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Review

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Assessment of Recent Process Analytical Technology (PAT) Trends: A Multiauthor Review

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ABSTRACT: This multiauthor review article aims to bring readers up to date with some of the current trends in the field of process analytical technology (PAT) by summarizing each aspect of the subject (sensor development, PAT based process monitoring and control methods) and presenting applications both in industrial laboratories and in manufacture e.g. at GSK, AstraZeneca and Roche. Furthermore, the paper discusses the PAT paradigm from the regulatory science perspective. Given the multidisciplinary nature of PAT, such an endeavour would be almost impossible for a single author, so the concept of a multiauthor review was born. Each section of the multiauthor review has been written by a single expert or group of experts with the aim to report on its own research results. This paper also serves as a comprehensive source of information on PAT topics for the novice reader.

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1. INTRODUCTION

Chemists and engineers working in Process R&D and Manufacturing aim to minimize the variability in the processes they design and operate, whether these processes are batch or continuous. The understanding of these manufacturing processes is key to their control. But most processes are exceedingly complex multifactorial systems and require new technologies to assist in their understanding.

Process analytical technology is defined as a system for designing, analyzing, and controlling manufacturing processes through timely measurements (i.e., during processing) of critical quality and performance attributes. The measurements may be on raw materials, intermediates, and products, but often they are of key process parameters which affect the efficiency of the process and the quality of the final product of the process. It is important to state that, in this context, the term analytical in PAT can include chemical, physical, microbiological, mathematical, and risk analyses possibly conducted in an integrated manner. Thus, the topic is extremely broad, and experts in the field of PAT may come from a variety of backgrounds, particularly in engineering and instrumentation.

This is a hot topic at present, particularly in the pharmaceutical and fine chemical industries, who are trying to come up to speed with a subject where the bulk chemical industry has, surprisingly to some, been ahead of the game. Since regulatory authorities are now becoming more involved in processing issues such as process understanding and PAT, it is timely to assess the current state of PAT and its applications in industry. There have been a large number of publications in the last 5−10 years, and it is difficult for those not directly working in the field of PAT to comprehend the current state of the art.

This review article therefore aims to bring readers up to date with some of the current trends in PAT—the list of topics discussed should not be considered exhaustive—by summarizing each aspect of the subject (sensor development, PAT based process monitoring, and control) and presenting applications both in the laboratory and in manufacture. This paper also serves as a comprehensive source of information on PAT topics for the novice reader.

Given the multidisciplinary nature of PAT, such an endeavour would be almost impossible for a single author so the concept of a multiauthor review was born. This is a new format for this journal, and we hope that it sets a trend when a complex subject needs a comprehensive review which may tax the knowledge of even a small group of authors.

Each author in this review is an expert in a particular aspect of PAT and is therefore able to give a concise up-to-date account of a small but important area of the PAT landscape. Each section of the multiauthor review has been written by a single expert or group of experts, so there will, understandably, be variations in style and approach, but the heterogeneity has hopefully been minimized by the editing of the lead author, who has brought the individual sections together.

The paper is structured as follows: first, a discussion on the value of PAT in various stages of pharmaceutical process development is presented, followed by a section covering recent advances in the field of sensor development. The subsequent section discusses novel PAT based process monitoring and control methods with laboratory-scale applications. This is followed by examples of laboratory scale PAT implementations in academia and industry, e.g., crystallization optimization at AstraZeneca. The last section of the paper presents an example of a production scale PAT implementation at GSK and Roche, Ireland for a highly exothermic reaction. Also in this section the SIPAT PAT software platform is discussed. Due to confidentiality, the examples contributed by the industrial authors are limited in terms of technical details.

Trends and developments in the field of PAT[1−3] have been regularly discussed in review papers on wide-ranging topics such as near-infrared (NIR) spectroscopy applications,[4−8] crystallization monitoring and control,[9−12] chemical imaging,[13] terahertz spectroscopy,[14] particle size analysis,[15] Raman spectroscopy,[16] imaging sensors for bioprocess monitoring,[17,18] sterile product production,[19] fluidized bed granulation,[20] film coating,[21] and multivariate data analysis and chemometrics.[22−25] These reviews are of course valuable; however, they serve a

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different purpose—to provide a detailed overview of one specific PAT related aspect—compared to this multiauthor review which aims at giving the broader overall picture of the PAT field.

2. PERSPECTIVE ON THE VALUE PROPOSITION OF PAT IN VARIOUS PHASES OF PHARMACEUTICAL PROCESS DEVELOPMENT AND MANUFACTURE

For over a quarter of a century, process analytical technologies (PAT) have been adopted across a wide cross-section of applications for drug-substance manufacturing in the pharmaceutical industry.[26,27] The FDA's initiative on the Pharmaceutical cGMPs for the 21st Century, aimed to encourage adoption of new technological advances by the pharmaceutical industry, and the subsequent issuance of the FDA PAT guidance of 2004,[28] led to increased impetus and focus on this arena and raised significant expectations of greater adoption of PAT in all phases of development by the pharmaceutical industry. While it can be argued that the overall adoption of PAT by the pharmaceutical industry has since increased significantly, Reid et al.[29] point out that the majority of PAT applications in the past few years are still mainly in the R&D space, aimed predominantly towards understanding in the early (lab-scale) process development phase and, to a lesser extent, towards the support of late-phase development and scale-up activities.

The use of PAT as a real-time control tool in commercial manufacture, however, continues to be very limited. An analysis of the impact of recent advances in PAT as applied to the various phases of drug substance process development and some possible explanations for the observed trend (Figure 1) are presented in the following paragraphs.

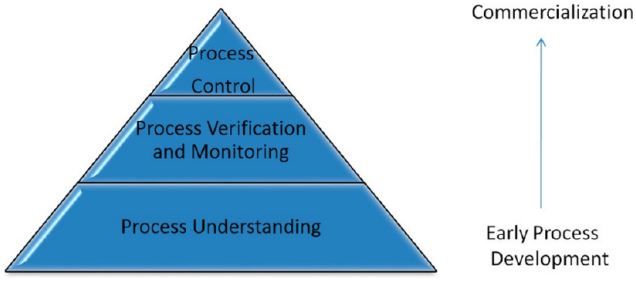

Figure 1. PAT applications in various phases of process development.

2.1. Early Process Development. The value proposition for PAT in early process development, as an enabler of increased mechanistic and process understanding, has already been validated by academia and the broader scientific community over decades. The rich data sets that PAT enables can be often combined with modeling tools to obtain in-depth mechanistic understanding in an efficient manner.[30,31] Recent advances in PAT have continued to lower the barriers for their use while simultaneously increasing the level of knowledge that can be gained, leading to increased adoption. For example, advances in inline mid-IR probe technology have led to "flexible" silver halide (AgX) and virtually eliminated the need for cumbersome probe alignment, something that was essential even five years ago. Greater integration of chemometric analysis techniques into spectral collection software has enabled scientists to obtain quantitative/semiquantitative information on the processes with reduced effort. Novel technologies as well as novel uses of existing technologies have now extended the applicability of PAT to virtually all of the typical unit operations that constitute a drug substance process and shown to result in rapid knowledge generation required to support the rapid development of novel medicines.

2.2. Scale-Up to Pilot Plant. The benefits of using PAT during scale-up from lab to pilot plant are also well-recognized. As in the case of early development, PAT facilitates process understanding, but with the transition in batch size and purpose upon scale-up the benefits include options for PAT implementation for process verification and process control.[32] Thus, PAT can be part of the risk-mitigation strategy during scale-up to ensure that the operation is proceeding as intended, to develop a "process signature" to monitor batch-to-batch reproducibility or to assist in process transfer between different vessels or sites. PAT has also been shown to ensure safe scale-up of processes that have traditionally been considered to pose a safety risk.[33−37] Real-time monitoring can be advantageous as an alternative to traditional off-line analysis in that it requires no sample preparation and data can be analyzed rapidly compared to chromatographic techniques. It is also an attractive option in cases where the samples are difficult to access due to safety considerations or sampling concerns (e.g., thick slurries), when an off-line sample may not be representative (multiphase systems or extreme operating conditions) or where frequent sampling is desired. The knowledge-rich process details/information obtained with PAT may allow for rapid troubleshooting in instances where such a need arises. One of the more compelling uses for PAT involves the use of on-line monitoring as an integral part of the control strategy—an example of this is continuous processing where real-time monitoring and feedback is essential to ensure that the process is within control.

2.3. Considerations in Manufacturing. However, in contrast to its use in the lab, there are several considerations that come into play for the on-scale implementation of PAT. A recent publication by Guenard and Thurau provides an excellent outline of the workflows for implementing PAT in an industrial setting.[38] Some of the most important considerations include: instrument deployment in a hazardous processing environment, requirements for implementation in a cGMP setting, data management and interface with plant systems, interfacing sampling probes with the process, and method development. Hazardous process classifications typically associated with chemical processing areas require the instruments to be rated for use in these environments and these requirements could change for operation in various countries (e.g., UL certification in USA, ATEX in Europe, and CSA in Canada). Operation of these systems in a GMP environment also necessitates development of SOPs and workflows for procedures including instrument qualification and change control. Adequate interfacing of the sampling probes with the process stream is key to ensure a successful implementation of PAT—options include use of long probes, where the PAT technology and the vessel configuration are amenable to such an option, recirculation loops,[39] use of probes in dip-tubes,[37] and probes in bottom valves of vessels.[40] More recently skid-based configurations[41] have been developed to enable rapid interface of various PAT sensors with the process. The actual location of these sample probes in the system has also been shown to have a significant impact on the measurement, especially for heterogeneous systems.[39,42] Finally, instrument method development for on-scale implementation of PAT can

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also be a challenge—while a high degree of sensitivity is typically required, a key condition for reliable measurements is that the methods should be robust to typical variations in a chemical process environment. A common approach for method development include the use of the plant instrument in a lab setting to develop the model or to rely on instrument-to-instrument transfer procedures which, for certain technologies, still remain an issue. This approach typically necessitates refinement of the models with on-scale data. Some of the issues and challenges of the calibration transfer have been discussed by Miller.[43] More recently, "online-calibration" methods[44] and approaches obviating the need for calibration[45−47] have been outlined. Recently, Brearly and Foulk[48] have discussed challenges and strategies for applications where the analyzer must be calibrated on-line.

The applications of PAT in the commercial arena can also be broadly categorized into two groups—one is the use of PAT as a knowledge gathering tool to support process robustness (i.e., the "process signature" concept), to enable continuous improvement, and as a valuable tool for troubleshooting quality event situations and process robustness issues. The second is the use of PAT for control, either to replace traditional off-line measurements or in instances where on-line monitoring is an integral part of the control strategy (e.g., continuous processing), or when the process is not amenable to control by other techniques (e.g., unstable samples). Implementation of on-line monitoring in a commercial setting to enable control represents a huge step up for several reasons. Regulatory filing of PAT methods entails several detailed considerations around model development, validation, and lifecycle management. These include investigations into specificity and matrix interference, examination of the effects of sample handling and preparation, understanding, documentation, and control of the effects of the environmental variables on the spectral response, understanding and controlling for the variance in sample presentation to the detector, potential use of orthogonal reference methods for calibration, validation procedures, and development of lifecycle and postapproval requirements. This may often require gathering on-scale batch data for several batches to fine-tune the model. While there have been recent draft guidances[48] that have provided more clarity about the methodology for PAT filings vis-a-vis regulatory expectations, and some industry efforts are underway to develop methods which conform to these requirements[49] and overcome limitations,[50] there are relatively few published examples in the literature of on-line PAT applications that have been successfully filed and are in commercial use in the drug substance arena. Another important requirement to integrate PAT into a control loop is that of data management in a CFR Part 11 compliant manner and the use of software that can integrate with plant control systems. Several data management solutions including SIPAT[50] and Optimal SynTQ[51] are recently being evaluated in the pharmaceutical industry to address this need. Furthermore, while significant progress has been made, instrument robustness for a typical 24/7 operation still remains an issue for certain PAT technologies.

2.4. Value to Commercial Manufacturing. The value of real-time monitoring in the commercial manufacture of drug substances has been a topic of great discussion within companies and also in various industry consortia.[52] From the above discussion, it is clear that, while there are noticeable benefits, there are also significant trade-offs in the larger scale and commercial space. On balance, it is accepted that there still exists a clear value proposition for use of PAT as a knowledge gathering and monitoring tool in the commercial space. The value proposition for replacing traditional off-line analyses with real-time monitoring is less apparent. Mojica et al.[53] argue that the value proposition of replacing potentially time-consuming off-line analyses with real-time monitoring realized by the food, petrochemical, and polymer industries does not necessarily translate to the pharmaceutical industry. They consider that the unique aspects that characterize the pharmaceutical industry today—a predominance of batch processing with fewer opportunities for feedback control, necessary tight regulatory oversight, and multipurpose plants typically producing limited batches of a given product (as opposed to commodity chemicals, for example) may still make the cost-benefit proposition less compelling and fraught with greater risk from a technical implementation and regulatory acceptance perspective. Therefore, the value proposition for the process control application is likely to be limited to instances where PAT is an integral part of the control strategy and its advance will closely mirror growth of such applications in the commercial arena.

An alternate explanation for the limited utilization of PAT in manufacture is consistent with the risk-based approach to process development that is being adopted by the industry today. It can be argued that, from the point of view of process knowledge, the risk to the process is highest in early development when the process is still not well understood (Figure 2).

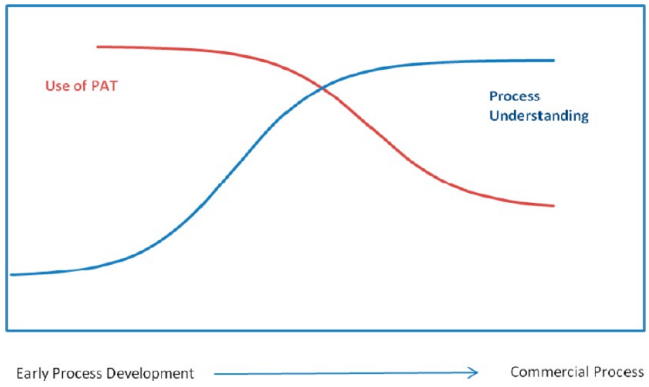

Figure 2. Value proposition of PAT during various phases of development from a process understanding risk viewpoint.

Extensive use of PAT at this phase is warranted to help develop the understanding and mitigate this risk. The same can be said for PAT utilization during the initial scale-up phase. For processes that are scale-dependent and require optimization, PAT is increasingly being used during scale-up for control, optimization, and to develop further understanding. Paradoxically, the increased knowledge gained during this phase also serves to obviate the need to use PAT in the commercial phase. As the process enters the commercial phase, development following the Quality by Design (QbD) paradigm should ensure that the process is well-understood, designed to be robust, and consistently produces material of high quality. The role of PAT at this phase would therefore predominantly be for process knowledge to verify that the process is performing as expected and to support process robustness and continuous improvement.

In summary, the observed trends in the use of PAT during the various phases of industrial process development can be

attributed to the value proposition of on-line monitoring throughout the different stages of the development. It is important to point out that in the manufacturing space this value proposition is a reflection of the state of technology, the existing regulatory landscape and the current role that PAT plays in the overall control strategy. Advances in these various arenas, which are likely to occur in the coming years, will merit a periodic re-evaluation in the future.

