reaction when performed in batch mode. In this case a sequence of a metalation reaction, electrophile trapping to a benzoxazole followed by a continuous electrophilic addition and oxidation step was developed and successfully piloted. Systematic optimization of the very fast benzoxazole formation based on modelling and simulation of the reaction kinetics including by-product formation led to a significant improvement of the yield by 50% in a continuous reactor cascade.

In the third example the footprint of the production plant and reaction yield were the motivation for CM development in the manufacturing process of a valuable and large volume API. The reaction of an aryl-magnesiate and a lactam under turbulent conditions in a tube reactor showed strong benefits in CM compared to batch. Byproducts resulting from consecutive reactions could be successfully suppressed by ensuring plug flow conditions. Parallel reaction to an enolate was suppressed by fast mixing of the educts. The advantages in footprint and yield justify investment into a continuous plant. Two 10,000 L batch reactors (see vessel in background of 3D-drawing, Fig. 1) can be replaced by a 16 L tube reactor in CM (see below: tube reactor on left side of 3D-drawing).

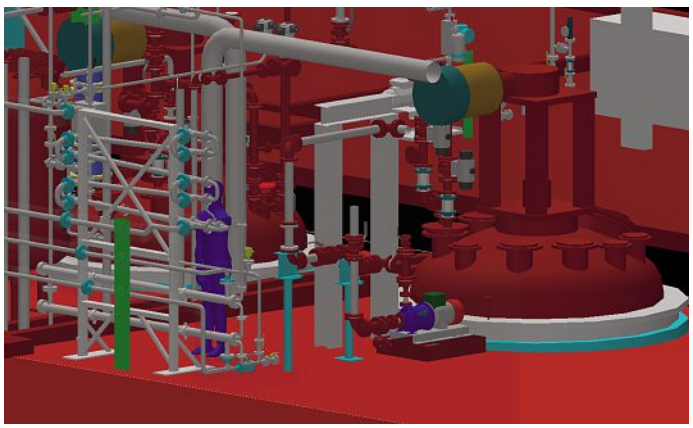


Fig. 1.

Currently the main objective in CM at Novartis is to launch in 2017 the production of an API *via* the so-called end-to-end approach. This strategy implies coupling of chemical manufacturing of an API with pharmaceutical manufacturing of the Drug Product in one continuous chain from chemical reagents to tablets. One candidate for this approach is presented including the final chemical step to API, salt formation and crystallization. In the reaction step an amine is activated with an organometallic reagent, followed by reaction with a carbonyl compound and hydrolysis. In the work-up steps metal hydroxides are removed by counter-current extraction followed by distillation to adjust the product solution to the right concentration for final salt formation and crystallization. Feasibility and robustness of the continuous process were shown in bench scale. As a result of this optimization work, processing time was reduced from 50 h to 6–10 h, and excellent overall yield of 88% and purity of 99.9% were achieved. The process would be a suitable candidate for implementation in the multipurpose CM Pilot and Production Plant of Novartis.

4. How to improve Production Capacity through Efficient Diagnostics

Dr. Gérard Gandillon, ***Daniel Claret***, PMAX, Saxon, Switzerland

PMAX is focused on:

- Optimization of industrial processes
- Electricity consumption savings
- Optimization of heating network, which means basically the optimization of steam distribution and energies consumption
- Performance improvement of cold production and heat pumps. The methodology is the same because one is the reverse process of the other.

Our approach is based on a very efficient technology. This methodology has been used in several areas of the industry with great successes: chemistry, mining, urban heat distribution, pharma, fruit distillation, *etc.*

The way we look at your processes is different from the regular process optimization usually in place in the industry.

It is an additional point of view which can raise different solutions from classical approaches.

It is a very systematic analysis which can often be driven in parallel to regular engineering work.

PMAX is able to adapt the detailed design of the process to the desired functionalities.

If we want to highlight the main characteristics of our approach, we can say that solutions we have found take into consideration:

- A better use of the in-place equipment
- A different way to use the regulations
- A more precise control of the parameters used to characterize the process
- An addition of elements or new connections to leverage the already existing pieces of equipment.

In our approach we always take into account a holistic approach, considering the process itself but also the interconnection with the way energies are produced or used.

In most of the cases we have seen strong synergies between

process and connected infrastructures, very often considered as side-problems.

One of our strengths is the fact that we can diagnose a process in a very short period of time.

For example, infrastructure examination of a simple process will take place in half a day, maximum one full day.

Multi-step processes take a bit longer to evaluate, typically one week.

This particularity reduces the delivery time of these diagnostics, which are very short compared to more classical investigations.

PMAX has acquired a strong experience in regulation problems.

To solve various problems and benefit the power of the industrial controller, PMAX has developed a unique and very robust algorithm which can be used:

- To collect all the relevant parameters
- To prevent drift of the process and alarm the operators
- To fine tune the regulation itself
- To consider all the actors in the process: from energies production to energies consumption, amended by the process itself in a very accurate manner.

PMAX can offer a large domain of competencies which are essential to face your problems. From physics to industrial production with always a very pragmatic approach.

PMAX is highly concerned to propose solutions with a rapid payback, typically half a year to 2–3 years.

Improvements suggested by PMAX are modular solutions and can be implemented according to: customer needs, customer purse, customer will or customer obligations.

