**Conference Report**

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*From Reaction to Technology Trends in Chemical Production*

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1. Entwicklung eines kontinuierlichen Verfahrens in der Spezialitätenchemie – Reaktion mit Keten

Wolfgang Wenger, Cornelia Zur Taeschler, Niklaus Kuenzle, Daniel Zollinger, Lonza AG, Visp, Schweiz


**Verfahrensentwicklung für einen Prozess zur Ketenisierung von Orthoformiaten**


Der zweistufige Prozess zur Herstellung der Alkoxypropionsäureester wird heute regelmäßig in einer Grossanlage gefahren, die Produktionsmenge liegt im Bereich von >100 to/Jahr.


2. Hazardous Reactions on Industrial Scale

Dr. Günter Weingärtner. Dottikon Exclusive Synthesis AG, Dottikon, Switzerland

**Introduction**

DOTTIKON EXCLUSIVE SYNTHESIS AG (Switzerland) has a 100-year history in the production using hazardous reactions on an industrial scale. DOTTIKON was founded 1913 as Schweizerische Sprengstoff Fabrik (SSF) to produce explosives, especially for the construction of the tunnels in the Alps. Over the years the focus moved to industrial fine chemicals and later to Active Pharmaceutical Ingredient (API) production on an exclusive basis for various pharmaceutical companies worldwide. Hazardous reactions on an industrial scale are an important basis of our main business as a custom manufacturer.

**What is a Hazardous Reaction?**

After a short introduction of DOTTIKON and our core activities, DOTTIKON’s definition of hazardous reactions is explained.

- **DOTTIKON defines four categories:**
  - Highly exothermic processes (*e.g.* nitrations, oxidations, metallation, *etc.*)
  - Reactions with highly reactive compounds (*hydrides, diborane, POCl₃, or similar halogenation agents, etc.*)
  - Highly potent compounds (*e.g.* HAPIs)
• Thermally or mechanically unstable compounds or mixtures (nitro/diazo compounds, nitrate esters, peroxides etc.)

Benefit versus Process Risks
The case studies focus on the handling of unstable compounds and mixtures and their transformation to industrial scale. Since hazardous reactions can certainly lead to process risks, it is necessary to acquire a profound understanding of the chemistry and the associated safety aspects. The control of the risk is the key. However, hazardous reactions can benefit from shorter synthetic routes and subsequently reduced costs as well as from better reaction profiles leading to higher product quality. In early project phases medicinal chemists often apply hazardous reactions to use these benefits in order to produce first amounts of their products. Later in the development phase process chemists spend a lot of time and effort on changing synthetic routes to avoid such reaction types. However the ability to perform hazardous reactions on an industrial scale expands the choice of possible reaction significantly and their benefits can be used.

Process Safety Investigations
To handle hazardous reactions it is essential to have an established safety culture in place and a profound understanding what you are doing (and what you should avoid in any case). Therefore process safety, control of reaction and risk management, gas formation up to waste handling are of great importance and these issues are discussed in detail in the presentation. The process development of safety critical reactions is directed in the beginning to gather basic safety data and process understanding for a profound risk analysis. Calorimetric investigation of the desired reaction to determine the reaction heat and the accumulation of energy as well as the decomposition (potential and onset) of various mixtures are the basis to simulate a runaway scenario.

Special Safety Tests
Beside the standard thermal safety testing additional safety data are often needed for a complete safety assessment. In case of nitrations or reactions using azides or similar high energetic compounds reaction mixtures with explosive properties can be formed during the process: Special detonation tests give an indication of such behavior. In the presentation it is shown how such tests are made and how explosivity areas of certain mixtures must be interpreted.

If the critical process steps cannot be adapted the process must be run in dedicated equipment e.g. in a bunker, with the possibility of an emergency quench to avoid a thermal runaway. In this specialized plant equipment, first quantities of product can be produced to supply first amounts in short time frames.