3. PAT FROM REGULATORY SCIENCE PERSPECTIVE

The pharmaceutical quality initiatives advocated by the US Food and Drug Administration (FDA)[54−56] and endorsed by International Conference on Harmonization (ICH) regions in the past decade have populated two science-based innovative concepts, PAT[57] and QbD,[58] for the benefits of protecting and promoting public health. The implementation of these two innovations differentiates two possible approaches in developing a drug substance or a drug product, i.e., traditional approach and enhanced approach.[59] In a traditional approach, set points and operating ranges for process parameters are defined, and control strategy is typically based on demonstration of process reproducibility and testing to meet established acceptance criteria. In an enhanced approach, risk management and scientific knowledge are used more extensively to identify and understand process parameters and unit operations that have an impact on critical quality attributes (CQAs) and to develop appropriate control strategies applicable over the life cycle of the drug substance or drug product, including the possible establishment of design space(s). It is important to recognize that traditional and enhanced approaches are not mutually exclusive; a combination of both might work fine, too. Regardless the approach, the goal of the manufacturing process development for the drug substance is to establish a commercial manufacturing process capable of consistently producing drug substance of the intended quality. ICHQ11 indicated that the intended quality of the drug substance[59] should be determined through consideration of its use in the drug product as well as from knowledge and understanding of its physical, chemical, biological, and microbiological properties or characteristics, which can influence the development of the drug product. Drug substance CQAs typically includes those properties or characteristics that affect identity, purity, biological activity, and stability. An enhanced approach to pharmaceutical manufacturing development could include three essential steps: (i) the identification of CQAs. For example, physical properties that are important to drug product manufacture or performance and purities that are important to drug product safety can be identified as CQAs: (ii) linking material attributes and process parameters to drug substance CQAs and (iii) establishing control strategies and process design space. It has been well-recognized that the crystallization process parameters can have great impact on the crystallization product quality attributes such as purity, morphology, size, polymorphic form, impurity profile, solubility, dissolution rate, etc. Each or all of these quality attributes can either independently or collectively impact dissolution, bioavailability, efficacy, and in some cases safety of the drug product. Therefore, detailed description of the drug substance crystallization process and key quality attributes of crystalline materials are required to be included in the regulatory submissions in chemistry, manufacturing, and control (CMC) sections for evaluation. The ICH Q11 Guideline[59] on development and manufacture of drug substances is particularly relevant to the preparation and organization of the contents of sections 3.2.S.2.2−3.2.S.2.6 of Module 3 of the Common Technical Document.[60] The potential CQAs of drug substances that are related to pharmaceutical crystallization includes: polymorphic form, crystal size distribution, crystallinity, morphology, etc., given their impacts on solubility, dissolution, bioavailability, and pharmacokinetics/pharmacodynamics (PK/PD) profile. Because of the critical importance of crystallization process and crystalline materials, several relevant regulatory guidance documents were published to address various quality and safety aspects of drug substances.[61−65]

For a traditional approach, material specifications and process parameter ranges can be based primarily on batch process history and univariate experiments. An enhanced approach can lead to a more thorough understanding of the relationship of material attributes and process parameters to CQAs and the effect of interactions. Typically, a linkage between them can be identified and confirmed by designing and conducting studies, e.g., mechanistic and/or kinetic evaluations,[66−72] multivariate design of experiments,[70,71] and simulation and modeling.[73] With the linkage identified and confirmed, control strategies and design space can be established to achieve high level of process understanding and confidence on quality.

The design space can be developed based on a combination of prior knowledge, first-principles,[67] and/or empirical understanding of the process. Our studies[71,74] demonstrated that integration of design of experiments (DOE) and PAT can lead to the establishment of a dynamic process design space and to quantify the effect of pharmaceutical process dynamics on process performance or process outcome.

3.1. Crystallization Monitoring and Control from the Regulatory Science Perspective. There are a number of PAT tools and techniques available[10,66,71,75−81] that could be used to monitor and control the pharmaceutical crystallization process, to characterize the crystalline materials, and to gain better product and process understanding for the ultimate purpose of ensuring product quality and safety. Of particular regulatory science importance, novel PAT methods can be used to address several vital aspects: (i) monitoring and control of critical process parameters (CPPs) or essential process phenomena such as polymorphic conversion[82] and phase transformation[83−86] during pharmaceutical processing; (ii) monitoring and control of CQAs such as particle size[87] via real-time or in situ method; (iii) identification of active pharmaceutical ingredient (API) in drug substance and drug product (e.g., via spectroscopic method or XRD method); (iv) quantification of polymorphs[88] and crystallinity[89] via spectroscopic method or XRD in conjunction with chemometrics; and (v) monitoring formulation stability, such as identification of degradation impurities[90] of the polymorph form selected in both drug substance and drug product, prevention, and reduction of the formation and levels of genotoxic and carcinogenic impurities[91] in drug substances and products. The regulatory science significance of those vital aspects has been well-justified by previous lessons and examples,[92−96] given their adverse impacts on current good manufacturing practice (CGMP) compliances regarding identity, strength, purity, and stability of the drug substances or drug products, and their adverse impacts on drug safety. It is important to recognize that the design and implementation of a PAT system for pharmaceutical application creates unprecedented opportunity for scientific innovation. The FDA's PAT Guidance[57] discussed

the general PAT philosophy, PAT principles, and tools. Depending on the specific application and goal, a different set of PAT elements might be needed to achieve the necessary process and product understanding which can support regulatory decision. For specific PAT elements to be included in a specific regulatory submission, the applicant is encouraged to contact the relevant regulatory division(s) for application-specific discussion.

3.2. Regulatory Science Considerations: Process and Technology Validation, Continuous Manufacturing. The CGMP regulations for validating pharmaceutical (drug) manufacturing requires that drug products be produced with a high degree of assurance of meeting all of the attributes they are intended to possess (21 CFR 211.100(a) and 211.110(a)). The FDA's Process Validation Guidance[97] provided recommendations that reflect some of the goals of FDA's initiative entitled[55] "Pharmaceutical CGMPs for the 21st Century—A Risk Based Approach", particularly with regard to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality system tools and concepts.

Consistency, repeatability, and reliability are some of the key elements for validation activity, to ensure that product meets the release specification and building the quality into the product. Scientific validation of emerging technologies for crystallization process monitoring and control could be a challenging task, in which case first-principle modeling[81] might provide one alternate approach. To the best of our knowledge, there is no specific regulatory guidance available to discuss what kind or type of PAT data should be included in the process validation section of a regulatory submission, except some general considerations for process validation that have been highlighted in the FDA's Process Validation Guidance:[97] "More advanced strategies, which may involve the use of PAT, can include timely analysis and control loops to adjust the process conditions so that the output remains constant. Manufacturing systems of this type can provide a higher degree of process control than non-PAT systems. In the case a strategy using PAT, the approach to process qualification will differ from that used in other process designs". Therefore, the applicant is encouraged to contact appropriate Center for Drug Evaluation and Research (CDER) review and inspection division(s) for discussion related to a specific submission.

Current pharmaceutical regulation has successfully handled batch processing for decades. Product release has relied on the batch concept and batch release specification. The disadvantage of batch processing has been highlighted in a relevant FDA Guidance and document.[55,57] Continuous crystallization has been the norm for other industrial sectors (e.g., petrochemical, chemical, etc.) for several decades already. Research and development on continuous pharmaceutical crystallization is expected to boost in the next few years because it is one of the essential unit operations for drug substance manufacturing. Continuous manufacturing of pharmaceuticals has certain advantages[72] over batch processing and has been a very active area for research and development. It is anticipated that continuous manufacturing will become an excellent choice for the next generation of the pharmaceutical manufacturing technology.[98] Should continuous manufacturing data and information be included in the CMC section for regulatory evaluation and approval process, the traditional regulatory concepts (such as batch and batch release) would have to be reexamined in order to move forward.

3.3. Concluding Remarks. Application of PAT for pharmaceutical crystallization process and product understanding, process monitoring and control, and formulation stability in a changing environment presents unprecedented opportunities for innovations in the areas of pharmaceutical development, manufacturing, and quality regulation. The wealth of various tools and technologies available, the significant scientific and technological advancement being made, and proactive regulatory pathway being advocated by the FDA and endorsed by ICH regions, has collectively created a stimulating environment for the implementation of novel technologies and new manufacturing concepts in pharmaceutical sector for better product quality, safety, and public health.

Disclaimer: The views and opinions presented in this section of the paper are only of Huiquan Wu and Mansoor Khan and do not necessarily reflect the views or policies of the US FDA.

4. PAT SENSOR CONCEPTS

This section of the paper discusses recent developments in the field of sensor concepts. The first four subsections focus on the implementation of low-cost sensors mostly for crystallization process monitoring, e.g., single frequency ultrasound, dielectric constant, conductivity monitoring, and imaging using endoscopy.

4.1. Single Frequency Ultrasonic Sensor for Crystallization Monitoring. The development, principle, and implementation of the single frequency ultrasonic crystallization monitoring (UCM) technique is discussed. It is shown that the three most important process parameters to control industrial crystallization processes (liquid concentration/supersaturation, mean crystal size, and suspension density) can be monitored simultaneously in-line by means of only one measuring technique holding two sensors. Therefore, the real time control of the nucleation and the crystal growth based on the information from the ongoing process (liquid and solid phase) is of high importance to obtain the desired product amount and quality which refers to the purity, the crystal size, and the CSD.[99] Therefore, PAT technologies have been developed which are able to provide a wealth of real-time data for the understanding and control of crystallization processes, especially, for in situ use.[100]

In this section a simple, less complex, universal applicable and robust ultrasonic technique referred to as "Ultrasonic Crystallization Monitoring Technique—UCM", based on commercially available instruments, is presented. Here, the time needed for sound to travel a known distance is measured. The influence on the speed is given by the media in-between the sender and the receiver of the sound.

Omar and Ulrich[101] established and evaluated the ultrasonic velocity technique to determine the concentration in the liquid state by using a commercial available sensor. It has been found that the ultrasonic technique, used in situ, is capable of measuring on-line the concentration even if the supersaturation is within the metastable zone. Figure 3 shows the determination of the metastable zone width for solutions of citric acid carried out with the ultrasonic measuring device.

Tititz-Sargut and Ulrich[103] applied an ultrasonic measuring technique using a protected sensor (shielded by a sieve in order to avoid that crystals disturb the reading for the "clear" liquid) to determine the change of ultrasonic velocity and temperature of the liquid phase in a reliable and appropriately sensitive manner in the presence of crystals. Equipped with a cage (the protection), crystals larger than 90 μm were hindered from

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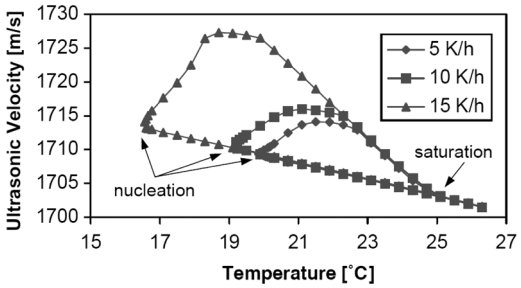

Figure 3. Determination of the metastable zone width between nucleation and saturation point at different cooling rates using the ultrasound technique.[102]

passing the measuring section of the sensor. In the case of an exclusive measurement of the metastable zone width in the absence of crystals, the usage of an unprotected sensor is sufficient as described in the works of Omar and Ulrich[101] and Omar et al.[104] In order to control the crystal size and the suspension density (two of the three key parameters to indicate the progress of a crystallization process), the solid phase has to be considered. For the description of the solid phase in the dispersion the dependence of ultrasound velocity and attenuation on the particle size distribution and suspension density can be used.[99] Pertig et al.[99] demonstrated that the combination of different signals, i.e., the ultrasound velocity and the attenuation obtained at only one frequency provides accurate information on the solid phase in a saturated solution, a mean size (100−800 μm), and wide range of suspension densities (5−40 wt %). Exemplarily, different suspension densities with several particle size fractions of urea crystals were investigated by an ultrasonic probe. The data of the model identification and the results of the fit, represented as lines, are shown in Figure 4.

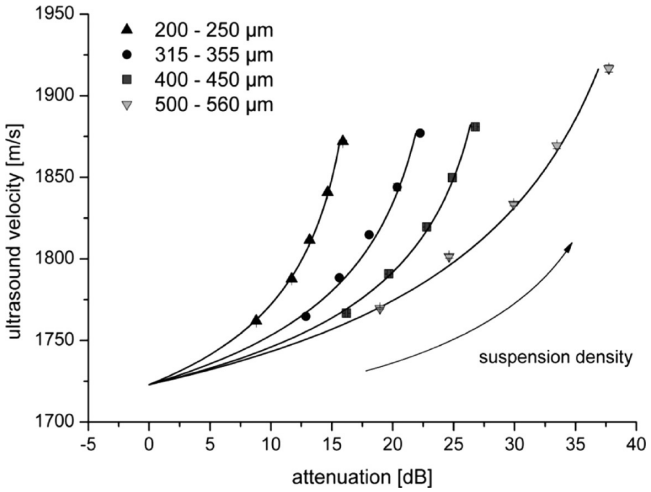

Figure 4. Ultrasound velocity and attenuation measured as a function of suspension density and different particle sizes of urea.[99]

As a consequence, only one measuring technique with two sensors, one protected for the liquid and one unprotected for the solid side, is required to monitor a crystallization process (more specifically the mean particle size and the suspension density).[99] It needs to be emphasized that the UCM technique is proposed as an inexpensive and reliable PAT alternative to monitor and/or control industrial crystallization processes.

The first steps for the implementation of the UCM are calibration experiments to determine the parameters for the mathematical model (model identification) which is required for the calculation of the liquid and the solid phase.[105] Stelzer et al.[105] carried out a total of 20 calibration experiments for the solid and 5 for the liquid phase. A reduction to only 3 experiments for the solid phase with an appropriate accuracy was also demonstrated.[106] The next step of the UCM procedure is the in-line measurement of ultrasonic velocity and attenuation during the crystallization process for the calculation of concentration, suspension density, and mean crystal size as process parameters. Finally, the fast Fourier transformation, covering 30 data points to reduce the scattering of the experimental signals, was applied to smooth the calculated data.[105]

Figure 5 shows the in-line monitored results of the solid phase during a crystallization process for the system urea−

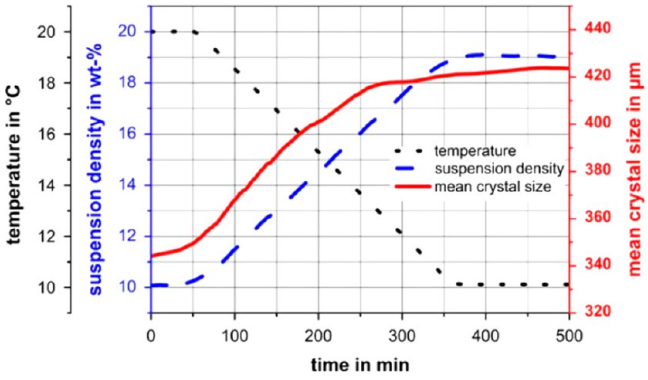

Figure 5. Suspension density, mean crystal size, and temperature as a function of experimental time measured by UCM.[105]

water. The suspension density and mean crystal size are increasing with decreasing the temperature of the urea solution caused by the supersaturating of the solution and, consequently, by the growth of the crystals.

In order to quantify the accuracy of the UCM, Stelzer et al.[105] compared the obtained data (concentration, suspension density, and mean particle size) with values from the literature, preset conditions, and 3D ORM (MTS 523 PsyA CSD particle analyzer, Sequip S+E GmbH, Germany). It was shown that the deviations related to the model were very small which underlines the accuracy of the UCM technique. Furthermore, Pertig et al.[99] obtained promising results while investigating ammonium sulfate suspensions. That indicates the transferability of the presented model to other substances.

To summarize, the UCM technique can be applied on the laboratory scale for the determination of the metastable zone width, nucleation and growth kinetics, seeding events, and detection of phase transitions (e.g., model substance citric acid[107]) for a wide range of materials. The range of measurements with high accuracy in the desired field of industrial crystallization is ensured, also as in-line process control, through particle sizes between 100 and 800 μm and suspension densities between 5 and 40 wt %. Thus, the application, even in optically nontransparent media where other optical processes fail, clearly show that the presented UCM technique provides sufficient in-line process control of the liquid and the solid state.

4.2. Dielectric Constant Sensor for Metastable Zone Width Determination. Dielectric constant measurements have been widely used for characterizing pharmaceutical systems[108] investigating solution and molecular structures,[109]

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detecting phase separations,[110] and determining solubility.[111] These generally exploit the sensitivity of dielectric analysis to changes in physical properties. Recently, Tan and co-workers have successfully utilized a simple and low-cost dielectric constant method for in situ determination of metastable zone width (MZW) of solution crystallization.[112] Figure 6

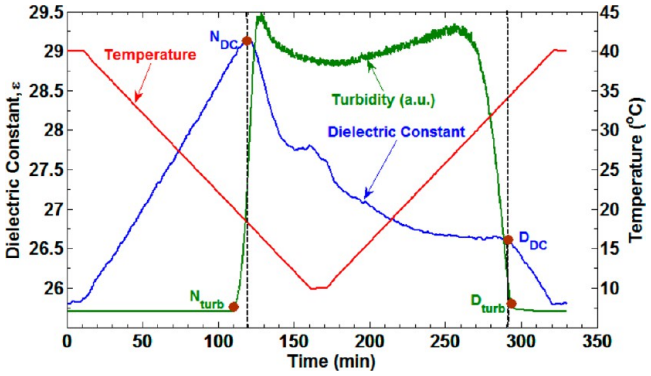

Figure 6. Dielectric constant, turbidity, and temperature profiles for a typical crystallization experiment of paracetamol in ethanol (240 g/kg solvent), at the cooling/heating rate of 0.2 °C/min. Reprinted with permission from ref 113. Copyright 2011 Elsevier.

shows the dielectric constant, turbidity, and temperature profiles of a typical experimental run of solution crystallization. The MZW is obtained by subtracting cloud point (N) from clear point (D).