PMAX is active for only 10 years but its contribution to energy savings reach now 15 GWh.

This has been achieved by industrial companies like Dupont, Ciba or Syngenta for example or by public communities.

Four examples are given:

Example 1: Large distillation of solvents

The overall results were the following.

The global savings were 230'000.–/year. With of course a reduction of CO_2 produced.

The mix of energies saved correspond to 2.3 GWh.

The total invest was 100'000.– which gives a pay-back of 5 months.

Example 2: Improvement of a classical synthesis

The second example comes from Monthey. The studied process was a classical synthesis.

Each of these steps revealed a different problem but all impacted the productivity.

The diagnostic was made in one week.

The overall optimization brought an increased capacity of 20% which is quite remarkable for a process run for many years.

Example 3: Crystallization

In this example we have shown improvement at different steps:

a) crystallization, with cycle time reduced by 50% by changing the cooling curve,
b) filtration, using elution of the rest of solvent instead of standard washing
c) drying, improvement of productivity by 28% by modifying the operation conditions

Example 4: Energy optimization

PMAX has developed an algorithm to increase the yield of heat pumps and cooling stations. This algorithm is worth installing if the pump or the cooling station has a power of more than 80–100 kW. If not, the payback of the algorithm implementation will be too long.

In these conditions, the payback is normally less than 2 years.

It is possible to place the algorithm on old or brand new heat pumps. We have done both.

The algorithm doesn't modify the intrinsic regulation of the compressor. It is an add-on which only collects the information of the system, compiles the information and gives orders to the compressor.

5. Development of a Heterogeneous Catalyzed Gas-phase Process for the Synthesis of Butenone

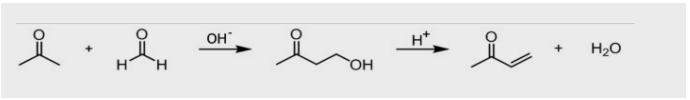
Dr. Martin Häfele, ***Ingolf Gummin***, DSM Nutritional Products, Lalden & Sisseln, Switzerland

DSM, founded in 1902, has transformed from a coal mining to a life and material science company. Its portfolio comprises a wide variety of products including vitamins, carotenoids, fragrances or PUFA's as well as high performance and bio-plastics. The company is a global player with some 21'400 employees. Vitamins are produced at the business group DSM Nutritional Products with approximately 2'000 employees working in Switzerland.

Butenone Synthesis

Butenone, an intermediate of the vitamin A process, is highly flammable, very toxic, environmentally harmful with a strong tendency for polymerization. It has strong tear gas characteristics as well.

Butenone is synthesized in two reaction steps *via* aldol condensation of acetone and formaldehyde.



Addition: base-catalyzed, continuous, in a tube reactor followed by purification

Elimination: acid-catalyzed, batchwise, in a reactor vessel followed by purification

The current process showed some fundamental drawbacks which are low yields, high energy consumption, corrosive waste streams to incineration as well as poorly degradable waste streams to wastewater treatment plant and formation of deposits causing a complete shutdown of the plant for cleaning purposes nearly all 2 months.

New Process

A completely new process design based on a heterogeneous catalyzed, one step gas phase reaction as key step solved these issues. Furthermore, the gas phase reaction provided a positive impact on the following work up as well.

The new process is characterized by three aspects:

- High temperature (T >350 °C) which results in direct condensation
- A low active SiO_2-catalyst with high selectivity to reduce parallel reaction
- A high ratio of acetone to formaldehyde to prevent consecutive reaction

Piloting

The Piloting was split in two steps – the continuous gas phase reaction including recycling of unreacted acetone and the purification to the final product (due to the fact that the mass flow rate

of the gas phase reaction was too low for a continuous rectification in mini-plant scale).

The piloting reactor consisted of one tube heated by melted salt with the dimension 2000 mm x ø30 mm. The reactor was operated at Bo = 800 with a pressure drop of p <0.5%. Later on, scale up trials were done at MAN DWE with a tube dimensioned on production scale (length 4000 mm x ø50 mm). Directly connected to the reactor was a rectification column to separate raw butenone from acetone and remaining formaldehyde. The acetone mixture was recirculated to the process. Raw butenone was worked up *via* low boiler and high boiler distillation in mini-plant scale. Further extraction and drying steps were carried out in the laboratory.

Next to process data experience especially with regard to polymerization issues could be gathered:

- Paraformaldehyde deposit formation at the evaporation step could be avoided by injection of aqueous formaldehyde solution into hot acetone gas flow (heat transfer *via* acetone molecules).
- Deposits of paraformaldehyde and butenone polymer at condensation steps of distillation units could be avoided by using falling film condenser technology with high recirculation.
- Polymerization of butenone in rectification columns could be reduced significantly by addition of a radical catcher and lower temperature which was achieved by vacuum distillation.

The key performance indicators of the new process were promising:

- Significantly increased selectivity towards butenone (> +30%),
- reduced waste streams (> -50%),
- reduced energy consumption (> -30%),
- polymerization issues under control.