Realization on Industrial Scale
The focus of the further process development is always to improve the process in such a way that a transfer into a large-scale multi-purpose plant is possible. Optimization by reduction of large excess of critical compounds, process control by addition mode, control of gas formation over time etc., are valuable starting points. Especially the control of gas formation is a key for the realization, but also the monitoring of critical gases like hydrazoic acid, diborane or hydrogen cyanide can be essential for the reaction control because of their explosive properties and high toxicity. Analytical online techniques are beneficial in the development and production environment to monitor e.g. the venting system. Additionally gases must be scrubbed efficiently by an appropriate absorption system or incineration of the venting gas may even be required.

Realization Batchwise or in Flow?
The control of hazardous reactions can be improved by running them in a continuous flow mode, especially for the manufacture of larger quantities. The intrinsic advantage of a flow mode (low critical volume, high heat exchange capacity etc.) can be used to control hazardous reactions. As an example various nitroxylenes or nitrate esters were produced at DOTTIKON by continuous processes. But dinitro- or azido- or even diazo-compounds are manufactured batchwise on scale in a safe way.

Examples are discussed in the presentation in more detail to demonstrate how these processes are developed and established on larger scale.

Conclusion
The establishment of hazardous reactions on scale requires intensive process development work to gain enough process understanding and safety data for the risk assessment. Control of the reaction is the key for the realization, but at the end economic processes can be established to benefit from shorter routes and high quality products.

3. Organocatalysis on Scale
Dr. Stefan Abele, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland

Several decades passed before the seminal work by industrial chemists at Hoffmann-La Roche and at Schering AG on the proline-catalyzed aldol reaction in the 1970s[1] resulted in a surge of interest in asymmetric organocatalysis. Nowadays, it is a general concept that has been applied to many reactions in academia.[2] However, publicly available examples on industrial scale are still scarce. The first part of this presentation shows examples of asymmetric organocatalytic reactions that are produced at an industrial scale, i.e. more than a few kilograms.

The second part is devoted to a recent example from Actelion Pharmaceuticals Ltd. Enantiomerically pure phenylbicyclo[2.2.2]oct-5-en-2-one (1, Fig. 1) was required for the manufacture of ACT-280778, an L/T calcium channel blocker in clinical phase. The published route to 1 afforded it in <0.5% yield, following a long sequence with steps that were not acceptable for scale-up.[3] Material for first clinical supplies was produced by a Diels–Alder approach, followed by a chiral separation of rac-1 on a 14-ton scale.[4] An enantioselective route was required for larger scales. Two practical routes to 1 have been developed as 2nd generation routes.

Fig. 1.

The first approach to 1, a nine-step route with 22% overall yield on a kg-scale features an intramolecular Crystallization Induced Diastereomer Transformation (CIDT) as pivotal step, delivering the crystalline intermediate (1R,4R,53,6S)-6-hydroxybicyclo[2.2.2]octan-2-one (2). [5]

The detailed mechanistic understanding of this intramolecular aldol reaction paved the way towards the second approach to 1 cutting out six out of the nine steps[6] the same pivotal chiral intermediate 2 was obtained in an organocatalytic tandem-Michael-aldol reaction from cheap 2-cyclohexenone and phenylacetaldehyde, catalyzed by l-proline in toluene on kg-scale.
Although the yield remained similar and the enantioselectivity of the organocatalytic step was moderate, the cost of goods and the environmental burden were lowered significantly. Assets are the low cost of all reagents, solvents and l-proline as organocatalyst, the simplicity and robustness of the unit operations (reactive crystallization, filtration), and the ease of upgrade of the enantiomeric excess by a simple crystallization. The three routes to access I are compared considering key parameters.