Although the clear point obtained from dielectric constant measurement was very close to that obtained from turbidity measurement, this was not the case for the cloud point. A slight discrepancy was observed between the cloud point determined by the dielectric constant measurement and turbidity measurement. A plausible explanation of this discrepancy is the coupled effect of solute concentration and temperature on dielectric constant.

To improve the accuracy of the cloud point determination using dielectric constant measurements, a suitable calibration model based on log-polynomial expansion was developed to decouple the effects of solute concentration and temperature on dielectric constant for the given solution.[113] The calibration model was further utilized to transform the dielectric constant profile into a solute concentration profile. The cloud points determined from the solute concentration profile are more accurate than those determined directly from the dielectric constant profile as confirmed by turbidity measurements (Figure 7).

The accuracy of dielectric constant for MZW estimation was further compared to those obtained from turbidity measurement and focused beam reflectance measurements (FBRM) for three different systems, namely, stearic acid−ethyl acetate, paracetamol−ethanol, and carbamazepine−methanol.[114] The accuracy of MZW obtained by dielectric constant was found to be reasonable (i.e., within 1 °C), thus enabling the use of dielectric constant as an alternative PAT for MZW measurement.

4.3. Conductometry Based Concentration Control of Crystallization Processes. One of the most adopted methods of feedback control for crystallization processes is concentration control (C-control), which usually employs ATR-FTIR for solution concentration measurement. However, the investment for ATR-FTIR sometimes can be quite costly (about $70 000) and difficult to justify. Alternatively, a conductivity meter can

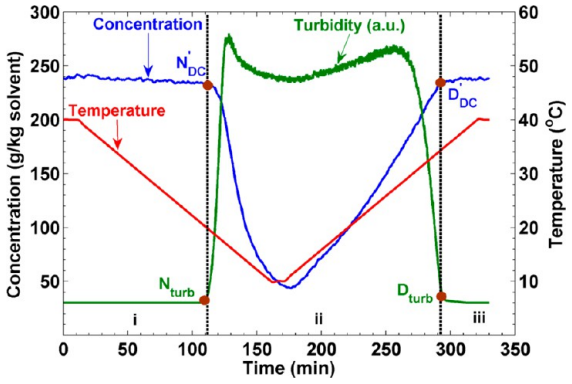

Figure 7. Predicted concentration, turbidity, and temperature profiles during a typical crystallization experiment of paracetamol in ethanol (240 g/kg solvent), at the cooling/heating rate of 0.2 °C/min as shown in Hermanto et al.[113] Reprinted with permission from ref 113. Copyright 2011 Elsevier.

serve as an inexpensive sensor (less than $2000) for solution concentration measurement of applicable systems. For instance, a conductivity meter is generally applicable for inorganic chemicals, but may not be sensitive enough for most organic chemicals. In addition, a conductivity meter can only be used to track the concentration of single components and generally is less accurate than ATR-FTIR. Nevertheless, when a conductivity meter is applicable, it can be used to implement C-control.

Recently, Hermanto et al. proposed a reduced calibration approach to implement concentration control using conductometry.[115] In this work, the following polynomial form is considered to relate solution concentration and temperature to solution conductivity (eq 1):

$$\kappa(C, T) = pC^2 + q(T)C + r(T) \quad (1)$$

where C and T are solution concentration and temperature, respectively, p is a constant coefficient, and $q(T)$ and $r(T)$ are arbitrary functions of T. This polynomial form can accommodate mild nonlinearity with respect to concentration and allows temperature−concentration interaction terms. The conductivity difference that needs to be followed during crystallization can be expressed in terms of the desired supersaturation (S), solubility $\kappa(C^*)$, and temperature as follows (eq 2):

$$\Delta\kappa(S, C^*, T) = \kappa(C, T) - \kappa(C^*, T) = [p(2C^* + S) + q(T)]S \quad (2)$$

Obtaining p and $q(T)$ requires two types of experiments and simple data fittings (Hermanto et al.[115]), which can be performed relatively faster compared to full calibration experiments (i.e., about 50% time saving with respect to full calibration experiments with five different concentrations). For the potash alum−water system, the $\Delta\kappa$ profiles corresponding to constant supersaturation values of 5, 7.5, 10, and 15 g/kg-water are shown in Figure 8a. To assess the accuracy of the proposed method, the respective supersaturation profiles are calculated from the $\Delta\kappa$ profiles by performing full calibration, and they are shown in Figure 8b. It can be seen that the $\Delta\kappa$ profiles yield sufficiently accurate supersaturation, with root-mean-square prediction error of 8.589×10^{-2}, 1.339×10^{-1}, 1.855×10^{-1}, and 3.000×10^{-1} g/kg-water, for supersaturation values of 5, 7.5, 10, and 15 g/kg-water, respectively.

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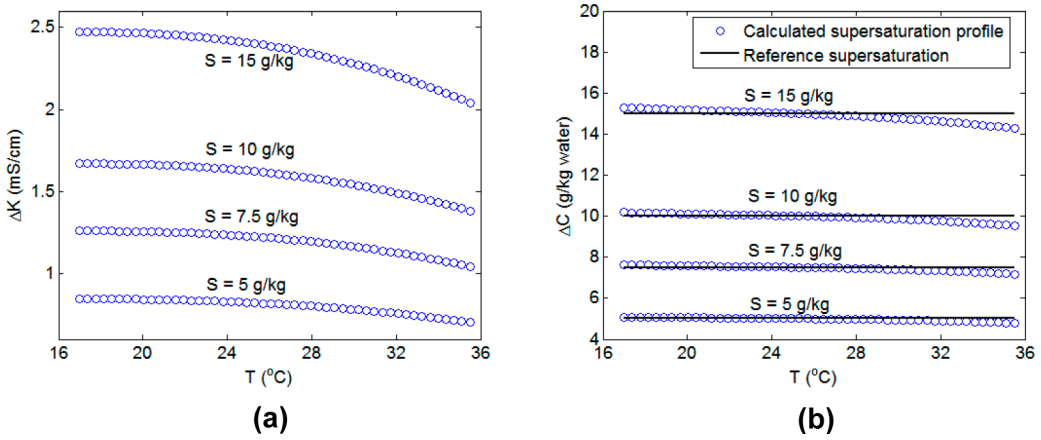

Figure 8. (a) $\Delta\kappa$ profiles corresponding to constant supersaturation of 5, 7.5, 10, and 15 g/kg-water for potash alum−water system; (b) supersaturation profiles obtained from the $\Delta\kappa$ profiles in (a) if full calibration equation are used. Reprinted with permission from ref 115. Copyright 2013 Elsevier.

To verify that the proposed reduced calibration approach is able to perform constant supersaturation control, the product CSDs of crystallization resulting from C-control with full calibration and C-control with reduced calibration are compared in Figure 9. Both experiments are performed with

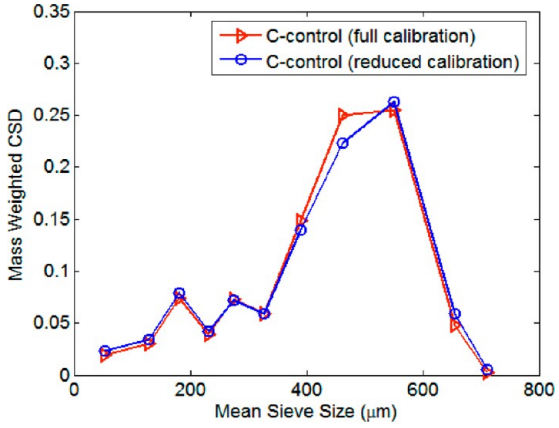

Figure 9. Comparison of potash alum product crystals CSD obtained by C-control with full calibration and C-control with reduced calibration. Reprinted with permission from ref 115. Copyright 2013 Elsevier.

the same seed size (106−125 μm) and seed loading (1.5%). It is clear that both CSDs are almost identical, implying that the C-control with reduced calibration is as effective as and requires less experiments than the conventional C-control with full calibration approach and requires less experiments.

4.4. Endoscopy Based Monitoring of Crystallization Processes. Endoscopy based imaging (Figure 10) has been proposed as a low-cost probe for the monitoring of crystallization processes;[116,117] however, it can also be applied to other particulate processes. The probe consists of a light source, the optics, and a color video camera. This latter characteristic opens new opportunities since color related information of the crystal slurry can be acquired. Also the information content of color images is higher as compared to gray scale images which favor the implementation of multivariate image analysis methods to deal with multispectral data.[118,116] Endoscopy assisted polymorphic transformation process monitoring and comparison to turbidity, FBRM,

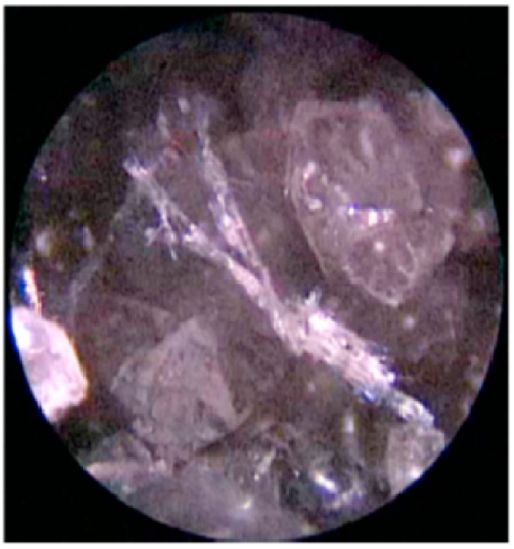

Figure 10. Monohydrate citric acid and flufenamic acid (needles) crystals. The size of citric acid is in the 400−500 μm range. Reprinted with permission from ref 117. Copyright 2009 Elsevier.

FT-Raman, and FT-NIR spectroscopy is discussed in Simon et al.[119]

Another conceptual development in the field of imaging based monitoring is the use of imaging hardware as non-contact turbidity sensors.[120] In this case the main information retrieved is the intensity of the pixels, which can be calibrated to slurry properties, e.g., solid concentration. Another application of image intensity trends is to design statistical process control charts[118,121] as a tool for robust process monitoring. Future applications of on-line imaging based quality control (crystal size, shape) are relevant in the context of continuous pharmaceutical production as presented by Simon and Myerson[122] using an FBRM probe.

4.5. Ultrasonic Resonator Technology and Diffusing Wave Spectroscopy for Oral Liquid and Semisolid Pharmaceutical Formulation Analysis. Reduction of the number of manufacturing failures is an important objective for the pharmaceutical industry as well as for the regulatory authorities. The American Food and Drug Administration (FDA) encouraged pharmaceutical producers to increase their product and process understanding as part of the QbD

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initiative.[123] To design quality into a drug product, it is important to monitor material attributes and process parameters that are critical to the quality of the final dosage form. Process analytical technology (PAT) plays here a key role, and much pharmaceutical research has been invested into studying solid dosage forms as well as biopharmaceutical drug products. However, only a few reports of process monitoring are about oral formulations liquid-filled into pharmaceutical capsules. These formulations are mostly lipid-based and can be considerably complex, which makes use of, for example, vibrational spectroscopy quite a challenging task. Moreover, it is often the rheological formulation properties that should be monitored, and therefore novel process analyzers are required. This section of the paper discusses two analytical technologies that exhibit high potential for such process analytics, i.e., ultrasonic resonator technology (URT) and diffusing wave spectroscopy (DWS).

4.5.1. Ultrasonic Resonator Technology. Different acoustic methods have been applied to process monitoring in the field of semisolid pharmaceutical products; Medendorp et al.[124] pioneered using acoustic resonance spectrometry for drug quantification. The high-resolution URT has even earlier been proposed to study liquids in general.[125]URT has later been proposed as a novel QbD option for self-emulsifying drug delivery systems.[126] The goal was here to characterize the evolving nanoemulsions in contact with aqueous media such as intestinal fluids. URT has been further used as a tool for physical stability studies of such dispersions to differentiate nanoemulsions from microemulsions.[127] Such studies primarily help in the formulation development phase, whereas PAT in manufacturing is focusing directly on the self-emulsifying concentrates. URT was recently compared with Raman spectroscopy for drug quantification in self-emulsifying drug delivery systems.[128] A Resoscan system (TF Instruments Inc., Monmouth Junction, NJ) was employed, which uses two identical resonator cells with a path length of 7.0 mm. The temperature was adjusted by a Peltier element-controlled thermostat with a stability of less than 5 mK. A fundamental frequency of approximately 10 MHz was used for the measurements of drug-containing formulations compared to placebo in the reference cell. A schematic of the instrument is depicted in Figure 11.

Results are shown for the drug fenofibrate (Fen) in a lipid formulation that contained polysorbate 80 as surfactant (PO). The delta of sound velocity (ΔU) and the delta of sound attenuation (ΔA) both changed linearly in the tested concentration range. These acoustic responses exhibited further linearity with the concentration of other drugs in different formulations.[128] Depending on the given system, it was possible to obtain rather low limits of quantification as well as fairly low relative standard errors of prediction.[128]

Apart from drug quantification, the URT method has also been proposed to test the quality of gelatin nanoparticles.[129] Interesting is further the use of this technique to monitor manufacturing of nanosuspensions. We measured at-line samples of aqueous and oily nanodispersions during manufacturing in a homogenizing vessel under vacuum.[130] For the tested systems, a first-order change in ΔU was empirically found. This ability to monitor as well as to model the homogenization process is of high industrial importance. It helps to cope with batch-to-batch variability and from the early time-points of the manufacturing process; it was already possible to predict the end point of homogenization for an individual batch. This saves

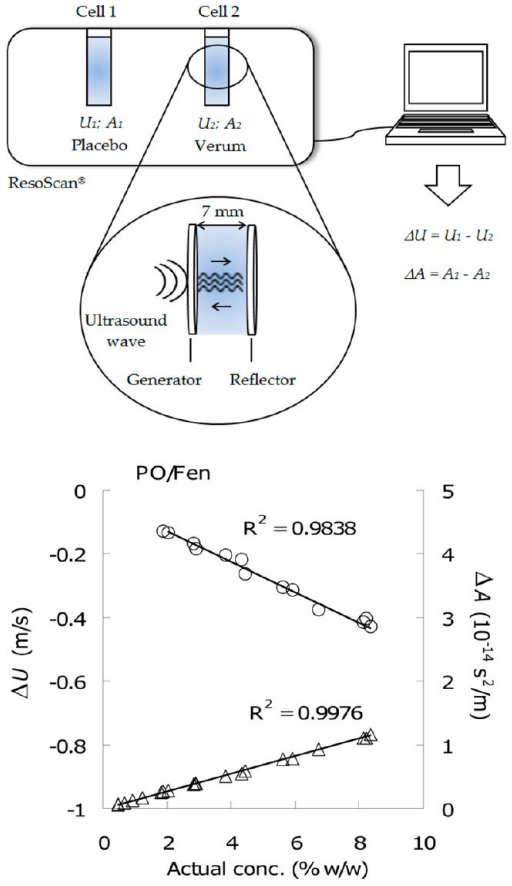

Figure 11. Basic principle of the URT measurement using a sample (Verum) and a reference (Placebo) cell for determination of the delta of sound velocity (ΔU) and acoustic attenuation (ΔA). Results are shown for different drug concentrations using a model system.

process time and bears high potential for cost savings in production. However, it is expected that such homogenization monitoring would be limited to formulations that exhibit a change in their effective compressibility, κ_{eff}, during processing. For ideally homogenous systems, the Newton−Laplace equation (eq 3) describes the speed of a sound wave, U, as a function of compressibility, κ, and density, ρ, of the medium.

$$U = \frac{1}{\sqrt{\kappa\rho}} \tag{3}$$

Theoretical considerations of the ultrasonic approach in solutions can be inferred from Tikhonov et al.[131] From an experimental viewpoint, a next step in the evolution of URT is to move from at-line to on-line analytics. In a current research project at the University of Applied Sciences and Arts Northwestern Switzerland, Institute of Pharma Technology, a flow-through cell that takes samples from a manufacturing vessel has been evaluated (Swiss CTI project no. 13154.1 PFFLE-IW). A combination with MEMS-based on-line density measurement was developed so that the different sample properties can be determined simultaneously. The on-line measurements currently work in a stop-flow mode using a peristaltic pump. A more technical development is needed to achieve robust on-line URT measurements for a broad range of pharmaceutical formulations. This research should lead to a similar level of technical maturity as, for example, with on-line acoustic methods for particle sizing.[132,133]