Deactivation

Deactivation of the catalyst became evident during the trials. Conversion related to formaldehyde dropped below <95% within 100 h operation time caused by coke formation. Deactivation can be reduced by increased reaction temperature and high acetone to formaldehyde ratio but with negative impact on selectivity and efficiency of the set-up. Reactivation can be achieved by burning off coke periodically in a controlled way, considering type of coke and the axial distribution of coke inside the reactor. To ensure full activity regain and to avoid catalyst or reactor damage by hot spots a two-step regeneration process has been developed, using diluted air (air off-gas mixture) followed by complete regeneration with air. Surprisingly this procedure is not more time-consuming than air usage from the very beginning, but avoids any hot sport formation. However, total regeneration time necessary is approx. 48 h ending up in a 100 h operation and 48 h regeneration process.

Realization

As a result of the piloting a full continuous industrial process was designed, compromising two gas phase reactors – always one in production and the other one in regeneration mode. Due to the high investment costs for the required installation (especially the two high temperature gas phase reactors) the new process has not been implemented, however, knowledge gained from the development work was adopted in current set-up.

Conclusion

A successful piloting does not automatically lead to an implementation. But ultimately, the existing process profits by the knowledge gained from the piloting.

6. Daring the Challenge and Thinking Big: The Value of Early Process R&D

Dr. Stefan Abele, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland

Lecture Sandmeyer Award 2015

"*Es ist nicht genug zu wissen – man muss auch anwenden. Es ist nicht genug zu wollen – man muss auch tun.*" J. W. von Goethe

Enantiomerically pure 5-phenylbicyclo[2.2.2]oct-5-en-2-one (**1**) was required as intermediate for the synthesis of the L/T channel blocker **ACT-280778** (Fig. 1).[1] The published route afforded **1** in <0.5% yield, following a long sequence with steps that are not acceptable for scale-up. A series of different processes to bicyclic ketone **1** was developed to best fulfill the increasing requirements of the successive clinical supplies.

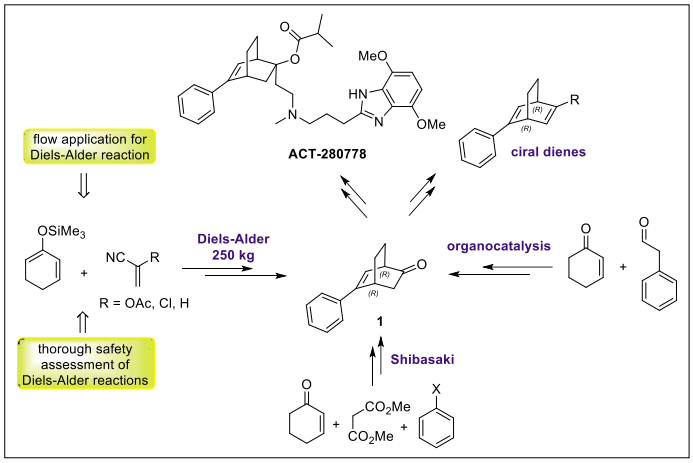


Fig. 1. Synopsis of the three approaches to bicyclic ketone **1**, the pivotal intermediate for the manufacturing of the L/T channel blocker ACT-280778.

Each of the three routes is characterized by an outstanding asset. (1) The first route focused on the scale-up of Diels–Alder reactions with highly reactive reagents. This culminated in the production of 90 kg enantiomerically pure **1**.[2] A flow application was developed for the Diels–Alder reaction at 215 °C to mitigate intrinsic safety risks.[3] (2) The detailed mechanistic understanding of a stereoselective intramolecular aldol reaction enabled the development of a Crystallization Induced Diastereomer Transformation (CIDT) as pivotal step of an enantioselective route that starts with the Shibasaki reaction.[4] This route removed the need for enantiomer separation on the large scale and paved the way to an even shorter access to **1**: (3) this second enantioselective route represents one of the rare examples of organocatalysis on scale and allowed us to skip six out of nine steps with a significant impact on the cost of goods. As a welcome 'side effect' of this work and as segue into academia we found a simple and short synthesis of Hayashi's chiral diene ligands (bod*) that were so far lacking an affordable access.[5]

Two recent paradigms in the pharmaceutical industry have been successful guiding principles: the tactical and strategic outsourcing of parts of the work and the collaboration with academia. Both the safety assessment by the Swissi Process Safety GmbH and the catalyst high-throughput screen by Solvias AG have been instrumental for the present work. Actelion's collaboration with Universities of Applied Sciences (Zurich and Fribourg) brought about a new flow process and research that could hardly be run under the constant pressure to deliver drug substance for clinical studies. Although the Diels–Alder and organocatalytic reactions

are nowadays textbook examples, they did not (yet) find their way into the standard repertoire of industrial chemists. A recent review in *Angewandte Chemie* on the Diels–Alder reaction underpins this dichotomy.[6]

Process chemists have to constantly balance the short-term benefit of a fit-for-purpose route with the long-term benefit of a route destined for ton-scale manufacturing. The overarching goal is to reduce the time to the Phase I clinical studies, and, ultimately, to market. Fixing the route early in development saves later expensive route changes that are associated with a high regulatory burden. Another, more practical argument is that route development close to the first kg batches is typically much faster due to the immediate availability of process know-how and ideas of the involved chemists and intermediates at the site of manufacture.