Two steps are required to synthesize chiral diene ligands (like Hayashi’s bod* ligands\(^1\)) from the now readily available I. These powerful bod* ligands suffer from an availability and cost issue (>CHF 700/500 mg). Eleven new chiral dienes have been accessed from I by straightforward chemistry. As an efficient access to bod* ligands was still missing, this protocol should be beneficial for the widespread use of this new authoritative ligand class. First applications of the new C\(_2\)-symmetric dienes in benchmarking reactions are presented.\(^8\)

4. Importance of Industrial Biotechnology for the Chemical Industry

Dr. Gunter Festel, FESTEL CAPITAL, Fürgen, Switzerland

An increasing number of chemicals and materials are produced using biotechnology in one or more of the process steps. In 2010, sales of products made using biotechnological processes were 92 billion Euros representing 6.2% of total chemical sales (without biofuels and finished pharmaceutical products). Although basic chemicals, including polymers and fibers, made up around 60% of global chemical sales in 2010, only 4% of these (35.3 billion Euros) were produced using biotechnological processes representing 38.4% of total biotech sales. Active pharmaceutical ingredients (APIs) is the segment with the highest percentage of biotech sales: 28% of the total sales in this segment are based on biotechnological processes.

Looking at the regional level in more detail shows that the strongest region within most of the segments and sub-segments is Asia. In 2010, bio-based polymers and fibers had around 6 billion Euros sales in Europe, around 4.5 billion Euros sales in North America and around 7.5 billion Euros sales in Asia. APIs produced using bioprocesses have more than 4 billion Euros sales in Europe, around 4.5 billion Euros sales in North America and nearly 7 billion Euros sales in Asia. Important sub-segments are also organic chemicals, agrochemicals, cosmetics, detergents.

In 2015, estimated sales of products made by biotechnological processes will be 228 billion Euros representing 12.1% of total chemical sales which means an annual growth rate from 2010 to 2015 of 20%. In all segments and sub-segments it is expected that by 2015, the percentage of products produced using biotechnological processes will increase. Base chemicals, including polymers and fibers, will account for around 94 billion Euros, specialty chemicals around 51 billion Euros, consumer chemicals 43 billion Euros and APIs 40 billion Euros. Again, in 2015, it is expected that APIs will be the chemical segment with the highest biotech sales percentage with 40.1%.

In 2020, it is expected that around 515 billion Euros, representing 21.6% of total chemical sales, will be biotech products with a growth rate of 18% from 2015 to 2020. Biotech-based base chemicals including polymers and fibers will achieve the highest sales figures in total terms in 2020 with around 238 billion Euros. Consumer chemicals will be the next most important biotech segment making up around 104 billion Euros. By 2020, it is expected that APIs produced using biotechnological process will again be the biotech segment with the highest sales percentage with 53.2% of chemical sales.

Commercial development is mainly driven by multinational enterprises, whereas small and medium enterprises contribute primarily to the technological development. Especially the latter group faces several challenges during their development. These mainly concern business models and growth strategies as well as financing strategies and resources. Investors have not yet fully identified the area of industrial biotechnology as an attractive investment field but they could become a major capital source as they start to understand more the potential of industrial biotechnology.

The industrial biotechnology industry needs more entrepreneurial spirit especially in the context of founding more start-ups to commercialize new technologies. Compared to other regions, like North America, Europe is lacking this spirit despite a strong technological basis. Founding angels (www.founding-angels.com) act as the driving force for the foundation of new start-ups by supporting scientists from the generation of the idea to the building up of a company. The engagement of founding angels is compensated not monetarily but through an equity share of the new company as a member of the founding team. Successful examples are Autodisplay Biotech (www.autodisplay-biotech.com), Butalco (www.butalco.com) and Greasoline (www.greasoline.com).

5. The Irgacure 819 Sodium Process: 5 Years after the Sandmeyer Award

Dr. Reinhard H. Sommerlade, BASF Schweiz AG, Switzerland

The first phosphorus-based photoinitiators were the monacylphosphine oxides (MAPO) commercialized by BASF in 1987 under the trade name Lucrin. MAPOs are synthesized by the Michaelis-Arbuzov reaction of dialky phosphonites or trialkyl phosphites with acyl chlorides. The former Ciba-Geigy later developed the first bisacylphosphine oxide (BAPO) photoinitiator, Irgacure 819. It is manufactured in a three-step process that begins with the lithium metalation of dichlorophenyl phosphine. Acylphosphine oxides are thermally stable compounds which cleave into radicals upon irradiation, thus triggering the polymerization of unsaturated monomers or oligomers in an environmentally friendly manner without the need for solvents.