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4.5.2. Diffusing Wave Spectroscopy. The field of microrheology has been evolving in recent years and especially diffusing wave spectroscopy (DWS) has raised much scientific interest.[134] The technique enables a rheological characterization of samples in a contact-free manner, which is attractive for process monitoring. As an optical laser-based technique, the measurement is similar to classical dynamic light scattering (DLS) for particle sizing. Both techniques analyze the correlation function of scattered light intensity. In contrast to the classical particle sizing by DLS, multiple light scattering is here not a problem but even required to have adequate statistics for the determination of a mean square displacement of particles. It is beyond the scope of this article to provide a detailed description of the technique with the data treatment because excellent review articles have been written on this topic.[135−138] However, Figure 12 tries to highlight the most

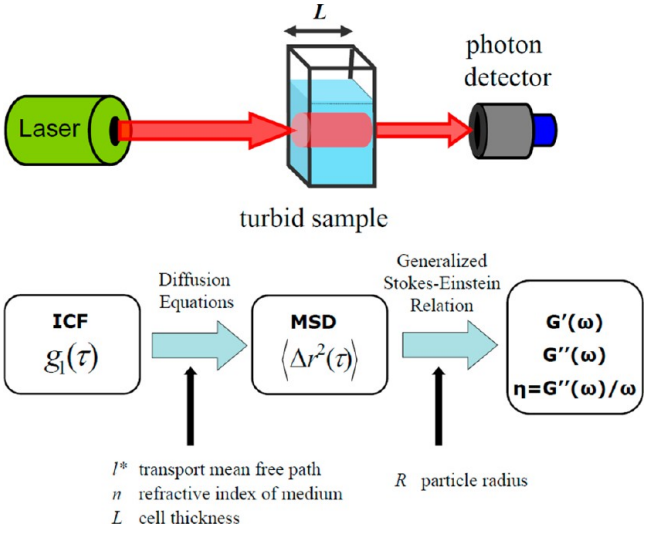

Figure 12. Basic scheme of DWS in transmission. From the intensity correlation function (ICF), the mean square displacement (MSD) is determined. This property is used in the generalized Stokes−Einstein relation to calculate the rheological moduli $G'(\omega)$ and $G''(\omega)$.

important aspects of DWS that start with the measurement of the dynamic light scattering fluctuations of a turbid sample. It is preferred to employ detectors of high temporal resolution instead of simple CCD cameras to measure the intensity fluctuations in transmission. From the intensity correlation function (ICF), it is possible to determine the mean square displacement (MSD) for a broad range of frequencies, ω. Using the generalized Stokes−Einstein equation, these data can be used to determine the mechanical storage modulus, $G'(\omega)$, and loss modulus, $G''(\omega)$, of a sample. We employed a DWS instrument that included the so-called echo technique[136,139,140] by the company LS Instruments Ltd. (Fribourg, Switzerland).[141]

A broad range of self-emulsifying formulations was measured. Most of these low-to-medium viscous formulations displayed existence of a notable $G'(\omega)$ at relatively higher frequencies. Such frequencies of one to several krad s^{-1} were especially considered because also the industrial capsule filling process takes place on such a rather short time scale. It has been earlier shown for Newtonian oils that splashing around the machine filling nozzle can lead to weight variations of liquid-filled capsules.[142] It was therefore aimed to correlate the mechanical moduli as obtained by DWS with the coefficient of weight variation from machine-filling (LFCS 1200, Capsugel, France) of capsules. Significant correlations were indeed found for G' and G'' at 5 krad s^{-1} regarding capsule weight variability.

The novel DWS approach was highly attractive for this application of industrial capsule filling. It enabled measuring of the mechanical moduli in a frequency range that is otherwise barely accessible with conventional rheological methods. Moreover, the measurements were contact-free with the potential for process monitoring. A recent collaborative research effort was related to the development of a flow-through cell for DWS (Swiss CTI No. 13084.1 PFNM-NM). However, a continuous flow is limited by a critical speed for which the determination of mean square displacements is no longer reliable based on the correlation function. An alternative procedure was therefore to draw samples in a stop-flow mode into the flow-through cell, which provided suitable process monitoring for model dispersions manufactured in our laboratory. More research efforts will surely be dedicated to this intriguing new PAT approach.

4.6. Photometric Stereo Imaging Based Granulation Monitoring. This section of the paper describes photometric stereo imaging approaches that have been developed and mostly used in particle sizing applications in a PAT context. The development of this approach has shown advantages especially for samples that are moist or cohesive, when the dispersion of particles is challenging or sometimes impossible. The main focus of this text is in the use of photometric stereo imaging in measurements in different pharmaceutical granulation processes. In this overview the use of the technique is demonstrated mainly in at-line and on-line particle size measurements during granulation, and also extraction from image information is discussed.

The control of granulation processes requires an understanding of the evolvement of the granule size during manufacturing. Many approaches from at-line to on-line measurement exist. Real-time information on granule growth behavior is often key for optimal and desirable control of the process. Imaging techniques are attractive as they optimally provide visual information on the processed material and numerical information on actual particle size. Particle size measurement by imaging is commonly carried out with suitable camera-based optical systems, which measure single particles dispersed in air. Many examples of these exist, but the most interesting are the recent advances in image-based dynamic particle sizing that have taken image-based sizing to a new level, enabling measurement of a large number (up to several millions) of particles using automated systems.[143,144] The utilization of image information on bulk materials without dispersing particles has drawn interest over the past years. For example, Bonifazi et al.[145] and Novales et al.[146] have discussed the perspectives in particulate solid control of bulk or collection of particles instead of measurement of dispersed single particles. Also, Huang and Esbensen developed an imaging approach that excludes the dealing with individual particles and acquired images directly from in situ powders.[147] The entire field-of-view of powders was shown to contain information related to individual particles but mainly the bulk powder. They concluded that these images contained complex bulk properties, such as flowability and fluidization velocity. Earlier a photometric stereo imaging approach was introduced to calculate the particle size from undispersed particles/granules under strictly controlled illumination conditions.[148]

This technology has then been used in a variety of applications to measure the particle size.

The aim of this overview is to give examples of the use of photometric stereo imaging in particle sizing. The technique reconstructs three-dimensional (3D) images of objects when at least two light sources are used as illumination, and the information on multiple (at least two) images are combined. 3D features can be revealed using lateral illumination as described by Pons et al.[149,150] These features are created through shading effects and expose the topography or texture of surfaces. In early studies we developed a parameter called the gray scale difference matrix (GSDM) for calculations of the particle size from undispersed bulk powders and granules.[148,151,152] This approach took advantage of the shading effects under controlled illumination conditions. In photometric stereo imaging the concept is based on varying the direction of incident illumination between successive images whilst the viewing direction is detained constant. The concept was introduced by Woodham in 1980.[153] We have developed an alteration of photometric stereo imaging using two white-light sources to create a 3D surface of a sample of interest. Illumination sources have been placed 180° from each other in a horizontal plane; surfaces (bulk powders/granules) of interest are imaged through a glass window, and two images are taken. The gradient fields acquired that results from the imaging setup contain direct information about surface normal in a *xz*-plane and indirect information about surface normal in *yz*-plane. In order to obtain a 3D surface, line integration is utilized in the horizontal direction. The cumulative error that is distinctive of in-line integration-based approaches is removed with a suitable high pass filter. Peaks on the 3D surface are assumed to be particles, which then allows one to measure the particle size of, e.g., granules during processing.[144] The field-of-view will vary depending on the optical solution that is used. Typical sizes for an image for a particle sizing application vary from a few millimeters up to a few centimeters, and the optical solutions give pixel resolutions from a few microns upwards. An example image of powder surface is presented in Figure 13.

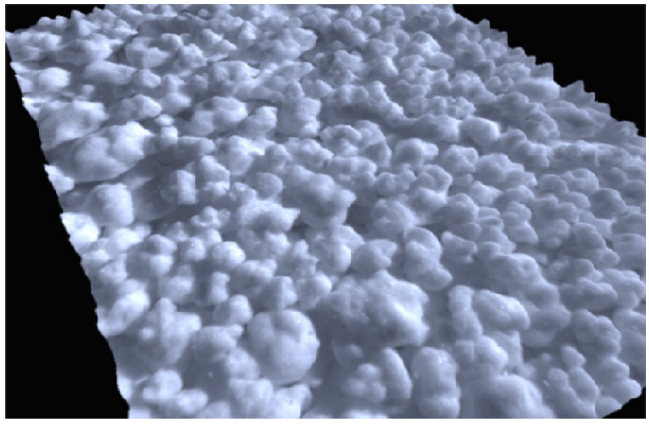

Figure 13. A typical granule surface image from on-line measurements during fluid-bed granulation visualized in 3D.

The GSDM approach has been employed in at-line measurements using a pilot-scale fluidised bed granulator (Glatt WSG 5, Glatt GmbH, Binzen, Germany) by Laitinen et al. (2004).[152] The granulation setup has been described in detail by Rantanen et al. (2000).[154] The process conditions followed an experimental design where three process variables were altered on three levels: inlet air temperature, nozzle spraying pressure, and granulation liquid flow rate. The study clearly indicated that the method was suitable in process measurements of wet/moist and dry granules, i.e., during all process phases, with a wide particle size range. The recent use of the photometric stereo algorithm has shown that it is possible to generate high-quality topographical 3D images which allow surface inspection, roughness measurements, and the particle size analysis.[144]

One of the greatest challenges with regard to process monitoring is the interface of any given measurement equipment with the process. In granulators, the monitoring of moving powder beds is often made, but measurements can be extremely challenging due to the dynamic nature of the powder movements in, e.g., fluidized beds. Successful examples have been reported by Burggraeve et al.[155] using spatial filter velocimetry. An interface by creating on-line double-cuvette measuring system (Intelligent Pharmaceutics Ltd., Turku, Finland) was introduced by Närvänen et al.[156] The sample in measurement is forced to a static phase against the cuvette window for the duration of the measurement, and the sample is then returned to the process without any loss of material. This sampling unit consists of a special frame which can be mounted on a process chamber, e.g., granulator (Figures 14 and 15).

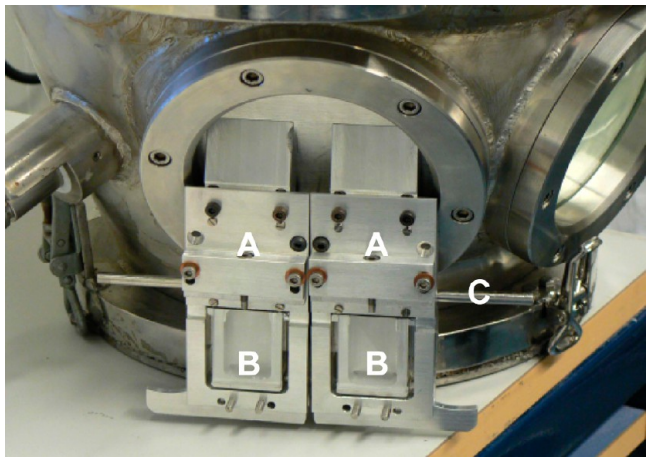

Figure 14. On-line sampling system (Smart Q, Intelligent Pharmaceutics Ltd., Turku Finland) designed for a fluid-bed granulator. Sampling cuvettes (A), measurement window (B), and pressurised air blow system for discharging the sample (C).

The sampler and the frame have been explained in studies by Närvänen et al.[156,157] A highly turbulent air-jet pulse empties the cuvette (and the sample is pushed back to the process). The short air pulse also cleans the walls of the cuvette. Närvänen et al.[156] demonstrated the use topographic 3D imaging method in which a flat granule bed surface was illuminated from three different directions, using three primary colors (red, green, and blue). Only one color picture is taken, and a topographic image of the object surface can be constructed using the color information.

The monochromatic photometric stereo approach has been recently employed in a study by Soppela et al.[158] The study compared the use of the 3D photometric image analysis technique to sieve analysis and spatial filtering technique with nearly 30 granule batches. The aim was also to evaluate the technique in flowability screening of granular materials. The conclusion was that the 3D imaging approach allowed rapid

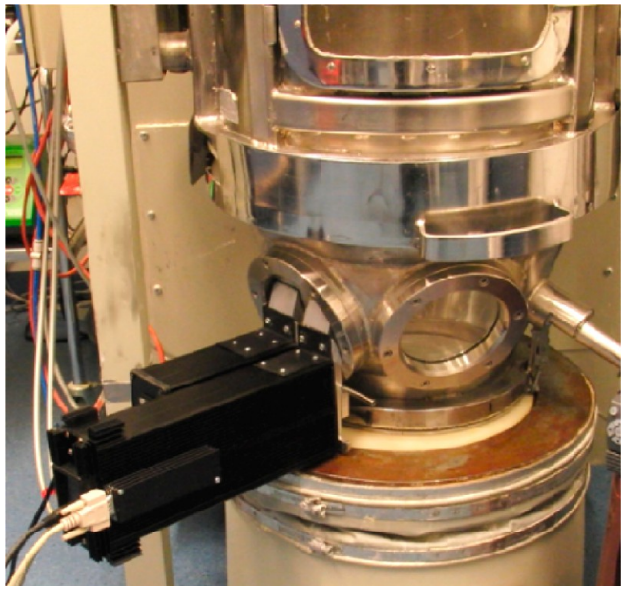

Figure 15. A photometric stereo (Flashsizer, Intelligent Pharmaceutics Ltd., Turku Finland) image analysis installation with a Smart-Q cuvette system designed for a pilot scale (Glatt WSG5) fluid-bed granulator in combination with a NIR probe.

analysis of large amounts of sample and gave valuable visual information on the granule surfaces in terms of surface roughness. The setup was also useful in powder flow assessment. Recently Silva et al.[159] compared a variety of different particle sizing techniques, and the purpose of the study was to review several in-process techniques for particle size determination (Spatial Filtering Velocimetry, FBRM, Photometric Stereo Imaging, and the Eyecon technology) and compare them to well-known and widespread off-line reference methods (laser diffraction and sieve analysis). Particle sizing using the photometric stereo approach was also successfully done on a set of roller compacted granules produced by pneumatic dry granulation.[160]

Burggraeve et al.[161] studied photometric stereo imaging in real-time during the final steps of the extrusion−spheronization pelletisation process (spheronization and drying). Pellet samples were taken at 20 time points during spheronization and were imaged at-line (during spheronization) and off-line (after spheronization). Particle size distribution and visual image information were both used to study spheronization behaviour of different formulations. Also particle size distribution and surface brightness values were calculated from the at-line obtained images during fluid bed drying of pellets. The particle size distribution and brightness value changes occurring during pellet drying could be explained by the reduction in residual moisture content and drug solid-state transition. They concluded that the rapidness of the technique with regard to sample preparation and sample measurement in combination with the ability to measure undispersed wet samples, valuable information on spheronization, and drying characteristics of different formulations can be obtained in real time.

To conclude, the development of high-resolution camera systems and increase of computing performance enables advances in development of image-based PAT solutions in the future. Automated image processing for feature extraction offers possibilities to extract objective measurements of image content and is particularly useful for analysis of large image data sets containing features that are very subtle, for reliable human evaluation.

4.7. Photoacoustic Gas Analyzers: Novel Detector and Signal Processing for Reduction of Vibration Sensitivity.

Photoacoustic detection has been the first method for continuous process gas analysis. Thousands of analyzers based on photoacoustic detection have been applied in a plethora of fields, including chemical, combustion, medical, and refining applications. Over the years, photoacoustic detection technology has been continuously improved and became one of the most successful and versatile techniques for gas analysis. On the other hand, mechanical shocks and vibrations can degrade the measurement accuracy when the analyzer is installed, e.g., near rotating machines, furnaces, or agitators. This section of the paper describes how photoacoustic gas analyzers can be made more robust to vibrations and shocks by resorting to improved detector designs and novel signal processing techniques.

4.7.1. Photoacoustic Gas Analyzers and URAS Measurement Principle. Photoacoustic gas analyzers measure the concentration of a certain gas by quantifying its characteristic fingerprints in the absorption spectrum. Generally, the setup of such gas analyzers consists of (a) a light source, (b) an analytic (absorption) cell, and (c) a photoacoustic detector. The higher the concentration of a certain gas component in the analytic cell, the more energy is absorbed at certain wavelengths (i.e., absorption lines) from the optical spectrum emitted by the light source. The detector unit measures the intensity of the optical radiation transmitted through the analytic cell at gas-specific wavelengths. The ABB URAS is a popular photoacoustic gas analyzer, the simplified sketch of which is depicted in Figure 16.