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7. Sedaxane™, Isopyrazam™ and Solatenol™: Novel Broad-spectrum SDHI-Fungicides – Synthesis Challenges and Biological Aspects

Dr. Harald Walter*, Dr. Hans Tobler, Dr. Denis Gribkov and ***Dr. Camilla Corsi,*** Syngenta Crop Protection Münchwilen AG, Switzerland

Lecture Sandmeyer Award 2014

Sedaxane (SDX), isopyrazam (IZM) and solatenol (STL) are broad-spectrum pyrazole carboxamides which originate from novel classes of agrochemical fungicides. Their mode of action is inhibition of succinate dehydrogenase (SDH), a well known fungicidal mode of action. Carboxin, the first representative of the SDHI carboxamide class was introduced to the market in 1966. For a long time the SDHI mode of action was recognized to deliver only compounds with a narrow biological spectrum. This view changed with the market introduction of boscalid in 2003. BASF was the company who first elucidated the potential for broader spectrum of this mode of action. With boscalid, BASF mainly filled their Botrytis portfolio gap, but boscalid also controls other important pathogens such as *Alternaria solani* and *Sclerotinia sclerotium*. Syngenta entered the SDHI area in 1998 and a first goal was the delivery of a foliar cereal compound controlling leaf spots (including *S. tritici*) and rust. With the discovery of the SDHI benzonorbornene amide subclass in 2002, a first breakthrough could be achieved. IZM was derived from this subclass, first prepared in 2003 and entered the market in 2010 (UK). Following up the benzonorbornene area a next breakthrough could be achieved with the synthesis of STL in 2005. STL is a highly efficient fungicide, active against a broad range of pathogens including soybean rust. The high efficacy against soybean rust makes this compound very special and creates huge new business opportunities. STL was introduced to the market in 2012 (Paraguay) and will be introduced to the major soy market Brazil this year. Whereas the two Syngenta benzonorbornene compounds have been tailored for foliar use, SDX was specifically designed for seed treatment use. SDX was first prepared 2002 and entered the market in 2011 (Argentina). All three Syngenta SDHIs are very complex from the chemistry synthesis perspective (multistep synthesis and use of new technology). In the lecture the synthesis challenges of SDX, IZM as well as STL were discussed in detail. New cost-efficient synthesis strategies for the preparation of *o*-biscyclopropylaniline, new benzonorbornene intermediates and the key pyrazole carboxylic acid intermediate being part of all three Syngenta SDHIs, were in the center of the discussions.

8. Key Considerations and Design Criteria Realized in CARBOGEN AMCIS New Clean Room

Dr. Scott A. Miller, CARBOGEN AMCIS AG, Bubendorf, Switzerland

Antibody Drug Conjugates (ADCs) are key anti-cancer treatment platforms that combine the desirable properties of monoclonal antibodies (elevated target selectivity) specific to antigens, which are preferentially expressed on cancer cells, with the potency of highly cytotoxic molecules to reduce systemic toxicity and eventually increase the therapeutic benefit for the patients. The drug conjugate can act by endocytosis, releasing its cytotoxic payload within the cancer cell, or as a vascular-targeting agent selectively attacking the blood vessels of the cancer leading to the tumor's necrosis after the rapid shutdown of its blood supply.

The recent approvals of Adcetris® for Hodgkin's lymphoma and Kadcyla® for Her2-positive breast cancer have provided further evidence of the potential of ADCs in the treatment of cancer. In addition, there are roughly 30 ADCs in clinical and 160 in preclinical development, so there is a need for high quality manufacturing to bring new products into the clinic and ultimately to the public.

The conjugation of the antibody to the cytotoxic drug *via* specific linkers poses several challenges during the development and manufacturing phases. Facilities where the manufacture of highly potent active pharmaceutical ingredients (API) is performed are designed with an emphasis on worker safety. Linking a highly potent API to a potent antibody, however, requires additional stringent environmental controls to protect the product from contamination.

CARBOGEN AMCIS AG recently completed the construction and qualification of a clean room laboratory for the GMP manufacture of ADCs. Evaluation of common conjugation, purification, and packaging processes led to the following considerations for the new laboratory (Table 1).

The final laboratory design and construction was realized in the following configuration.

Grade D and Grade C aseptic manufacturing areas with separate material and personnel airlocks and a positive pressure cascade (+30 Pa, +15 Pa, –15 Pa, 0 Pa). To be able to meet pre-

Table 1.

Criteria	Preliminary Considerations
ESH and GMP	HiPo Drug-Linker & Aseptic Processing
Scale	Up to 300 g ADC Batch Size
Toxin Handling	Barrier System or Isolator
Buffer Preparation	Up to 200 L for TFF
Equipment	Storage & Sanitization
Conjugation	Fixed, Dedicated, or Single Use Reactors
Purification	Type and Scale
Packaging of BDS	BSC II or Other Options
Cleaning	ESH, GMP, and Cost Considerations

clinical and early clinical scale manufacturing, conjugation scale up to 20 L with TFF and chromatography buffer preparation up to 2×200 L scale. Toxin dispensing and handling will be performed exclusively in an isolator. Within each area, the equipment as listed in Table 2 was installed.

