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Conference Report

Symposium on Process Analytical Technology (PAT) at ILMAC Lausanne 2018

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On the occasion of ILMAC Lausanne on October 3, 2018, SCS organized the 2nd Swiss PAT Symposium with six experts that talked about latest developments in the field and gave an outlook to where the PAT approach could lead the production in the future. After a very successful first event at the SCS Fall Meeting 2017 this event again offered a unique platform to exchange latest trends and developments. Many thanks to the experts that contributed a lecture and to Tobias Merz from Lonza who chaired the symposium in a very competent way.

Use of Process Analytical Technology (PAT) for Monitoring and Optimizing Powder Mixing Processes

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The Process Analytical Technology (PAT) approach, which is well established in the pharmaceutical and chemical industry, was successfully applied on food manufacturing. PAT is about the IDENTIFICATION of critical process parameters in the manufacturing process as well as in-line sensors enabling real time process MONITORING and CONTROL for the continual improvement of quality and costs.

A food manufacturing process was analyzed in view of critical unit operations and process parameters. A strategy to assess and develop in-line sensors to monitor and control the critical unit operations was put in place. Sensors were used to make the invisible visible, which further improved our process understanding and enabled the optimization of the manufacturing process. The advantages and limitations of PAT were discussed for powder mixing, which is one of the most important unit operations when producing powdery products. During mixing, the foundation of a compliant and consistent product is laid. But the homogeneity does not only effect product quality but quite often also the asset intensity of downstream unit operations. For a given installation and recipe, the homogeneity of the mixed mass is mainly influenced by the mixing time, the speed of the mixing devices as well as the filling degree of the mixer. Traditionally, the analysis of the powder mixer performance is quite time intensive, which makes the studies of parameter variations difficult. Several samples are taken after different mixing times, analyzed with off-line analytics and the variance is calculated to assess the mixing progress with time.[1]

In his PhD thesis 'Continuous dynamic mixing of cohesive powders',[2] Volker Kehlenbeck has already shown the power of near-infrared (NIR) spectroscopy to access continuous and batch powder mixing processes.[3] Industrial application of the developed self-cleaning near-infrared probe (air flushing) was not possible as a contact between probe and product was required:

- In contrast to the model ingredients maize starch and calcium carbonate used in the framework of the PhD thesis, most food powders are moisture- as well as temperature-sensitive and tend to form layers in the mixer. After a short time of operation, a layering on the measuring window of a near-infrared spectrometer would occur, which cannot be removed by air flushing and would cause an incorrect measuring result.
- Furthermore, industrial mixers do not have openings to allow immersion of near-infrared probes in the fluidized mass without drilling holes.

In the meantime, powerful near-infrared spectrometers for a contactless measurement in distances of up to 60 cm have become commercially available. The assessment of this technology for process monitoring and optimization was successfully restarted in pilot and industrial scale.

The following topics were covered during the lecture:

- Process Analytical Technology in general
- Impact of the mixer filling degree on the mixing homogeneity
- Impact of the sample size on the measuring result
- Use of near-infrared spectroscopy for monitoring continuous and batchwise working powder mixers in pilot and industrial scale (time and trajectory plots)
- Comparison of off-line reference and in-line near-infrared measurements

[1] V. Kehlenbeck, K. Sommer, 'Different methods to determine the mixing performance of a batchwise working screw mixer', *Powder handling & processing* **2003**, *15*, 318.
[2] V. Kehlenbeck, 'Continuous dynamic mixing of cohesive powders', PhD Thesis, Technical University Munich, **2016**.
[3] V. Kehlenbeck, 'Use of Near Infrared Spectroscopy for in- and off-line performance determination of continuous and batch powder mixers: opportunities & challenges', *Procedia Food Science* **2011**, *1*, 2015.

How Can you Get more out of your Data? Datamining @ Bosch Packaging

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The lecture introduced the concept of i4.0 and how it is related to pharma. Use cases from laboratory and production-scale equipment were demonstrated and showed how valuable knowledge can be extracted from process data. The proposed method underlined the concept of the PAT, QbD and CPV Framework, or demonstrated how it can also be used for root cause analysis and continuous improvement projects.

Chemometric Modelling to Predict Concentration of API in a Solution Flow

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API concentration is obviously a critical Quality Attribute (cQA) of any Drug Product. In this work, a continuous process to manufacture aqueous solutions has been developed. The target is to develop a fast, precise and accurate method to determine the API content in the outgoing flow. A chemometric model has been applied to UV/Vis spectroscopic data in order to predict online the API concentration. This information would then be used to serve multiple purposes: real-time release of the solution, feedback to the manufacturing process in order to adjust critical Process Parameters (cPP) and, if necessary, divert non-conforming portions of the product.

Digitalization in the Pharmaceutical Industry

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The digitalization of the pharmaceutical industry is driven by regulatory initiatives (*e.g.* Quality by Design, Process Analytical Technology, Continuous Process Validation) and pressure on the process development timelines ('Time to Market') and reduced production cycle times ('Real Time Release Testing').

Different drivers for digitalization require different solutions – not only concerning the differences of the data which have to be analyzed for different purposes. Also the tools for visualization, trending and reporting are different. Production sites and laboratories are spread over different countries and are characterized by different IT systems, infrastructure and data acquisition systems.

The presentation showed some concepts how integration of systems can be achieved and how the various requirements for data management and data analytics in production, QC and research can be met.

Preventing Overflow Metabolism in Crabtree-positive Microorganisms Using the PAT Approach: Progress and Challenges

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At growth rates above a particular critical value, Crabtree-positive microorganisms exceed their respiratory capacity and enter diauxic growth metabolism. Excess substrate is converted to an overflow metabolite, resulting in decreased biomass yield and productivity. To prevent this scenario, the cells can be cultivated in a fed-batch mode at a growth rate maintained below the critical value, µcrit. This approach entails two major difficulties: accurately estimating the current specific growth rate and controlling it successfully over the course of the fermentation. In this presentation, the results obtained with *S. cerevisiae* and *E. coli* fermentations will be reported with a focus on the specific challenges that were encountered.

Identifying Process Critical Parameters through the QbD Approach

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Process analytical technology (PAT) requires knowledge of critical process parameters and their effect upon critical quality attributes of the process. The quality by design (QbD) approach builds this information and makes it accessible through statistical models. Both concepts share a lot of methods for data analysis. In the interest of a lean development and application it is important to see the communalities and to make best use of it. Experimental design (DoE) is a focal aspect in this development, it provides the base for the identification of driving factors, that are linked to the critical quality parameters through a statistical model. This in turn can be used for simulation studies that help to describe the design space in a way that is easy to use and understand. A case study is used to demonstrate this process. It is the direct path to a reliable result that is obtained with the minimal amount of resources.