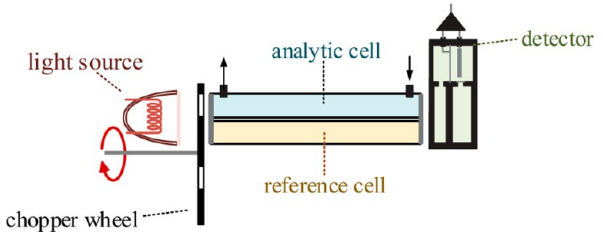

Figure 16. Simplified description of a URAS gas analyzer. Reprinted with permission from ref 165. Copyright 2014 Elsevier.

The optical radiation is pulsed by a chopper wheel and sent alternately through the analytic cell and the reference cell. When the light passes the reference cell, no absorption takes place. In contrast, when passing the analytic cell, the light is partially absorbed at specific gas absorption lines. Therefore, the detector is exposed to alternating optical intensities at the frequency of the chopper wheel (subsequently referred to as modulation frequency and denoted as f_m) which carries information on the gas concentration to be measured. Optical heating of the gas leads to a pressure increase in the closed detector cell which can be detected by a microphone—such as in the URAS sensor—or by microflow sensors that measure the gas flow between detector chambers.

Unfortunately, very strong mechanical vibrations can disturb the measurement, e.g., by causing intensity fluctuations of the light source, or exerting inertial forces on the pressure sensitive elements of the detector. The resulting measurement signal is a superposition of the concentration- and vibration-induced signal

components. In fact, strong mechanical vibrations in the proximity of the modulation frequency manifest in an oscillation of the sensor signal around the true gas concentration. Several methods have been proposed in the literature for the reduction of the vibration sensitivity of photoacoustic detectors, and this contribution describes a novel approach based on signal processing.

4.7.2. Detector Design Optimization. In gas analyzer systems, photoacoustic detectors are generally most sensitive to mechanical vibrations due to their high-pressure sensitivity. One possibility to suppress vibration sensitivity, proposed by Pederson and McClelland,[162] is to use lighter and thinner elements in the detector that reduce inertial forces on the moving parts. Further reduction can be achieved by compensating the effect of vibration generated by different detector parts.

Jackson et al.[163] have installed two identical microphones mounted in opposite directions with respect to the acceleration. Thus, the inertial force acts in opposite directions on the microphone membranes such that the acceleration effect can be canceled out by summing up the signals of the microphones. In contrast, a pressure increase in the microphone cells drives both membranes in the same direction. Jackson et al.[163] reached an improvement of the vibration suppression of up to 40 dB in this way.

To compensate for membrane movements caused by inertial force, Koskinen et al.[164] positioned the center-of-mass of the gas cells appropriately. In the presence of vibrations, both the center-of-mass of the gas volume and the membrane move in the same direction, which results in a pressure drop that compensates for the inertial force acting on the membrane. The vibration sensitivity suppression was improved by 20−50 dB.

The compensation methods discussed here require an exact balancing of the parts in play. For demanding industrial applications, the practical realizability is limited by manufacturing tolerances.

4.7.3. The Signal Processing Approach. In contrast to the approaches described above, the overall sensor vibrations sensitivity can also be reduced by resorting to signal processing techniques. Specifically, the effect of vibrations is removed with the aid of the acceleration signal measured using an accelerometer. Indeed, since the vibration disturbance is additive, the original vibration-free signal can be recovered by subtracting a filtered version of the measured acceleration signal. The selected filter must mirror the mechanoelectrical transfer function between the electrical detector signal and the vibration signal produced by the accelerometer. Its selection is of paramount importance for the performance of the cancellation method. Hereinafter, two methods are proposed.

In the first method, referred to as *off-line*, the transfer function of the filter is determined prior to normal operation, while the sensor is not performing any measurement. To do so, a known frequency-rich acceleration signal is applied to the sensor. During off-line calibration, the light source is turned off, and estimation of the filter representing the mechanoelectrical system can be achieved, e.g., via least-squares methods.

The benefit of the off-line method is that the mechanoelectrical system identification is done in absence of the modulated signal. Therefore, the system can be identified at any frequency (including the modulation frequency f_m). On the other hand, because of ageing, the mechanoelectrical system characteristics will change over time, and the model identified during calibration might not be valid after some operation time. To cope with this challenge, the rationale of the *on-line* method is to continuously adjust the estimated mechanoelectrical system in order to track its variations. The main difference with respect to the off-line method is that the on-line method is employed during the normal sensing operations; therefore, the useful signal is not zero (i.e., the light source is on). Moreover, the vibration signal cannot be freely selected but stems from the actual application. The on-line method relies on adaptive filtering and has been thoroughly described by Maret et al.[165]

Laboratory tests were performed using the continuous gas analyzer AO2000 from ABB equipped with the analyzer module URAS26 fitted with a single CO detector. To produce different vibrations, the gas analyzer has been placed on a vibrating table. Sinusoidal vibrations have been generated with frequencies in the range of 4−15 Hz, and the modulation frequency is f_m = 7.3 Hz. A constant flow of different CO−N_2 gas mixtures is supplied to the gas analyzer. A three-axis accelerometer has been mounted onto the detector. The standard deviation of the concentration measurement has been measured at each vibration frequency.

Figure 17 shows the resulting improvements, i.e., the reduction with respect to the existing URAS signal processing

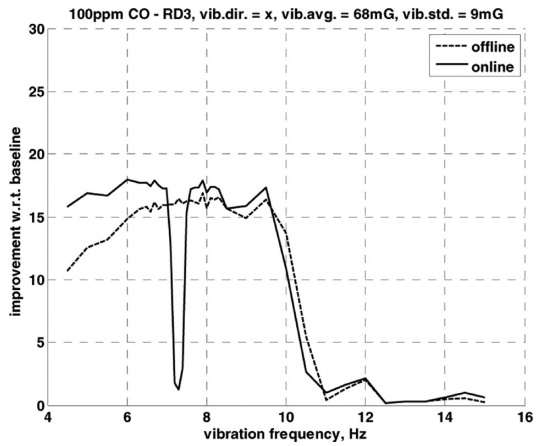

Figure 17. Improvement of the proposed signal processing method with respect to current implementation. Reprinted with permission from ref 165. Copyright 2014 IEEE.

in the standard deviation of the gas concentration measurement for a constant 100 ppm of CO concentration, both using the off-line and on-line signal processing method.

Improvement factors close to the modulation frequency range from 10 to 20. Clearly for vibration frequencies far from the modulation frequency, there is no improvement since URAS is not sensitive to those vibrations anyway. The on-line method leads to no improvement for *persistent* vibrations at the modulation frequency. In this case, one possible solution is to change the modulation frequency. It is concluded that the novel signal processing based detector significantly reduces the vibration sensitivity of the gas analyzer.

4.8. Operando Spectroscopy of Solid−Liquid−Gas Reaction Systems. In recent years, a major focus of the catalysis community has been on the development of techniques suitable to probe a solid catalyst under working conditions.[166,167] For investigating solid−liquid interfaces attenuated total reflection infrared (ATR-IR) spectroscopy became particularly useful. State-of-the-art methods are either suitable to probe the reaction in solution under working conditions[168] or to characterize the adsorption−desorption behaviour of reactants or products at the solid−liquid

interface.[169,170] While product formation can also be observed in in situ studies, that is, in the presence of liquid solvent saturated with gaseous reactant, the application of flow-through cells and low flow rates (~1 mL min^{-1}) does often not provide true catalytic activity/selectivity due to mass transfer influences and monitoring of the catalytic surface in the working state, e.g., as performed in a catalytic reactor, has not been developed yet.

As advancement of in situ spectroscopy, we recently developed[166] an *operando* methodology for monitoring solid–liquid–gas reaction systems that simultaneously combines catalytic activity and molecular level detection at the catalytically active site of the same sample. Semibatch reactor conditions are achieved with the analytical setup by implementing an ATR-IR flow-through cell in a recycle reactor system and integrating a specifically designed gas feeding system coupled with a bubble trap (Figure 18). To keep the

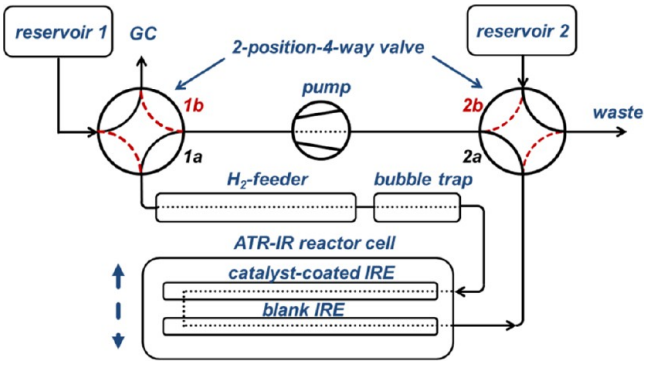

Figure 18. Schematic of the experimental setup showing the arrangement of the ATR-IR measuring cell, the hydrogen feeder, the bubble trap, the circulating pump and the two two-position-four-way-valves for admission of liquid solutions from two reservoirs. At the outlet solutions are collected in containers for GC analysis. The two valves allow for three operational modes: (1) filling (1b, 2a), (2) flushing (1a, 2b) (both opened-cycle modes), and (3) recycling (1a, 2a, closed-cycle mode). Reprinted with permission from ref 174. Copyright 2014 American Institute of Physics.

concentration of dissolved reactant gas very close to the saturation point, first the solvent stream is slightly oversaturated, and subsequently excess gas is filtered off. Basically, by the combination of the two devices, hydrogen feeding is achieved at a minimum additional volume added to the recycle loop (9_{BT} = 1 mL) and also at a minimized gas–liquid interface (depth × length of the bubble trap, 1.6 × 20 mm^2). In addition, the bubble trap also works as a liquid level buffer leading to smoother flow as the pressure fluctuation during switching from opened- to closed-cycle modes is dampened. Two-position four-way valves are used to smoothly exchange or recycle the reactor content without exposing the catalyst to air. Synchronization of the valves with the spectra acquisition allows for accurately controlling predefined reaction programs, e.g., periods of filling, recycling, and flushing. In opened-cycle mode, the micro annular gear pump installed within the recycle loop is suitable to transport liquid solutions with high flow rates (exceeding 22 mL min^{-1}) from the bubble reservoirs via the reactor system to (waste) containers which are open to the atmosphere. In recycling (semibatch reaction) mode, the high flow rate is maintained creating excellent mixing inside the reactor loop with recycle rates on the order of >7 min^{-1} (22 mL min^{-1}/3 mL = 7.3 min^{-1}).

By the use of only one spectrometer, the design of the new ATR-IR reactor cell allows for simultaneous detection of the bulk liquid and the catalytic interface during the working reaction. Holding two internal reflection elements (IRE), the sample compartments of the horizontally movable cell are consecutively flushed with reaction solution and pneumatically actuated, rapid switching of the cell (<1 s) enables to quasisimultaneously follow the heterogeneously catalyzed reaction at the catalytic interface on a catalyst-coated IRE and in the bulk liquid on a blank IRE. Similar to the real catalytic reaction in a slurry reactor, the void volume around the deposited catalyst particles is filled with liquid reaction solution giving also rise to bulk liquid absorption. As the void volume after slurry-drop catalyst deposition can easily account for 50% of the sample medium[170] at a liquid concentration level of approximately a few millimolar (critical concentrations are on the order of about ≥5 mM) absorption of dissolved species would dominate the spectrum measured on the coated IRE, thereby burying the desired signals of surface species.

Simultaneous monitoring of the solid–liquid interface at a coated IRE and of the corresponding liquid phase at a blank IRE facilitates considerably the spectral analysis and processing of the contingent signals allows for isolating signals belonging to only adsorbed species. The absorption of the bulk liquid contributing to the measured spectrum and the gain of information due to signal separation is illustrated by the three spectra shown in Figure 19A.

To justify the term "*operando* monitoring", experimental results obtained with the setup have been compared to the outcome of semibatch hydrogenations (30 mg catalyst, 1 bar H_2, 900 rpm, 9 mL toluene, same concentration) in terms of activity and enantioselectivity. For the heterogeneous asymmetric hydrogenations of methylbenzoylformate, ketopantolactone, and trifluoroacetophenone (TFAP), the same TOF and enantiomeric excesses (ee) were obtained.[171]

In Figure 19B, simultaneous ATR-IR monitoring of the solid–liquid interface and the liquid phase during several hydrogenation runs of 5 mM TFAP on chirally modified 5 wt % Pt/Al_2O_3 catalyst are shown. Prior to admission of ketone solution, the catalyst has been modified with 0.1 mM cinchonidine (CD) solution. After the quick filling of the reaction cycle, consumption of the dissolved ketone is observable by its decreasing carbonyl band. Furthermore, adsorption of ketone and product as well as the formation of a stable transient diastereomeric surface complex formed with preadsorbed CD could be followed. The transient diastereomeric surface complex[172] could be identified by the very weak stretch of the protonated tertiary amine moiety $\nu(N^+–H)$ of CD at around 2630 cm^{-1}. Such very low absorption signals arising from intermolecular surface interactions could be identified for the first time during the heterogeneous asymmetric hydrogenation.[171]

The new setup for *operando* spectroscopy proved to be a powerful tool to study solid–liquid–gas reaction systems under working conditions. It can also be combined with modulation excitation spectroscopy and phase-sensitive detection to exploit the advantages connected to these techniques (higher S/N ratio, active species detection).[173,174]

5. METHODS FOR PAT BASED PROCESS MONITORING AND CONTROL

5.1. Calibration-Free Supersaturation Monitoring Using ATR-FTIR and FT-Raman Spectroscopy. Routine

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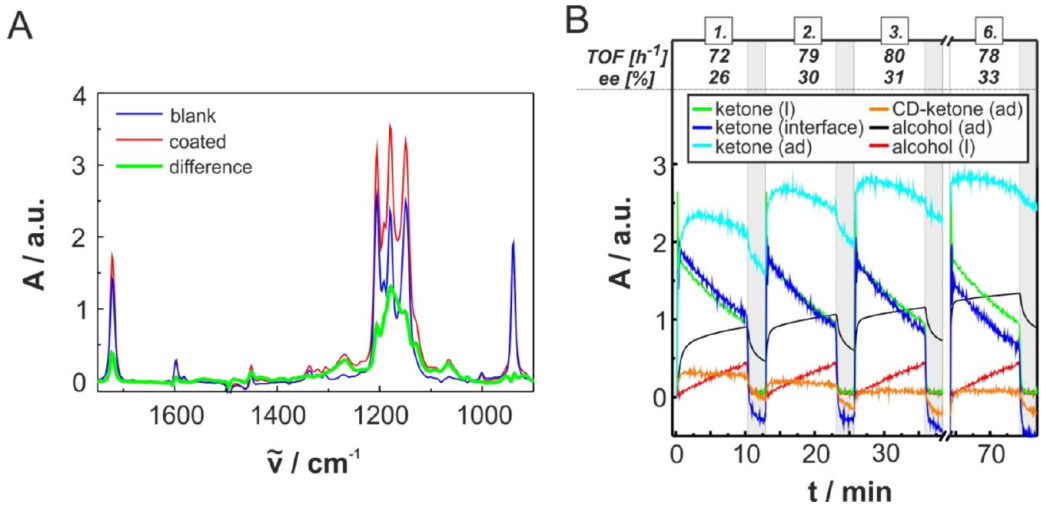

Figure 19. (A) Measurements on the blank and on the coated crystal acquired during the hydrogenation and the calculated differences spectrum. (B)*Operando* monitoring of the hydrogenation during six reaction cycles. The absorbance is scaled by 10^3. Reprinted with permission from ref 174. Copyright 2014 American Institute of Physics.

control of crystallization processes requires reliable, robust, and accurate measurement of the driving force for the kinetic processes. In particular, improved process design is facilitated by the ability to measure the process driving force in real-time, rather than reliance on off-line sample analysis. While there is currently no mechanism to directly measure supersaturation, much effort has focused on direct measurement of the dissolved concentration, from which the driving force can be inferred if knowledge of the solubility is available.[175−177] A particular challenge is that the level of supersaturation in many processes is of the same order of magnitude as the error in concentration measurement.