Table 2. Final Laboratory Configuration

Grade D Laboratory	Grade C Laboratory
Dry oven sterilizer and autoclave	Isolator for toxin dispensing and preparation of toxin solutions
Barrier System for weighing of powders for buffer preparation	Barrier System (BSC II) for aseptic packaging g of bulk drug substance
Single-Use mixer totes up to 200 L	Single-Use mixer totes up to 200 L
In process monitoring by various means such as:	Stand-up fume hood for solvent handling up to 10 L
• UV/Vis • pH and Conductivity • Endo-Safe endotoxin determination • Filter integrity testing	Project dedicated double mantle glass conjugation reactors (5 – 20 L)
	Single-Use TFF and Chromatography
	In-process monitoring (as in the Grade D Laboratory)

Particulate containment of the isolator was determined following installation as part of the qualification. Results from air and surface sampling during typical solid handling operations using naproxen sodium as a surrogate substance, confirm that in this isolator dry solids with OELs in the single digit nanogram-range can be safely handled.

Construction of the laboratory was completed May 2014 and operational qualification (OQ) documentation, December 2014. Following in-operation and hold-time qualification work, a six-month performance qualification (PQ) of microbiology and particle monitoring during operation was completed April 2015.

Acknowledgement

Key CARBOGEN AMCIS AG project team members and their groups were: Renato Fruchi (Head Maintenance & Engineering), Marcel Heimgartner (Architect), Luca Mannocci (Sr. Chemist PR&D), and David Brodmann (Chemist Quality System). Thanks also to Cécile Dumas, Colin McKee, and Jörg Neumann for consulting services and to Elena Perrino (Sr. Chemist QC&A ADC) for help in reviewing this document.

9. Evaluation and Scale-up of Miniaturized Rotor-Impact Milling Technology

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Introduction

Milling technologies like jet-milling and rotor-impact milling are frequently applied in drug development and manufacturing to engineer drug particle size after chemical synthesis and crystallization. Drug particle size may influence key quality attributes of drug products, *e.g.* dissolution, content uniformity, chemical compatibility, as well as the selection and performance of the related pharmaceutical manufacturing technology chain. Thus, drug particle size is an important subject and needs to be engineered according to the needs of the individual drug compound and drug product in relation to the selected route of administration.

Nowadays, drug development is characterized by a tight supply of drug compound, and the need to provide standard platform technologies according to the specific requirements across the drug development process and during commercial manufacturing. In this paper, the evaluation of two recently launched miniaturized rotor impact mills is shown, and results are compared to pilot scale equipment, to facilitate the strategic implementation of rotor-impact milling as standard platform technology for drug development and manufacturing.

Materials and Methods

Rotor-impact mill models PICOPLEX® and LPM-2 MIKRO®, both Hosokawa Alpine AG, Augsburg, Germany, were evaluated and compared to a rotor-impact mill at pilot scale, type 100 UPZ, from the same vendor. Fig. 1 shows the rotor pin discs of the different equipment models investigated.

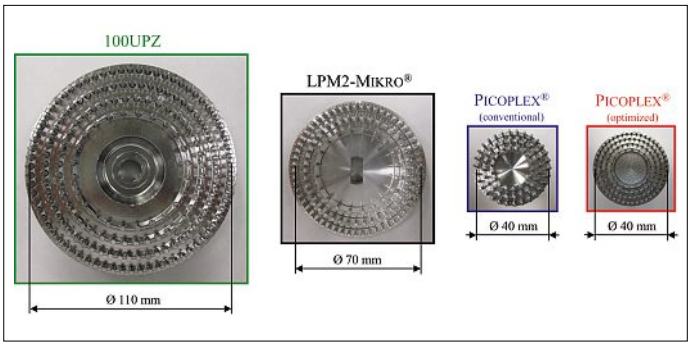

Fig. 1. From left, rotor pin disc 100UPZ (pilot scale), LPM2-MIKRO® and PICOPLEX® with conventional and optimized design.

Process parameters feed rate, rotor speed and gas flow were investigated for each individual equipment model. Experiments were performed with raw materials α-lactose-monohydrate, CAPSULAC® 60, Meggle GmbH & Co. KG, Wasserburg, Germany, and a proprietary drug compound from Novartis Pharma AG. Particle sizes were determined by laser light diffraction device Helos in combination with wet dispersion device Sucell, both Sympatec GmbH, Clausthal-Zellerfeld, Germany.

Results

As expected, particle size reduction was increased with increased rotor speed for all rotor impact mills. Interestingly, strong variations in feed rate resulted only in marginal impact on particle size in contrast to minerals.[1,2] Process parameter feed rate could be roughly correlated by a conventional scale-up concept considering a direct proportionality of feed rate with cylindrical pin surface.[3] In contrast, particle size results obtained upon

milling couldn't be correlated with classical scale-up of maximum specific stress energy ($SE_{m,max}$), respectively rotor speed[4] as shown in Fig. 2a. Therefore, a new scale-up concept for process parameter rotor speed was introduced by the cumulative specific stress energy ($SE_{m,cum}$) on the basis of a general energy concept.[5] $SE_{m,cum}$ corresponds to the cumulative specific kinetic energy of the rotating pins according to Eqn. (1), considering pin speed (vP) and number of rotating pins (nP) at pin row radius (r) for pin row i=1 to i=max.

$$SE_{m,cum} = \sum_{i=1}^{i_{max}} n_{P,r_i} \cdot \frac{1}{2} \cdot v_{P,r_i}^{\ 2} \qquad (1)$$

Fig. 2b shows the particle size results obtained for different feed rates against $SE_{m,cum}$ for each individual equipment model. The particle size results obtained are well correlated by $SE_{m,cum}$ across all equipment models. Therefore, cumulative specific stress energy ($SE_{m,cum}$) provides an adequate scale-up concept for process parameter rotor speed.