Irgacure 819 is the most important member of the photoinitiator class of BAPOs, with light absorption from 360 nm up to the visible region (\(\lambda < 440\) nm). The product is highly suitable for the curing of pigmented systems and thick layers.

In 2003, a new synthetic process for the production of Irgacure 819 was required for several reasons. Two research teams, one from the ETH Zurich under the guidance of Prof. Hansjörg Grützmacher, and an R&D team from Ciba Specialty Chemicals, developed a novel three-step process beginning with the Birch-like reduction of dichlorophosphine with liquid sodium in an isomeric xylene mixture in the presence of a sterically hindered alcohol. The resulting phenylphosphine is acylated with mesityl chloride in the presence of the alkoxide, formed

from the alcohol and the metalated phosphine. The bisacylphos- phine is then oxidized to Irgacure 819 with aqueous hydrogen peroxide. The successful implementation of the new process in production was honored with the prestigious Sandmeyer Award in 2007. Today, Irgacure 819 is produced at the BASF site in Mortara (Italy).

During the investigation of the chemistry involved in the metalation of phenyldichlorophosphine, a profound understanding of the mechanistic details of this reaction arose.

When elemental phosphorus or phosphorus trichloride is subjected to metallic sodium in the presence of a complexing agent and a catalyst, a sodium phosphate cluster is generated, which is practically insoluble in hydrocarbon solvents. On addition of t-butanol, a non-pyrophoric, thermally stable and soluble complex of NaPH, is formed, which can be selectively acylated/alkylated in a stepwise manner providing easy access to a variety of novel P-functionalized BAPO derivatives.[1]

6. An Industrial Route to Protoporphyrin IX – From Research to Production

Dr. Dirk Spielvogel, Solvias AG, Kaiseraugst, new address: F. Hoffmann-La Roche AG, Basel, Switzerland

The most predominant function of protoporphyrin IX (Fig. 1) in nature is its integral iron chelating capability to form heme and thereby contribute to the oxygen-carrying capability of hemoglobin and blood in general. Accordingly, the natural abundance of protoporphyrin is significant and modes of isolation from natural sources have been described. From the pharmaceutical perspective, blood as a ‘natural pool of building blocks’ represents a significant regulatory hurdle due to inherent contamination risks.

![Scheme 1](image)

Late stage elaboration of the vinyl side chains as well as saponification to the targeted disodium salt was established on the basis of reasonable precedence with the focus to meet high quality requirements for the product and its application as a co-factor in a biotechnological process for a vaccine manufacture.

7. PAT Implementations into Production Environment: Only a Nice-to-Have?

Dr. Tobias Merz, Thomas Waniek, Lonza Ltd, Visp, Switzerland

Custom manufacturing is intimately linked to developments in the pharmaceutical industry. Some trends in the pharmaceutical industry and drivers for its change could be observed in the last few years. R&D costs are the main cost drivers for new chemical entities. The decrease in number of newly approved products per year demonstrates the lack of innovation as well. One argument could be the tougher political and regulatory environment. The FDA as well as the EMA have started the Process Analytical Technology/Quality by Design (PAT/QbD) initiative to shift the regulatory burden to more regulatory flexibility by increasing process understanding. In order to gain a better pro-

cess understanding R&D work is necessary and will allow more knowledge-based decisions.\[1\] But at the same time the R&D costs have to be decreased. One way out is the outsourcing of high risk early phase projects within clinical phase I up to III. What does this mean for custom manufacturing organizations (CMO)?

To be successful as a CMO with the production of early phase projects two arguments are important: First, the time for delivery and second, the price has to be competitive. This is a trade-off between asset utilization and margin. Irrespective of other arguments like strategic collaborations or licensing deals, R&D work and production has to become more efficient.