The most successful approaches to concentration measurement have been based on the application of ATR-FTIR spectroscopy,[178] because of its capability to measure dissolved liquid-phase concentrations in the presence of significant levels of solids. However, the challenge of designing a reliable calibration procedure can be significant. Typically, the application of IR spectroscopy is based on establishing a relationship between individual peak heights in the associated absorption spectrum, either through direct correlation, or via chemometric techniques, such as PLS or PCR. For reaction mixtures, or for systems with narrow metastable zone widths, the generation of suitable calibration samples in the supersaturated region is time-consuming and challenging, as is the associated validation.

An alternative method is based on tracking the height of an individual peak, characteristic of the solute of interest, in the absorption spectrum.[179] This height is compared to the peak height corresponding to the saturated solution at the same temperature, providing the supersaturation at any point in terms of the difference in peak height.

So, at a temperature, T_i, the supersaturation is a function of this peak height difference, eq 4

$$\Delta c_i = f(\mathrm{ph}_i - \mathrm{ph}_i^*) \tag{4}$$

where ph_i is the characteristic peak height for dissolved solute and ph^*_i is the corresponding peak height for a saturated solution. In combination with a feedback control strategy (Figure 20), it is possible to dynamically control the batch

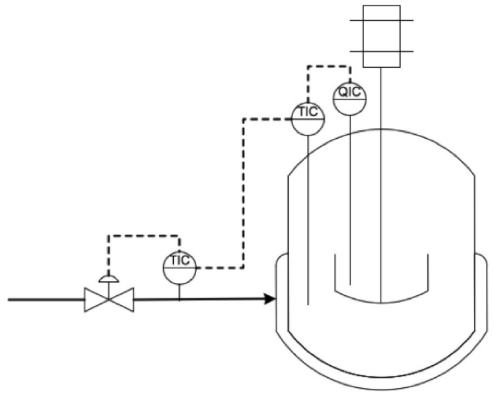

Figure 20. Feedback control of supersaturation.

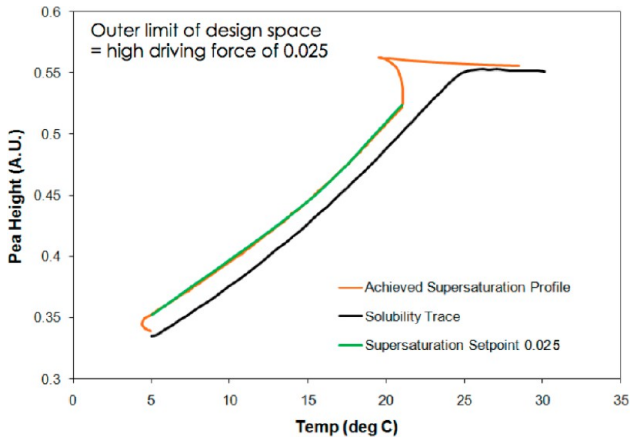

Figure 21. Supersaturation profile.

temperature to maintain a constant supersaturation, in terms of peak height difference.

In the example illustrated in Figure 21, the solubility trace is obtained by measuring the peak height while slowly heating a slurry of the solute crystals in the solvent system. Typically, heating rates of the order of 0.1 °C/min are required to ensure that equilibrium conditions are approximated during the data collection. The process itself involves implementation of a

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feedback control loop to maintain a constant driving force of 0.025, in terms on peak height.

The required temperature profile found to be required to maintain this level of supersaturation is shown in Figure 22.

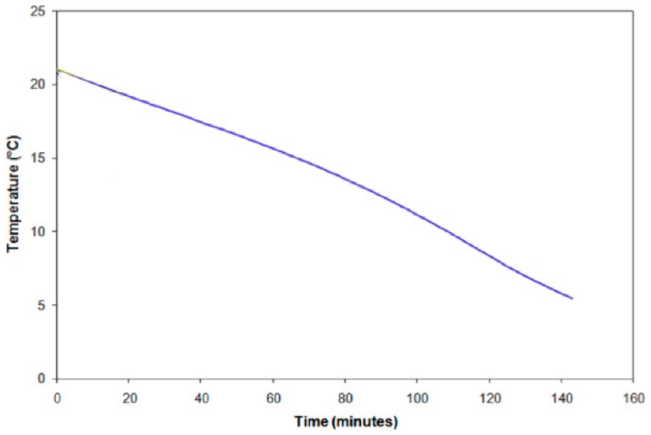

Figure 22. Temperature evolution.

In this particular example, the cooling rates required to achieve this profile are the maximum possible in the large-scale process. Therefore, the concentration profile shown in Figure 21 effectively represents the outer limit of the process operating space.

The process can be rerun for a series of alternative supersaturation trajectories, systematically establishing the associated cooling profile required to deliver this process performance (Figures 23 and 24). Through this approach,

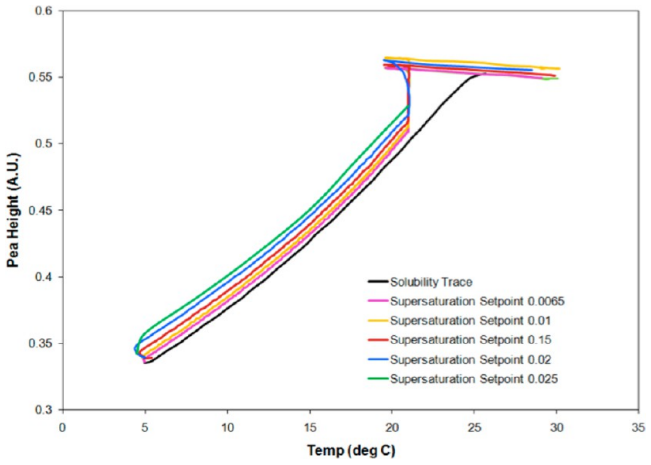

Figure 23. Crystallization operating space.

potential operating strategies can be readily interrogated. The impact of mixing conditions on the cooling profile required to maintain the supersaturation trajectory provides a reliable insight into the likelihood of hydrodynamic limitations on scale-up. A significant impact of agitation on the cooling profile is an indication that the process is mixing-limited, rather than controlled by kinetics. This calibration-free method can also be applied to antisolvent crystallizations. Duffy et al.[46] demonstrated consistent measurement of supersaturation in paracetamol-acetone solutions, with water as antisolvent (Figure 25). Hao et al.[47] has also successfully demonstrated a calibration-free supersaturation tracking method using in-process Raman spectroscopy.

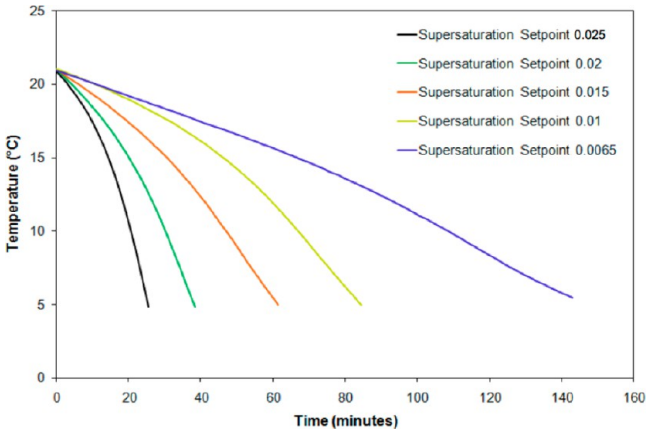

Figure 24. Cooling profiles to deliver corresponding desupersaturation profiles in Figure 23.

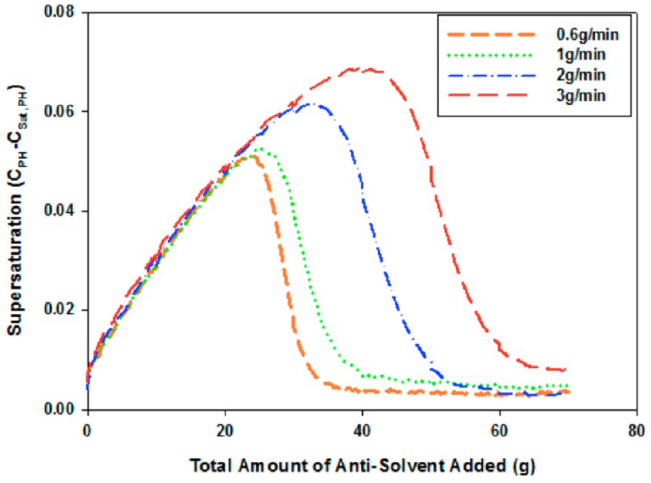

Figure 25. Supersaturation profiles versus antisolvent addition volume in unseeded crystallizations.[46]

5.2. Robust Concentration Feedback Control of Crystallization Processes. It was well-known in the 1990s that controlled operation along a specified path in the crystallization phase diagram, such as at constant supersaturation, would enable the ability to grow large crystals. This approach was experimentally demonstrated by 1990 using densitometry and a hydrocyclone to enable the measurement of the solute concentration,[180] but did not catch on, due to the potential complications associated with the equipment. In the mid 1990s, it was discovered that ATR-FTIR spectroscopy provided a much simpler approach for the measurement of the concentration of organic solutes in dense crystal slurries,[178,181] with high accuracy achievable by a combination of good experimental design, high quality FTIR spectrometers and ATR probes, and chemometrics (partial least-squares, principal component regression).[182−184] The availability of accurate in situ concentration measurement based on ATR-FTIR spectroscopy coupled with chemometrics enabled the application of feedback controllers that followed prespecified trajectories within the crystallization phase diagram using relatively hassle-free equipment (Figure 26). The metastable limit could be measured using FBRM and the solubility curve(s) by ATR-FTIR spectroscopy. The specification of batch recipes in terms of the crystallization phase diagram enabled a substantial decrease in the sensitivity of crystal size distribution to process

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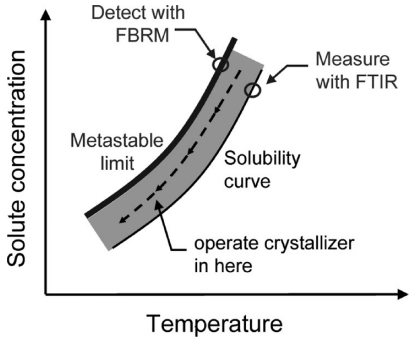

Figure 26. Feedback control of the solute concentration enables crystallizer operations to remain in between the solubility curve and the metastable limit, where uncontrolled secondary nucleation would occur, even when the process is subject to large disturbances. The metastable limit can be detected by (FBRM) and the solubility curve by ATR-FTIR spectroscopy.

disturbances that have the tendency to cause the crystallizer operations to drift in the crystallization phase diagram, to potentially cross the metastable limit and result in uncontrolled secondary nucleation. Controlled operation along a path in the phase diagram was initially demonstrated for the manufacture of large paracetamol crystals in aqueous solution with minimal aggregation,[185] which was an especially challenging system due to the low solubility of paracetamol in water, resulting in a lower signal-to-noise ratio than for most pharmaceutical crystallizations. The experiments demonstrated the ability to essentially turn off secondary nucleation, which was also demonstrated for various other combinations of solvents and organic molecules in other laboratories,[186] including for an active pharmaceutical ingredient at Schering-Plough.[176] Simulation studies with detailed models for time-varying disturbances and uncertainties demonstrated that concentration feedback control was much more insensitive to disturbances and uncertainties than the traditional set point of controlling the temperature profile.[187,188]

The feedback control of concentration within the phase diagram was later demonstrated for the antisolvent crystallization of a pharmaceutical compound at Merck & Co.[177] and then demonstrated for the combined cooling–antisolvent crystallization of lovastatin in an acetone–water mixture.[73] It was experimentally demonstrated (Figure 27) that the ability to operate along a specified path in the phase diagram enabled the robust control of the polymorphic form, including the ability to produce large metastable or stable crystals in either enantiotropic or monotropic crystallizations.[32,189,190] Recent reports describe the application of concentration feedback control to active pharmaceutical ingredients at Bristol Myers-Squibb, AbbVie, and Merck & Co.[191]

Unfortunately, the concentation control strategy suffers from the limitations of being less robust towards variations in solubility data and high nucleation rates.[188] Towards this end, strategies using additional process measurements like CSD to adapt the supersaturation set point for real-time control of crystallization processes were developed.[192,193] However, this adaptive C-control strategy not only lacks systematic approach for implementation in general but also results in varying batch time and even leads to long batch time in certain scenarios.[192] Thus, to alleviate the aforementioned limitations, a new modeling framework that integrates pattern classification and nonlinear process modeling methods is developed in a recent study, by which a systematic approach for the adaptive C-control has been developed.[194] Instead of expensive instruments like ATR-FTIR for measuring solute concentration, a simple method using conductivity meter has successfully demonstrated the implementation of C-control strategy for inorganic compounds.[195]

Alatalo et al.[196,197] investigated various process control policies with precipitation of L-glutamic acid. The feedback process control loop of the proportional-integral-derivative (PID) controller was built based on the in-line concentration measurement with ATR FTIR. The feeding rate of the sulfuric acid reactant was adjusted based on the determined momentary supersaturation level obtained from the ATR FTIR and solubility data and by comparing it with the set value. Hatakka et al.[198] studied seeding with desired polymorph seed crystals and ultrasound to induce the crystallization to ensure trouble-free processing and to ensure good uniformity between products obtained from several semibatch processes.

5.3. Nonlinear Model Predictive Control of Crystallization Processes. Very few control studies that make use of CSD measurement feedback are reported in the literature.[199−201] Multivariable feedback controllers using fuzzy logic, rigid logic, and neuro-fuzzy techniques and in situ

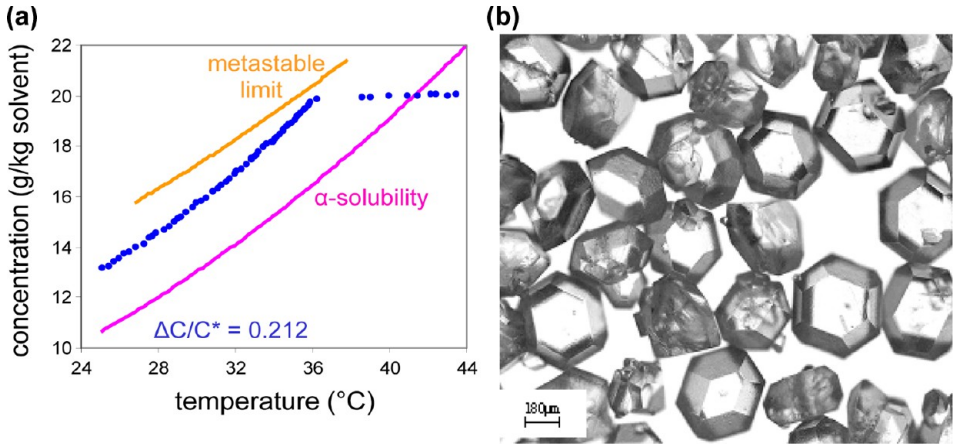

Figure 27. Feedback control of solute concentration to follow a specified path in the phase diagram for the metastable α-form of L-glutamic acid in aqueous solution. (a) The crystallization phase diagram with the metastable limit determined by FBRM and the solubility curve for the α-form crystals was determined by application of ATR-FTIR spectroscopy to a slurry of α-form crystals. The blue points are experimental measurements to follow a set point relative supersaturation of 0.212. (b) Microscope image of the large metastable crystals produced by the concentration feedback control shown in (a). For details on the experiments, see Kee et al.[189]

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measurements of supersaturation and difference in chord lengths of fine particles for real-time control of semibatch antisolvent crystallization processes have been recently developed.[202,203] Model predictive control or nonlinear model predictive control (NMPC) strategy is of increasing interest to both the academic and industrial sectors owing to its capability of handling important design issues like input constraints. However, its implementation to crystallization processes for both CSD and polymorphic purity control has been rather limited.[193,204−207] Real-time optimal control of semibatch antisolvent crystallization process for the desired product CSD has been recently demonstrated through experimental implementation.[208] A practical NMPC strategy based on extended predictive self-adaptive control (EPSAC)[209−211] is developed for the polymorphic transformation of L-glutamic acid from the metastable α-form to the stable β-form. Compared to the open loop implementation of the optimal temperature profile obtained for nominal operating condition, C-control, and quadratic dynamic matrix control with successive linearization, the EPSAC based NMPC strategy shows good overall robustness while satisfying all constraints on manipulated and state variables within the specified batch time.[207] Furthermore, exploiting the fact that batch processes are repetitive in nature, batch-to-batch (B2B) control, which uses information from previous batches to update the process model in the next batch, can be incorporated into the NMPC design (B2B-NMPC) to iteratively compute the optimal operating conditions for each batch. Simulation studies show that the B2B-NMPC control strategy produces faster and smoother convergence and satisfies all of the state constraints, compared to the standard B2B control strategy.[212] Motivated by the issues concerning the computational cost associated with the solution of the nonlinear optimization problem during the implementation of the (N)MPC, measurement based schemes that track the necessary conditions of optimality (NCO) have been developed in the literature.[213,214] Recent studies of antisolvent crystallization of paracetamol in the acetone−water mixture system show that the NCO tracking based methods for CSD control deliver better performance than those obtained by the open loop optimal flow rate profile and C-control strategy in the presence of process variations and disturbances, while it gives comparable performance to that obtained by the MPC strategy.[215]