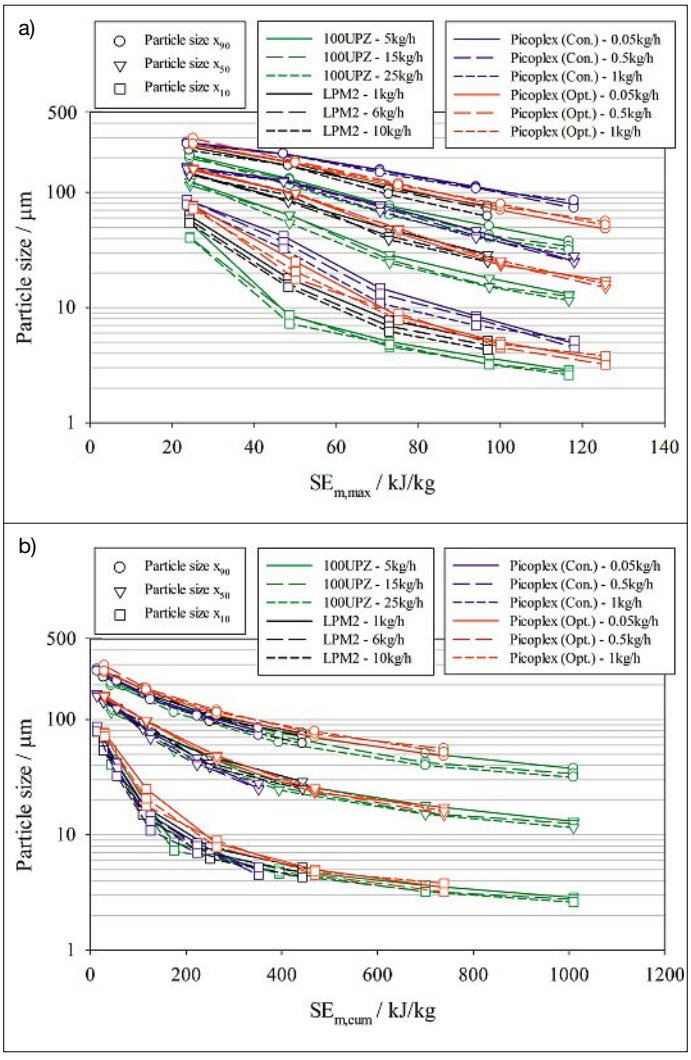

Fig. 2. a) Particle size against maximum specific stress energy $SE_{m,max}$, and b) cumulative specific stress energy $SE_{m,cum}$ for the different equipment models and feed rates investigated.

Limitations were identified for the dynamic range of $SE_{m,cum}$ for rotor impact mill LPM2-MIKRO® and PICOPLEX® with conventional rotor design. The dynamic range of $SE_{m,cum}$ could be significantly improved for rotor impact mill PICOPLEX® by the optimized rotor design shown in Fig. 1.

Conclusions

The miniaturized rotor impact mills LPM2-MIKRO® and PICOPLEX® were successfully evaluated, both providing a systematic and consistent response on product particle size by process parameter feed rate and rotor speed. Process parameter feed rate can be scaled-up from both equipment models to pilot scale by an established concept.[3] Scale-up of process parameter rotor speed could be established by the concept of cumulative specific stress energy ($SE_{m,cum}$) for all investigated equipment models. The minimum batch size at pilot scale of about 2-4 kg could be significantly decreased, *e.g.* for model PICOPLEX® to a minimum batch size of about 10 g. Finally, the evaluated equipment models enabling feasibility trials with decreased batch sizes, a strategic expansion of the platform technology rotor-impact milling to the early stage of drug development, and an increased data output or reduced raw material input, including reliable scale-up to pilot and manufacturing scale by engineering principles.

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10. Dividing Wall Columns at Lonza – Sustainable Process Intensification in Chemical Production Plants

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Introduction

Distillation is by far the most important separation technology in the chemical industry and is responsible for an important part of the world-wide energy consumption.[1] Rising energy and raw material costs over past decades, as well as increasing market competition have been the major drivers in the search for potential energy savings, even for a mature process such as distillation. This financial pressure is the major driver for the constant optimization of distillation processes with respect to energy consumption. In the application of energy recovery systems, this has yielded optimized column internals and intensified processes such as the heat integrated distillation column (HIDiC) or the dividing wall column (DWC). DWCs are able to divide ternary mixtures into the three pure components in a single column shell by the addition of a solid wall that separates the column into six compartments (Fig. 1). Contrary to the HIDiC, which is still to a great extent an academic field of investigation, more than 150 DWCs are already in operation in the chemical industry and their number is constantly rising. This booming development is due to considerable savings in both CAPEX and OPEX (about 30%).[2] On the other hand, DWCs show a higher degree of freedom compared to standard columns and therefore, it is believed that they demand greater efforts in terms of equipment design and process control. This prevents many companies from introducing the technology. Lonza introduced this technology in 2010 and operates four DWCs on the Visp site (one for a dedicated application in a mono plant, two multi-purpose DWCs and one DWC for extractive distillation). From Lonza's perspective, the design and operation of a DWC is straightforward and comparable to the design procedures of standard columns.