Many challenges have to be considered, such as the increasing complexity of processes, higher level of toxicity and cost pressure. The implementation of the QbD philosophy, which recommends the risk-based approach, is one way forward to address these problems. New PAT technology and methods enable the way for pro-active manufacturing.\[2\]

Gaining process understanding begins with the familiarization work of the process in the R&D phase. If the number of experiments is reduced, the output of each experiment has to be increased. The utilization and combination of online analytics delivers a huge benefit of information, e.g. measurements of temperature and turbidity gives information about the metastable zone or the combination of pH and turbidity gives information about precipitation. To transfer the knowledge, the sensors have to be in place also in production. One example, depicted in Fig. 1, shows the combination between the measurements of refractive indices and temperature for a solvent change. Due to the implementation in the first experiment, the solvent change could be shortened by 60 min/batch.

Even more complex methods like online mass spectrometry or Raman spectroscopy are really helpful in creating process understanding and finding out what is going on in e.g. a drying procedure, a reaction or crystallization. Especially in toxic environments, the Raman probe can be placed in the reactor even if the spectrometer is more than 100 m away. Another example is a suspension reaction, one step in an early phase project. The time-frame allowed only three experiments during the R&D phase. Furthermore, no reference analytics were available. The Raman probe was also installed in the pilot plant to follow the reaction and predict the endpoint. The advantage of online monitoring is that the reaction and e.g. up-scale effects during the first batches can be followed and knowledge based decisions can be made.

Summary

The pharmaceutical industry is going through a major change and this presents challenges to the custom manufacturing industry. One opportunity, which is one way forward, is a higher degree of innovation. To achieve this, the FDA or EMA supports this possibility by the QbD/PAT initiative. A higher level of process understanding enables more knowledge-based decisions during production. This is the fundamental basis of the validation process. All process knowledge which is gained during the work has to be implemented. To overcome the challenges in custom manufacturing, a higher degree of automation with the combination of online sensors will be necessary.

8. Automation and Continuous Manufacturing in Novartis’ Development Labs

Dr. Thomas Allmendinger, Dr. Jörg Sedelmeier, Novartis Pharma AG, Basel, Switzerland

Inventing and preparing drug substances spans various dimensions: Medicinal chemistry to explore the structural space in finding and optimizing a lead structure, development chemistry and engineering to elaborate a synthetic route and turning it into a robust process and finally chemical manufacturing to cover the full scale dimension.

When exploring the structural space (the preparation of so-called libraries) automation deals with the repetition of synthetic protocols for changing building blocks to obtain several 100s of different compounds on small scale. On the other side, drug manufacturing deals with only one compound of much larger quantity and the automated equipment is used to minimize fluctuations of processing parameters in order to achieve consistently high drug quality, whilst meeting at the same time the drug substance demand.

In the intermediate development phase different automation aspects are covered: a) For screening, simple machines perform parallel runs under different conditions; b) For the optimization of reactions the precise control of parameters like temperature or dosing regimen becomes important to discover their influence on yield and quality, hereby statistical design of experimentation finds widespread application. Finally c) engineering aspects like mixing behavior and heat transfer need to be covered for safe and reliable scale-up applying online and simulation techniques and so-called scale-down reactors. Examples for devices from several suppliers as well as applications for reactions (Grignard, crystallization) are shown.

Continuous manufacturing processes open many avenues to make organic synthesis more efficient and sustainable. Furthermore, the intrinsic microreactor design, particularly its ability to withstand harsh reaction conditions, permits reactions to be performed that were previously challenging when using the traditional batch mode. In addition, flow reactors offer improvements in mixing properties, mass- and heat management, energy efficiency and access to a scope of reaction conditions which are not accessible by conventional batch methods. A standard continuous flow system comprises pumps and reactors, pressure regulators and sensors as well as a mass flow controller unit to monitor the overall flow rate. The entire setup is software-controlled allowing for on-line monitoring of flow rates, mass flow, temperatures and system pressures. The integrated software
control features enable automatic safety shut-down or defined emergency actions thereby increasing the safety of the overall continuous flow process.