The conventional C-control strategy that has shown effective and robust control performance for batch/semibatch cooling and antisolvent crystallization is not feasible to be implemented for semibatch pH-shift reactive crystallization. To circumvent this problem, a variant of C-control strategy by incorporating the just-in-time learning (JITL) method to cope with strong process nonlinearity inherent in the pH-shift reactive crystallization of L-glutamic acid.[216,217] Likewise, it was noted that the EPSAC based NMPC design gave degraded performance for controlling pH-shift reactive crystallization. Therefore, to circumvent this shortcoming, a new JITL-based EPSAC design is developed for constructing a set of state-space models that are locally identified along the base trajectory. Simulation results of end-product quality control for the reactive crystallization process validate that this new variant of EPSAC algorithm provides better control performance than its previous counterpart.[218] Furthermore, a new integrated B2B-NMPC control strategy is developed based on the interaction between a first-principles model and a multiway partial least-squares (MPLS) model, where the MPLS model utilizes the initial conditions, measurement trajectories, and end-point product qualities to estimate the kinetic parameters in the first-principles model. In doing so, while the NMPC performs on-line control to handle the constraints and disturbances, the B2B control refines the model iteratively by inferring from the previous batch operations.[219]

5.4. Automated Direct Nucleation Control (ADNC) for Crystallization Control. While PAT tools have been extensively used for monitoring crystallization processes for the past more than two decades, a major recent advance consists of their use in real-time feedback control approaches. Feedback control approaches applied in crystallization generally can be divided into (i) model-based and (ii) model-free control approaches.[12,220] While several recent comprehensive applications of model-based techniques have been reported that use complex models of the crystallization processes for the real-time reoptimization of the operating profiles,[221−224] model-free control techniques have gained more intense industrial interest. Model-free control approaches include simple linear cooling (constant antisolvent addition), supersaturation or concentration feedback control (SSC/CFC),[187,188,224] direct nucleation control (DNC),[199,225−227] and combined SSC and DNC approaches (simultaneous and sequential).[220,228]

Direct nucleation control (DNC) is one of the most robust model-free control approaches, which has gained large popularity in recent years with an increasing number of industrial implementations. While other model-free approaches, such as SSC, control the crystallization by measuring solute concentration and manipulating the operating trajectory in phase diagram, the main distinguishing characteristic feature of the DNC technique is that it directly measures and controls properties of the solid particles. The original approach was developed to control the number of particle counts per second provided by FBRM measurement. This is possible since the number of particles in the system is in correlation with the CSD that can be achieved. If a smaller number of particles is maintained the resulting mean size of the product will be larger and vice versa. Correlations between the number of counts per second provided by the FBRM and the size of the crystals can be obtained off-line, and the DNC approach can be used to indirectly control product properties. The DNC technique detects directly the increase and decrease in the number of particles (or a measure related to this, such as turbidity) and automatically manipulates the supersaturation or creates dissolution to control the measured number of particles around the desired value, as shown in Figure 28.[227] The automated

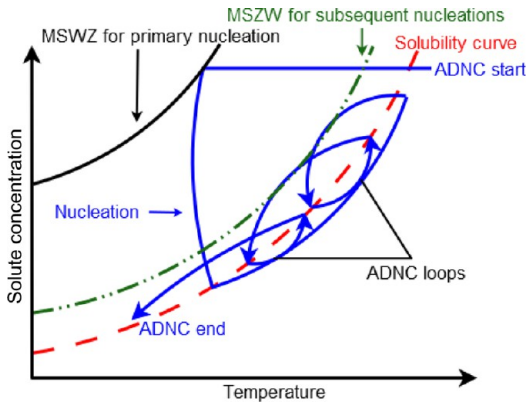

Figure 28. Schematic representation of the ADNC operating procedure in the crystallization phase diagram.[227]

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direct nucleation control (ADNC) approach automatically changes the heating and cooling rates, using a complex algorithm that takes into account the difference in crystallization dynamics before and after nucleation happens and during crystallization versus dissolution to achieve convergence in the temperature cycles.

The controlled growth and dissolution cycles (GDCs) are achieved by cooling/heating or antisolvent/solvent addition cycles (or a combination of the two). The GDCs have proved to have numerous benefits in achieving better crystalline product properties. DNC can be used for consistent in situ seed generation,[226] elimination of agglomeration, elimination of fine particles, to provide more uniform and larger particle size, elimination of problems with solvent inclusion,[227] and better polymorphic purity.[229] Additionally the GDCs have an effect of slow surface dissolution and regrowth, which can significantly increase crystal purity by decreasing the amount of foreign molecules that can be incorporated in the crystal lattice, or they can decrease crystal defects[230] which can be important to achieve higher quality products in the crystallization of energetic materials or for single crystal X-ray diffraction, e.g., for structural determination in proteomics and genomics applications.[220,12] Additionally, GDCs can also improve the aspect ratio of needle-shaped particles. Since the approach detects automatically and in situ the boundaries of the metastable zone, it can be used as a robust feedback control-based scale-up approach, that will automatically determine the required operating profile in the phase diagram in the case of variation in the MZW due the changing mixing conditions during scale-up.

Figure 29 shows sample results of applying ADNC as an automatic scale-up approach for the unseeded cooling crystallization of paracetamol. It can be seen that at 1 L scale the ADNC applied a total of 5 cycles. The first cycle is larger, and since the process was unseeded initially, a high supersaturation was created to induce nucleation for in situ seed generation. Since at very high supersaturation the nucleation rate was high, significant overshoot of the desired number of counts/s resulted, which induced the ADNC approach to start a heating cycle to dissolve the excess particles. Subsequent cycles were generated due to secondary nucleation events, which occur at a much lower supersaturation owing to the presence of particles in the system.

On the 100 L scale, a larger number of cycles (1 + 7) were required, due to the more pronounced formation of fine particles. Since at a large scale more secondary nucleation or attrition can occur due to the more intense particle−particle or particle−impeller collisions, the elimination of these fine particles required a larger number of the controlled dissolution cycles. The micrographs indicate that a very similar product CSD was obtained at both scales.

The ADNC approach is increasingly applied across various industries, and it has been implemented in commercial software packages, such as the CryPRINS and CryMOCO systems. The original ADNC approach is based on controlling the number of counts per second resulting from the FBRM. However, other properties can also be used in the control algorithm, such as number of counts within certain size ranges or other statistics of the distribution, e.g., standard deviation, as well as combination of statistics. Additionally, other PAT tools can be used in similar feedback control approach to generate GDCs to control different signals provided by the measurement device (e.g., turbidity or image analysis based techniques, including bulk video imaging).[220,12]

5.4.1. Composite PAT-Array and Crystallization Process Informatics System. The combined use of multiple PAT techniques to monitor and understand crystallization processes is very beneficial. Therefore, PAT tools are often used simultaneously together to monitor crystallization processes. For example, Simon et al.[119] presented the monitoring of citric acid transformation using FT-Raman, FT-ATR-IR, FT-NIR spectroscopy, turbidity, and endoscopy. More recently, the concept of crystallization process informatics system has been introduced, which is based on the use of composite sensor or composite PAT array (CSA or CPA), for monitoring multiple process parameters and quality indicators at the same time, rather than one at a time.[220,12] The concept of CSA is based on considering the combination of signals from various PAT measurements as a single bundle of complex information, which allows using simultaneously all signals from all measurement devices for automated decision support and feedback control of the crystallization process.[231] The complementarity and redundancy in the acquired information provided by the CSA allow the implementation of robust crystallization control strategies, such as the supersaturation control,[188] direct nucleation control,[226] active polymorphic feedback control,[232]

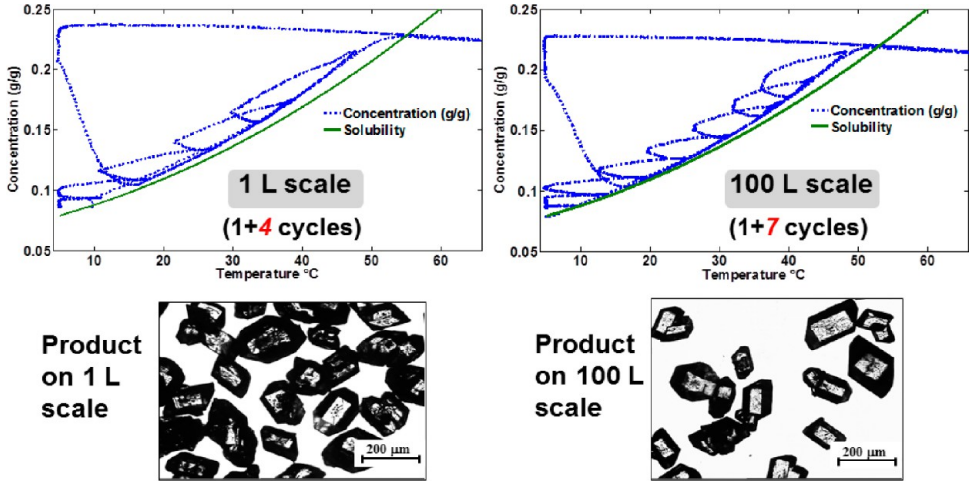

Figure 29. Results of the application of the ADNC approach at 1 L (left) and 100 L (right) scale. Although different number of cycles were required, very similar product was achieved at both scales.

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and combination of these approaches. The crystallization process informatics system also provide a generic communication interface based on industry standard protocols such as OPC (OLE—Object Linking and Embedding—for Process Control) or ethernet, to allow the communication between various PAT technologies provided by different vendors and the distributed control system (DCS) to implement the proposed control actions. The combination of the signals can be performed using model-based approaches or by applying chemometrics using simultaneously all signals from all measurement devices, with a system that automatically determines the most relevant combination of signals for a particular process or control objective.

5.5. Direct Polymorphic Control Using Raman Spectroscopy. Advanced PAT, e.g., Raman spectroscopy, offers the opportunity to improve processes in the pharmaceutical industry.[233−238] Effectiveness and profitability of the pharmaceutical production are significantly influenced by the drug crystallization as the polymorphism, purity, crystal size distribution, and crystal habit achieved in this unit operation has a critical part in the efficacy (bioavailability, tablet stability, toxicity), and formulation procedure (filtration, drying, feeding, granulation, tableting) of the drug. These characteristics are significant, of course, from the patentability point of view as well. Therefore, the development of crystallization control based on real-time quality monitoring provides the possibility for realizing efficient production and flexible product design.

Real-time Raman spectroscopy can be used to monitor exothermic reactions,[239] crystallizations, and solvent-mediated polymorphic transitions of drugs. In-line Raman spectroscopy has recently been applied in the case of carvedilol (nonselective β blocker) crystallization in order to implement a novel Raman-based PAT method, which required the examination of solvent mediated polymorphic transitions of carvedilol (as a function of temperature) and the cooling crystallization (as a function of drug concentration) under Raman monitoring.[240,241] It has been found that low temperatures (0−25 °C) were favorable for the formation of solvates (Form VI, Form VII) in ethyl-acetate, while higher temperatures (25−60 °C) facilitated the crystallization of the thermodynamically stable Form I polymorph. The kinetically preferred Form II polymorph can be crystallized from 9 to 16 w/w% drug solution with linear cooling, while solvates were formed at low drug concentration (2.9 w/w%).

The knowledge of these drug crystallization features established the implementation of Raman intensity based closed-loop process control.[242] The development of this model-free PAT based method provided a chance to ensure easily the final polymorphic form of a model drug. This was achieved by controlling automatically the process conditions (reheating period, changing cooling rate) on the basis of real-time Raman signals. The particular feature of this method is that knowledge of phase diagrams or detailed previous calibration procedures are not necessary for this closed-loop control. The closed-loop control utilized the change of the ratios of Raman intensity, corresponding to the relevant polymorphs, for directing the PLC (programmable logic controller). The undesired polymorph could be observed at low quantity. When it happens, the PLC automatically intervenes by modifying the crystallization conditions on the basis of the Raman information. If the undesired polymorph crystallizes, the PLC will reheat the suspension until the complete dissolution of solid particles, and then it will cool the drug solution with a different cooling rate than the previous one. The communication between the PLC and the Raman spectrometer was accomplished via serial port. The Raman spectrometer operation was controlled by a Visual Basic program using ActiveX interface of the spectrometer. This program serves for starting the real-time Raman detection, storing raw data, and sending the nominated Raman intensity values, belonging to different polymorphs, back to the PLC. Finally the production of the desired polymorph could be ensured in the presence of any disturbing factors (e.g., presence of the thermodynamically stable polymorph as an impurity). In compliance with this, the efficiency of this closed-loop control was tested in the cooling crystallization of carvedilol, where the aim was to produce the kinetically preferred Form II polymorph in the presence of a low amount of seeding crystals. Figure 30 shows the classical least-squares (CLS) based

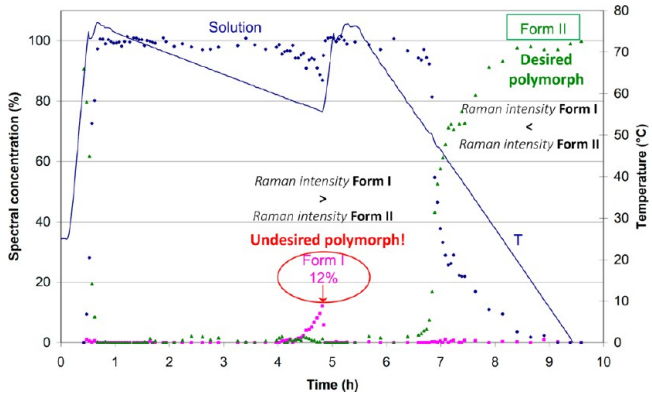

Figure 30. Quantitative evaluation of the Raman-based closed-loop controlled crystallization of carvedilol.[242]

evaluation of a closed-loop controlled experiment. The desired product morphology could be ensured in the second cooling period. The undesired Form I polymorph appeared during the first cooling as a result of seeding with Form I. At this time, the Raman intensity characteristic of Form I polymorph was higher than the other selected Raman intensity concerning desired Form II; thus, the PLC intervened in the process.

5.6. Control Charts for Nucleation Detection of Crystallization Processes. Induction time is one of the key parameters used in crystallization to describe nucleation events. It is defined as the time required for the first nucleation events to be detected in a solution kept at a constant level of supersaturation.[243] As the appearance of the first nucleus is impossible to detect accurately, induction time t_{ind} is often measured as the total time for nucleus formation t_n and detection of the grown nucleus[244,245] t_g: $t_{ind} = t_n + t_g$. Several experimental methods have been developed to determine induction times by measuring changes in nucleation-related physical quantities upon birth. Kubota classified these indirect measurements into two categories: methods detecting changes in the amount of grown nuclei and methods related to changes in solution concentration.[246] Belonging to the first class are visual inspection,[247] laser transmission,[248] FBRM,[243,249−254] particle video microscopy,[250,255] near-infrared spectroscopy,[250] and Raman[18] and turbidity meters.[256]

Recently, imaging sensors and image analysis techniques have been proposed to monitor the onset of nucleation and to determine metastable zone width, e.g., external bulk video imaging.[12,257] In a follow-up work the nucleation onset was systematically determined using multivariate image analysis, image feature descriptors, and control charts (see Figure 31).[121,258]

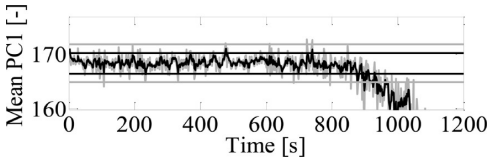

Figure 31. Shewhart (gray) and EWMA (black) statistical control charts of mean first principal component images; the decreasing trend is due to negative loadings. Reprinted with permission from ref 118. Copyright 2010 Elsevier.