Design Strategy

Lonza follows a four-step design strategy (Fig. 2) which focuses on simulation rather than on elaborate lab trials or piloting. Typically the piloting step is skipped and the large scale column is directly designed based on simulation studies.

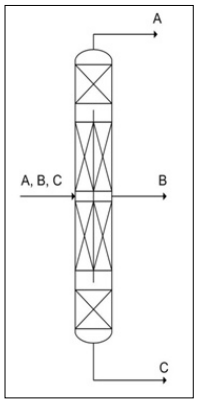

Fig. 1. Basic design for a dividing wall column.

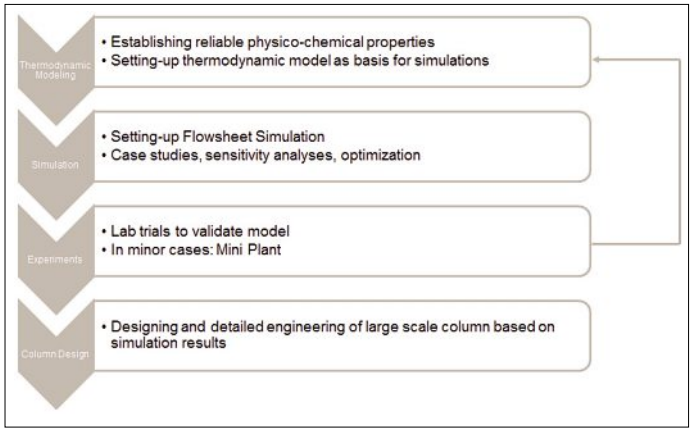

Fig. 2. Design procedure for dividing wall columns at Lonza.

This procedure requires a reliable thermodynamic model, which is the basis for all subsequent simulation studies. Since in many cases reliable pure component or mixture data from available sources (databases *etc.*) is missing, predictive models must be applied to gain the desired information. COSMO RS or different models from the UNIFAC family are widely applied for this purpose.

Lab trials are then performed to eliminate k.o.-criteria, which cannot be seen from the models, *e.g.* foaming or solid precipitation as well as to confirm the thermodynamic model. Once the model is confirmed, all design parameters of the column are obtained from simulation studies. If the model is not accurate enough, it is adjusted until experimental and theoretical results are in agreement.

Since commercially available simulation tools do not provide a unit operation model for a DWC the engineer has to build a model using standard distillation columns and combining them in a smart way. There are different approaches available in text books. Lonza initially uses a two-column model with a pre-fractionator (Fig. 3). At the beginning of the simulation, all side-streams are set to zero. Therefore, a standard distillation column with a condenser and an evaporator has to be initialized, meaning that no streams have to be estimated and convergence is likely. Then, step by step, the side streams are raised until the simulation runs close to the desired operation point. However, it is difficult to run sensitivity or optimization studies with this model. For example the liquid split cannot be directly manipulated. Because of this, we switch to a four-column model (Fig. 4). The results from the two-column model (*e.g.* temperature profiles) are used to initialize the four-column model, which then shows very good convergence behavior. All design studies are carried out using the four-column model. It must be emphasized that the models are equivalent from a thermodynamic point of view.

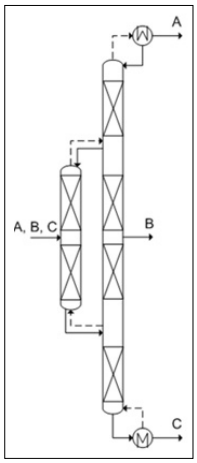

Fig. 3. Pre-fractionator DWC model.

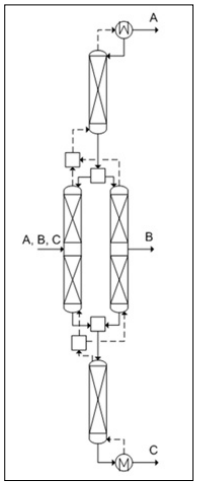

Fig. 4. Four-column DWC model.

DWCs at Lonza

Following the above-mentioned design strategy Lonza has built four commercial-scale dividing wall columns on the site in Visp since 2011: one for a mono-plant, two multi-purpose dividing wall columns and one extractive dividing wall column. All of them are very successfully applied in large scale production processes. The multi-purpose column is described in detail in ref [3]. The extractive column is used to separate the equal boiling 4-picoline (76 °C at 0.1 bar) from 2,6-picoline (76 °C at 0.1 bar) and 2,5-lutidine (85.5 °C at 0.1 bar) by using ethylene glycol (140 °C at 0.1bar) as the entrainer (Fig. 4). The hydroxy groups of the entrainer interact strongly with the nitrogen from 4-picoline and lower its boiling point. 2,6-picoline, therefore, is gained as the overhead product on the 'cold' left side of the dividing wall. 4-Picoline is recovered from the 'warm' right side of the wall. 2.5-Lutidine is the side product and the entrainer is the global heavy boiler, leaving the column from the bottom, and is sent back into the top part of the column. As indicated in Fig. 4, the dividing wall in this configuration goes up to the top end of the column, which makes two condensers necessary. The extractive dividing wall column, as well as the multi-purpose dividing wall columns are the first units of these types for commercial production.

Two more columns are currently under development: A column with three dividing walls, yielding four pure products and a reactive dividing wall column, where the chemical reaction and the separation of three fractions is done within one column shell.