The physical properties of a specific chemical transformation dictate whether continuous or batch technology is the most suitable approach for the required task. Slow transformations or chemical processes involving heavy suspensions are often best handled in batch reactors. Indicators for the preferential use of continuous techniques over traditional batch mode are as follows: a) dose controlled reactions where the rate and time of addition or if efficient mixing is a critical parameter, b) tight temperature control requirement for selectivity reasons, c) using or generating highly reactive intermediate(s) which require instantaneous consumption, d) possessing a high activation energy, e) involves a biphasic reaction mixtures where efficient mixing is important due to limited mass transfer and f) dealing with hazardous re-agents in a closed environment. A recent example of the successful application of flow technology is that of the synthesis of the biaryl building block 4, a key intermediate in a recent research investigation (Scheme 1). Here, we focused our attention on continuous flow techniques as we observed major drawbacks due to the presence of unstable intermediates, when applying traditional batch strategies. The flow-based synthetic route presented the opportunity for flash chemistry and telescoping of unstable intermediates.

The issues in the conventional batch synthesis were associated with the production of stable MIDA complex 3. The preparation required a lithiation and a quench with B(OiPr)3 at −78°C followed by the transformation to the MIDA complex in DMSO at high temperature. The intermediates were revealed to be highly fragile and rapidly degrading. Additionally, the transformation towards the MIDA complex in DMSO at 100°C can be considered as a potential safety issue. Not only that, the MIDA complex formation is costly and it also requires an additional chemical step compared to the telescoped flow process (Fig. 1) described below.

Using continuous manufacturing technology allows in-line synthesis of LDA followed by consecutive aromatic lithiation. The in situ quench of the aryl lithium intermediate with B(OiPr)3, minimized the hold-up time for the unstable intermediates, hence enabling reactions to be performed at higher temperatures (−30°C) compared to the batch process (−78°C). Immediate telescoping of the borate intermediate 2 in the Suzuki coupling reduced not only the decomposition of 2 but also shortcut the overall synthesis of the biaryl compound by one chemical transformation. In summary, a convenient, robust and reproducible flow process for the preparation of biaryls has been developed. This process involves a reaction sequence of lithiation, borylation and cross coupling in semi-batch mode. Overall this new approach has not only significantly reduced operational cost and material costs but has also proven to be superior over the batch process.

9. Chemical Processes through the Looking Glass: Use of Information Systems to drive Understanding

Barry Crombie, Thomas Salvesen, Syngenta Crop ProtectionMonthey AG, Monthey, Switzerland

Data is abundant. Within a physical science environment (particularly a production environment) there are few situations in which there is not a surfeit of data – it is perfectly possible to obtain a year of data on a process from 10 different sources at 2 minute intervals, and have all of this in a data table in a matter of minutes or seconds. However, data in itself has limited value and some work needs to be done in order to obtain the full benefit from it. Typically, there is a requirement to extract information from the data and process this to gain knowledge and understanding before this can be acted upon. Our experience is that there are two major stumbling blocks along this path:

i) The desire of the scientist to learn how to use data;

ii) The technical tasks of obtaining and working with data.

Learning how to use data is not simply a matter of using appropriate software tools. A prime example is the case of designing experiments. This is often viewed (and sold) as purely a case of entering a set of variables into appropriate software and using this to obtain a series of experiments to be undertaken. Obtaining good data tends to require more thought than this, and our experimental design training now reflects this – the real value is in the thought process of defining the clear objectives of the series of experiments as well as considering what measurements will be taken in order to achieve these objectives. The same principle applies to plant process improvement projects – it is essential to define what the requirement is and whether there is a realistic probability of being able to demonstrate the improvement.

Process understanding can often start out life within a designed approach to data and this is now certainly encouraged within the FDA ‘Quality by Design’ documentation. This is an approach that has been demonstrated in numerous cases and this will often provide valuable process models to aid the chemist in
process understanding. The value is often not in the mathematical model, but rather in a graphical representation of the process which enables the chemist to visualize the effect of important parameters.

Chemical processes are derived from the principles of organic chemistry to provide a useful molecule in an efficient manner. In a manufacturing environment there is a requirement to minimize the variability of the process used and consistently fulfill the business requirements in terms of capacity and cost. Manufacturing plants produce a wealth of data. The process chemist within this environment needs to be able to use the tools of a data scientist to extract value from this in order to understand and minimize variability as well as identify potential process improvements.

There is a technical question regarding use of appropriate software to process data in a suitable and robust manner. Commercial software exists which greatly aids in managing vast amounts of data, but this can be difficult to work with – the required information may be buried within the mass. One of our approaches has been to adapt available software to enable chemists to process data very rapidly and also carry out statistical analysis in a robust fashion based on their individual needs. The aim of this work has been to create a simplified life for the chemist enabling the chemist to concentrate on chemistry and minimize the level of effort required to obtain, process and understand data.

The hope here has been to start a dialog between data science and chemists which will accelerate the process of transforming data into understanding and allow better business decisions to be made more rapidly.

10. The Importance of Process Models for Polymer Product and Process Development
Prof. Dr. Klaus-Dieter Hungenberg, BASF SE, Ludwigshafen, Germany

Synthetic polymers are a typical example of man-made chemicals that demonstrates the strong interdependencies between their structure, their application properties and the chemistry and process by which they are produced. To handle this complexity, the use of models which quantitatively describe these interdependencies is inevitable (Fig. 1).

![Fig. 1.](image1)

Such models cover different length scales starting from basic kinetic and thermodynamic models to describe the reaction over engineering models for single process units to models for complex production plants and even an entire chemical site.

The lecture showed how models of different complexity and length scales are used over the whole lifetime of a product/process, starting from the first ideas until their on-line use in process operation (Fig. 2).

![Fig. 2. Models of different complexity and length scales.](image2)

When planning a new plant or a capacity increase for a certain product, balancing the necessary chemicals and utilities across the breadth of the process enables a thorough analysis of the entire value chain giving the necessary changes in all involved plants.

Steady-state mass and energy balancing involving the kinetics and thermodynamics of the system in a detailed flowsheet simulation of the plant itself allows the evaluation of alternatives of unit operations, their sizing and sequencing. Examples show how this can be used to minimize specific investment and the evaluation of alternatives for a capacity increase.

The detail and reliability of the layout of individual process units and the determination of their operation points can be greatly enhanced when detailed thermodynamic and kinetic models are used. Especially the coupling of kinetic models with CFD models can give a very detailed insight not only to the distribution of temperatures and concentrations inside a reactor but also to distribution of properties.

Besides the layout of hardware, naturally the product ‘layout’, i.e. the design of the polymer is a major field for model applications. Phase behavior of polymers is strongly determined by their composition. Controlling the composition distribution can help to avoid unwanted demixing, but on the other hand can be used to tailor polymer systems to provoke demixing under certain conditions to create switchable polymer systems. Composition control can be done off-line, but also on-line.

Here we enter another prominent field of model application – optimization of plant operation. This usually means increased productivity by designing – based on appropriate models – new
recipes which are closer to the process boundaries in terms of heat removal capacity, reactor safety, etc. (Fig. 3).

For a batch polymerization process this means optimizing the manipulated variables – temperature profile and initiator type and concentration – to shorten the batch time with the heat removal capacity as well as the product quality – here the molar mass distribution – as constraints.

While this is an example for an off-line application of a process model, the time and technology is now ready to apply such models on-line in the plant.

One example is a model-based safety concept for emulsion polymerization. Based on a detailed heat and mass balance together with a sophisticated thermodynamic model the unreacted monomer in the reactor is limited to such an amount that in case of an unexpected runaway reaction, temperature and pressure will never exceed the reactor limits. By doing this, the process can be run much closer at its limits. The economic benefit is mainly determined by the quality of the thermodynamic model.

The last example is a real-time optimization of a semi-batch polymerization process (Fig. 4). Here the feed rates are adjusted by a non-linear model predictive controller in such a way that the maximum cooling capacity is utilized at every instant of each batch. When comparing this kind of plant operation with the classical operation, this affords a serious paradigm shift. We have to switch from time-based recipes to state-based recipes, and this usually needs some discussion with quality control.

11. Industrial Application of Process Chromatography for Small Molecule Purification in Novartis Pharma

Dr. Felix Kollmer, Novartis Pharma AG, Basel, Switzerland

Large-scale chromatography is a key technology in the manufacture of active pharmaceutical ingredients (APIs). It is a powerful method for purification of molecules with complex impurity profiles such as peptides and (semi-synthetic) fermentation products. For substances that do not crystallize it is often the only way to achieve the required purity.