Summary

The Lonza strategy to design DWCs is based on simulation and modeling in order to avoid elaborate experimental work and piloting. A sound thermodynamic model is mandatory and is typically derived from predictive models, *e.g.* group contribu-

tion models for pure component data and UNIFAC as well as COSMO RS for mixture data. Four columns have been built since 2011 and are operating successfully. The duration from first idea to large-scale production is in the range of 12 months.

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11. Robustness of Bromine Recycling Loop

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Bromine is a key raw material for the Syngenta production site in Monthey. A recycling rate of 98.5% bromine is currently obtained. This bromine recycling loop contains several processes to treat the various streams of bromide water. This abstract describes the loop and several requirements to ensure a robust bromine recovery process.

For bromine recovery, we use the Kubierschky process. This process was developed in 1907 by a German chemist, Konrad Kubierschky. In Monthey, chlorine is used for oxidation of bromide (mainly KBr and NaBr). It converts aqueous bromide (Br^-) to liquid bromine (Br_2). Chloride formed during the reaction goes out with the wastewater of the process.

The Kubierschky process contains four main steps:

Step 1: Two pre-scrubbers fed by bromide water, this permits the treatment for the vent line of the process. After the pre-scrubbers, bromide water is heated at 60 °C.

Step 2: One column, here the reaction between chlorine and bromine occur and bromine formed is stripped by steam.

- At the bottom of the column, we have the inlet of steam.
- In the middle, we have the inlet of chlorine.
- At the top, we have the inlet of bromide water (Br^- aq.).

Wastewater which contains chloride goes out of the column by gravity. Bromine and water is condensed at the top of the column, to feed step 3.

Step 3: One column, here the total organic carbon (TOC) is removed by bromine distillation.

The mix of TOC and bromine is emptied to a buffer tank in a semi continuous way, where this mix will be treated. Bromine without TOC is removed in continuous by distillation, to feed step 4.

Step 4: One column, bromine is purified by rectification in order to reduce traces of water and chlorine.

- The Monthey production site requires a bromine recycling loop, for the following reasons:
- OTD (Ordonnance sur le traitement des déchets): **All that can be recycled must be recycled**
- Limitation of bromide in wastewater at the ETP → 500 kg/day
- Competitive cost for bromine supply
- Simplify logistics (replace fresh bromine by chlorine)
- Reduce storage of bromine (production on demand)
- Low production of waste (chloride water and organic residues treated by thermal oxidation)
- Synergies between different process steps

Four main states of bromine are currently obtained in the bromine recycling loop:

- Bromine (Br_2) : → from bromine recovery process (Kubierschky) to bromination process
- Brominated product (organic compounds): → from bromination process to process using brominated product
- Untreated bromide water (Br^- aq.) with approx. 2% of TOC: → from process containing bromine to bromide water pretreatment
- Treated bromide water (Br^- aq.) with approx. 0.2% of TOC: → from bromide water pretreatment to bromine recovery process (Kubierschky)

To ensure high robustness of our bromine recovery processes, there are several requirements.

An in-depth knowledge of the behavior along the recycling process for each stream of bromide water is necessary. The first goal is to identify which stream produces clogging and foam formation during the Kubierschky process. The second goal is to define best process parameters for TOC removal, during the pretreatment.

In 2014, a master student from HES-SO Fribourg carried out a study to characterize problematic by-products in each stream of bromide water. This has enabled us to confirm that problems of clogging are mainly linked with reaction of heavy organic compounds present in small amounts. Only a certain stream of bromide water contains these sensitive organic compounds, which produce sticky deposits when they are in contact with chlorine or bromine.

Also in 2014, an interesting possibility to improve TOC removal during solvent extraction process, with modification of solvent recycling, has been defined by **the company PMax**.

A consistent supply of brominated water to reduce clogging and foaming during the Kubierschky process, is useful. In our recycling loop, blending is done with several buffer tanks of treated bromide water, in order to get an optimized dilution of problematic streams. As with many waste treatment processes, large capacity of buffer tanks reduce variability at the inlet of the process.

As a palliative solution of robustness, the Kubierschky process must be equipped with an automatic washing system, using water and thiosulfate water. It is important to consider washing shutdown like another step of the process, in order to improve safety, productivity and efficiencies.

Finally, the thermal oxidizer is necessary to recover bromide from brominated organic compounds, or to remove high levels of TOC contained in the bromide water:

- Necessary to treat brominated organic residues
- This is useful in case of deviations in the pretreatment processes, which allows the rework of the treated bromide water.
- Possibility to treat external bromine sources to feed the bromine loop

In speaking about a thermal oxidation process, a less emotive name for incineration is used, this apparently simple process contains the following major elements:

- Combustion chamber
- Ash collectors
- Boiler – heat exchanger – waste heat recovery
- Quench – exhaust gas cooling to the dew point
- Scrubber
- Acidic scrubbing – acid removal
- Alkaline scrubbing – SO_2 removal
- Fine particle removal
- Venturi Systems
- Nox removal

In conclusion, our know-how from a production point of view about the requirements to prevent undesired reaction during waste treatment process using highly reactive compounds (like chlorine and bromine) permits us to share the following points:

- Identify problematic streams → by lab test
- Optimize dilution of problematic streams → by blending of streams
- Design of efficient washing of residues → with an automatic process
- Availability of highly efficient TOC removal treatment → the thermal oxidizer

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