Chromatography often is integrated in a sequence of purification steps with other separation technologies displaying complementary selectivity, such as adsorption, extraction or crystallization.

High production cost of crude materials typically adds to challenging separation problems. Therefore, to the largest part these drug substances are applied in specialty indications such as transplantation, oncology and other life-threatening diseases. Capacity figures range from several kilograms to up to 30 tonnes per year.

Although process chromatography applies the same physical principle of selective adsorption like analytical chromatography, there are substantial differences that can be attributed to the overloading of the column. Due to low amounts of analyte per stationary phase in analytical applications, there is no interaction between the different components on the solid surface, i.e. adsorption takes place in the Henry regime. Overloaded conditions though account for high surface coverage, which in turn impacts adsorption of target molecule and impurities, hence peak shape and width of main product and retention times of by-products.

Besides selective surfaces, fluid dynamics and mass transfer phenomena also play crucial roles in development and design of an efficient commercial separation process and its performance. Over the past decades substantial progress has been made in column technology and development of stationary phases. Dynamic axial compression (DAC) is a major leap to ensure density and uniformity of the packed bed. Sophisticated constructions at top and bottom of the column enable uniform liquid distribution over the radius which is key for high process performance and not trivial as production scale columns have substantial diameters up to more than 1.5 meter. Development and commercialization of mechanically stable spherical silica with narrow and defined particle and pore size distributions boosted process performance as well, since a maximum of active surface can be supplied at a given pressure drop.

Due to constrained development timelines and increasing production costs of pharmaceutical molecules, there is a trend in industry towards fast development of processes with simultaneously high yield and productivity. In addition, in the early phases there are often only limited sample amounts available for process development. Therefore, selection of a separation system, i.e. best combination of mobile and stationary phase, is based on screening programs performed on automated lab systems on milligram scale. Gradient elution is advantageous in reversed-phase (RP) systems and frequently applied in industrial practice due to availability of sufficiently precise pump systems. Prediction of separation and elution is not straightforward though and optimized and robust process parameters are not easily obtained by heuristic approaches. Therefore, process development is supported by rigorous modeling including mass transfer and adsorption isotherms and in silico optimization of robust process parameters.

Transfer of such processes developed on milligram scales to production level has been shown with scale-up factors of up to 20 000. Nonetheless, experiments in gram scale are still necessary for development of robust and plant fit production processes including suitable work-up methods. Also technical material for development of subsequent chemical and formulation steps needs to be generated.

Recovery of target product from dilute fractions poses a considerable challenge. In normal phase chromatography and in case of chiral separations, organic solvents can often simply be evaporated. In RP chromatography though, this is not a viable option since the mobile phase is rich in water and acid additives may be present. Moreover, in most cases the desired salt form of the API needs to be adjusted as well. There are several unit operations of choice including organic nanofiltration (ONF), liquid-liquid extractions (LLE), solid-phase extractions (SPE), ion-exchange over packed beds (IEX), crystallization, precipitation etc., all of which should not be underestimated in their complexity and potential for yield and purity losses.

When considering process economy, some general points can be stated: Equipment is expensive because of technical complexity and the required pressure rating. Additionally to the costs of
the pump module and column, massive investment for periphery such as fraction vessels, evaporators, solvent vessels, etc. is needed in order to handle the large solvent amounts. Solvent consumption itself is often not so much of a cost driver, as recycling and regeneration is common practice for established products with high production capacity. In terms of productivity, i.e. throughput per column (vessel) volume, chromatography is typically one or two orders of magnitude lower than a typical crystallization. This is due to high dilution, which in turn is caused by limited usage of active surface during the process. Mass transfer constraints due to pore diffusion cause comparably long elution times which are prolonged by cleaning in place (CIP) and equilibration steps.

Hence, even though being a powerful purification tool, process chromatography will remain a niche technology only to be applied when no other possibility exists to achieve the required product quality.