While many of the aforementioned PAT have been successfully implemented to facilitate in-line monitoring of the onset of nucleation, this still remains difficult to achieve when only few nuclei are present in solution. This is particularly the case for poorly soluble pharmaceutical compounds, which upon precipitating can produce a small number of particles. The lack of a large number of nuclei makes visual observation highly biased and often difficult to rely on. This is true particularly during the monitoring of precipitation of poorly soluble drugs in the gastro-intestinal tract. Since a small number of nuclei is often unable to change solution turbidity or light scattering, alternative methods which directly detect the newly formed crystals are required. One such method is to perform object identification in endoscopy images,[117] rather than to calculate bulk property descriptors, e.g., intensity of images.

To accurately measure induction times during the crystallization of poorly soluble compounds, recently a statistical process monitoring (SPM) approach was applied to crystal count time series data. The most common SPM methods include Shewhart control charts, exponentially weighed moving average (EWMA), and cumulative sum,[118,258] while the multivariate control charts are based on Hoteling's *t*-statistic.[259] It should be remarked that the use of these control charts is only valid when the time series is stationary and the conditions of randomness and normality are met.

In the study presented in this section of the paper, induction times during primary and secondary nucleation of dipyridamole, a BCS class II compound, were determined. This was carried out by applying control charts to the crystal count time series data, therefore automating the method of detection and minimizing user-bias. To obtain the number of counts, image processing and analysis techniques were used as the primary tool. Crystal images were captured at every second during the primary and secondary nucleation experiments using the Crystalline Particle Viewer camera setup (Avantium Technologies, Netherlands) and were further analyzed by ImageJ software.

Figure 32 shows a typical image after the onset of nucleation. To extract crystals present in each frame, image thresholding was used to select the particles from the background. Thresholding is a primary step in image processing used to obtain a binary image from its grayscale counterpart and can affect subsequent image analysis steps such as particle counting and image segmentation. While manual thresholding can be easy to implement, it relies heavily on the visual appeal to the human inspector, can produce inconsistent results, and therefore should be avoided. Several algorithms and thresholding methods have been developed to automate the thresholding process and have been categorized in six groups: histogram-shape based methods, clustering-based methods, entropy-based methods, object-attribute-based methods, spatial methods, and local methods.[260] While these automated

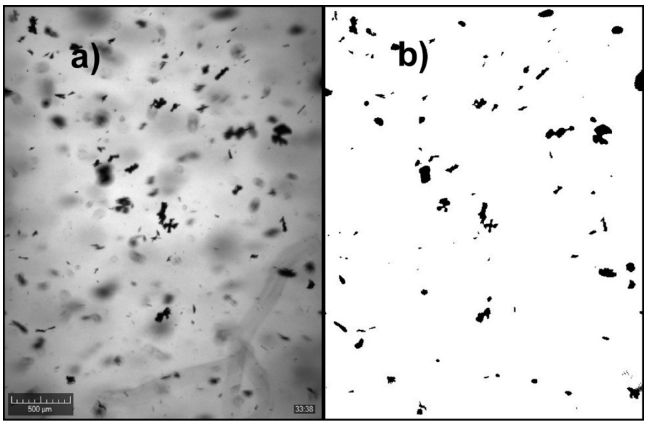

Figure 32. (a) Original and (b) thresholded images of dipyridamole crystals.

algorithms can help produce consistent results, the choice of the right method requires prior knowledge of the imaging technique, image brightness, etc. In this work, several threshold algorithms available in the ImageJ software were tested. A comparison of the results showed that the Yen threshold[261] is the most suitable one to apply to the camera images as it is nearly unaffected by changes in image brightness due to stirring (Figure 32). The thresholded images were then analyzed to count the number of particles existing in each frame and to obtain a crystal count time series. In this application the role of control charts is to separate the randomly occurring false alarms due to the thresholding from systematic process changes due to the appearance of crystals in images.

To ensure that the normality and randomness conditions are met, the autocorrelation function for the time series was obtained (Figure 33), indicating randomness of the data.

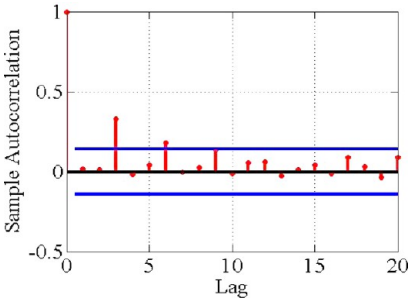

Figure 33. Correlogram of the crystal counts time series data.

Furthermore, to assess the normality of the data, the goodness-of-fit test was applied. The latter confirms that the hypothesis of the crystal count data coming from a normal distribution is true at the 5% confidence level. The EWMA control chart (Figure 34) was then applied to the time series, and the onset of nucleation was determined when 5 consecutive data points were beyond the upper control limit to avoid false alarms.

5.6.1. Control Charts as Automated Switching Mechanisms between Nucleation and Seed Conditioning Steps. Another use of the control charts is to serve as a switching mechanism, e.g., the switching from nucleation to seed conditioning as discussed in Simon et al.[121] The control charts can be regarded as the simplest feedback control structures and can be designed on time series generated by any sensor, e.g.,

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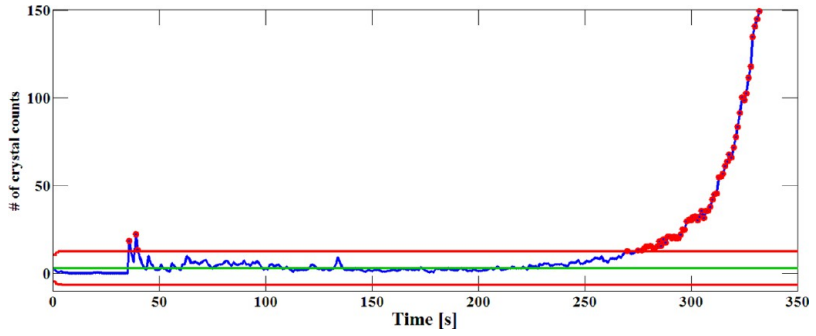

Figure 34. EWMA control chart applied to the crystal counts time series data; red circles indicate process outliers.

turbidity, FBRM counts, or on the intensity trend of the first principal component of color images.[118]

5.7. Robust Calibration in Spectroscopic Applications—The Impact of Process Variations and Calibration Transfer. During on-line quantitative monitoring[3] of processes using spectroscopic techniques, it is by and large the chemical and biological information (in most cases the concentrations of the chemical and biological compounds) inherent within the spectroscopic measurements, rather than the spectroscopic measurements themselves, that are needed for use in process monitoring and control. It has been suggested that PCA scores of the spectral data measured could be used for the in situ monitoring of some complex systems; however, in general, such indirect information is not suitable for closed loop process control. Calibration models are therefore needed to transform abundant spectroscopic measurements into the desired concentration information. The development of multivariate calibration models for on-line/in-line process spectroscopy that will then be used for process monitoring and closed loop feedback process control and optimization can present major challenges. Unlike in off-line assays, the spectroscopic measurements in industrial on-line and in-line applications are almost inevitably subjected to fluctuations and variations in process variables, e.g., temperature, flow turbulence, compactness, and other instrumental and external variables. These will generally invalidate the underlying assumption of most of the popular multivariate calibration methods, i.e., a linear relationship between the spectroscopic measurements and the concentrations of the target chemical components. The accuracy and reliability of multivariate calibration models for processes which are subject to variations in physical properties (such as particle size, samples' compactness, surface topology, etc.) as well as process variables is a matter of concern. Such variations can influence spectra in a nonlinear manner and hence lead to the poor calibration performance and potentially degraded closed loop process control. This makes the task of extracting the relevant chemical information, and ultimately reliable process understanding for process modelling, control, and optimization, from spectroscopic measurements beyond being routine. Robust and transferable calibration models are essential for the full implementation of PAT/QbD and closed loop process control.

In this section some spectroscopic data chemometric preprocessing methods are discussed aimed at contributing to the wider use of in-line and on-line PAT in process monitoring and closed loop process control for real-time release.

−Correction of temperature-induced spectral variations through loading space standardisation;[262]

−Correction of variations in optical path-length due to sample physical differences—optical path length estimation and correction[263] (OPLEC) and its use in challenging applications such as the quantitative monitoring of phase transitions in suspensions,[264] the analysis of heterogeneous mixtures through the correction of multiplicative scatter effects,[265] powder mixtures using Raman spectrometry,[266] the determination of analytes in turbid media[267] and extended to aid the calibration of multiplexed fiber-optic spectroscopy with multiple probes in multiple reactors;[268]

−Correction of combined temperature and multiplicative effects though extended loading space standardization (ELSS);[269]

−Maintenance of the predictive abilities of multivariate calibration models through spectral space standardization (SST)[270] and systematic prediction error correction[271] (SPEC).

In the article correction of temperature-induced spectral variations through loading space standardization[262] (LSS), the influence of temperature fluctuations on the predictive abilities of multivariate calibration models in process analytical was addressed by the loading space standardization methodology proposed. The basic assumption behind LSS is that the absorbance of each chemical species in every wavelength follows simple polynomials with respect to temperature. Through the application of LSS, multivariate calibration models built at temperatures other than those of the test samples can provide predictions with accuracy comparable to the results obtained at a constant temperature. Compared with other available methods designed for the same purpose in the literature, LSS has the advantages of straightforward implementation and good performance.

In the article describing the correction of variations in optical path length due to sample physical differences, optical path length estimation and correction (OPLEC),[262] an advanced calibration model has been developed for quantitative spectroscopic analysis of complex mixtures exhibiting sample-to-sample variability in physical properties. In the proposed calibration model, a multiplicative parameter was introduced to account for the dominant multiplicative light scattering perturbations resulting from the physical variations inherent within individual samples. Based on this model, a unique dual calibration strategy was proposed to separate the physical light scattering effects from the spectral variations related to the chemical components, and hence, the prediction accuracy of calibration models were significantly enhanced.[263−268]

In the article on improving the linearity of spectroscopic data subjected to fluctuations in external variables by the extended loading space standardization (ELSS), the influence of external variables on spectral data was classified into two different

modes, multiplicative influential mode and composition-related influential mode. An extended loading space standardization method was proposed to explicitly model these two kinds of influential modes.[269] This was achieved by first standardizing spectra measured at different temperatures into an arbitrarily selected reference temperature and then estimating the multiplicative parameters from the standardized spectra. The results on a benchmark ternary mixture data set and a real industrial data showed that ELSS could successfully model both the temperature-induced spectral variations and multiplicative effects caused by the fluctuations of other measurement conditions. Calibration models built on spectra preprocessed by ELSS were shown to have much better predictive performance than calibration models on spectra with temperature effects being removed by LSS or even global PLS model on raw spectra. The application of ELSS does not require any additional information about the spectral data being studied, except the corresponding temperature readings and the concentrations of the target chemical component in the training samples. Its capability in correcting external nonlinear effects as well as its simplicity in implementation makes ELSS a promising chemometric tool for in-line/on-line process monitoring as well as in closed loop process control applications where the spectral data are not measured under as well-controlled conditions as they are in a laboratory environment. This has major implications for the assured and robust application of PAT in closed loop process control applications. The applications of a number of these approaches were used in a PAT-based scale-up from 0.5 and 2 L laboratory scale reactors to a 250 L industrial pilot plant in another country.[272,273]

Research into the development of reliable multivariate calibration models for the on-line/in-line monitoring of chemical and biochemical processes has addressed the issues of robust and reliable long-term multivariate calibration models.[270,271] In many applications any change in the instrumental response or variations in the measurement conditions can render a multivariate calibration model invalid. A new method termed spectral space transformation (SST)[270] has been developed and has been shown to maintain the predictive abilities of multivariate calibration models when the spectrometer or measurement conditions are altered. SST eliminates the spectral differences induced by the changes in instruments or measurement conditions through the transformation between two spectral spaces spanned by the corresponding spectra of a subset of standardization samples measured on two instruments or under two sets of experimental conditions. The performance of the method was evaluated on two data sets comprising NIR and MIR spectra. The experimental results show that the proposed approach was able to provide satisfactory analyte predictions from spectroscopic measurements subject to spectrometer and probe alterations when only a few standardization samples are used. Comparisons were made with global PLS, univariate slope and bias correction (SBC), and piecewise direct standardization (PDS). SST was shown to provide very competitive calibration model maintenance method that should have wide applicability in on-line/in-line process monitoring.

However, SST requires the spectra of a subset of standardization samples measured on both instruments or under both sets of measurement conditions, which makes the procedure inapplicable to on-line/in-line monitoring of complex chemical and biochemical processes where such a requirement is difficult to satisfy in practice. To address this issue, systematic prediction error correction (SPEC)[271] was proposed. SPEC only requires the analyte concentrations in a few standardization samples and the corresponding spectra measured at the experimental conditions or on the instrument to which the calibration model is applied. The performance of the method was evaluated on two NIR data sets. One is a benchmark NIR data set of pharmaceutical tablets with changes in instrument responses: the other, a fermentation study by GSK with variations in experimental conditions. The outcomes compared with those of some popular methods—global PLS, univariate slope and bias correction (SBC), and piecewise direct standardization (PDS). The results showed that SPEC achieved satisfactory analyte predictions with significantly lower RMSEP values than global PLS and SBC for both data sets, even when only a few standardization samples are used. The implementation of SPEC is straightforward with only one model parameter (the number of chemical variation sources in the spectral data) needs to be identified prior to its application. This can be simply set to the number of the significant singular values of the spectral data. Consequently, SPEC has wider applicability than other standardization methods that need the spectra of the standardization samples to be measured under both the calibration and test conditions or on both the primary and secondary instruments and/or involve the problematic selection of the values of some meta-parameters without specific chemical sense.

5.8. Systematic PAT Design Method and Software Platform. In this section of the paper, the methods and tools needed for the design and implementation of PAT systems are reviewed, and a systematic framework for PAT system design is presented. Recently, interest has grown rapidly in the design and implementation of PAT systems for efficient QbD-based manufacturing. As a consequence, significant efforts have been made on topics such as QbD and PAT. Singh et al.[274] proposed a computer-aided framework including the methods and tools through which the PAT system for product quality control can be designed, analyzed, and/or validated. The design of a PAT system involves the identification of the critical quality parameters, the selection of economical and reliable on-line/in-line measurement tools, and integration of these in on-line/in-line sensors with an appropriate control system.[274] A user-friendly software tool has been also developed for PAT system design.[275] Real time on-line/in-line monitoring tools are the core element of the PAT system. Challenges, however, lie in identification of an appropriate monitoring tool for a control variable. Different criteria, such as accuracy, precision, operating range, response time, resolution, sensitivity, drift, and cost, need to be considered for the selection of monitoring tools. Singh et al.[275] have developed an ontological knowledge-based system for the selection of monitoring tools.

Validated mechanistic models play an important role in the design of PAT systems.[276,277] Extensive work has been done to develop mathematical models for pharmaceutical processes[275,278−288] as well as biopharmaceutical processes.[274,289,290] The application of mathematical models for PAT system design has been successfully demonstrated by several authors.[274,275,283,284,287,288] However, few attempts have been made in the area of design of monitoring and control systems for closed-loop pharmaceutical manufacturing. Singh et al.[275] suggested a monitoring and control system for a batch tablet manufacturing process. Hsu et al.[291,292] suggested a control system for a roller compactor, an important unit operation used for a dry granulated continuous tablet manufacturing process. Singh et al.[287] developed an advanced model predictive control system (MPC) for direct compaction continuous tablet manufacturing process.

Singh et al.[288] designed a control system for the roller compaction route of the continuous tablet manufacturing process. The control of granulation processes has been extensively studied.[293−296] An MPC strategy has been proposed for a wet drum granulation process.[297−299] The control system for flexible pharmaceutical process that includes direct compaction, wet granulation, and dry granulation routes of tablet manufacturing has also been designed.[300,301]

After design, the next step is to implement the PAT system for QbD-based manufacturing of the pharmaceutical product. Extensive work has been done to develop methods and tools needed for PAT system implementation. Several spectroscopic techniques have, for example, been successfully implemented in pharmaceutical manufacturing processes[7,16,302−307] and in food processes.[8,308−310] There are several distributed control system (DCS) as well as programmable logic controller (PLC) based control platforms commercially available to implement the control system. For example, Blevins et al.[311] described a DCS control platform (DeltaV) commercially available from Emerson. PCS7 is another DCS control platform commercially available from Siemens. PCA (principal component analysis) and PLS (partial least-squares) methods have been widely used to develop the calibration model for spectroscopic sensors (see for example, ref 307). Chemometric software tools can be used to perform the PCA and PLS and thereby to develop the NIR calibration models so that real-time on-line prediction tools can be used to generate the control relevant signals. Singh et al.[287,288,306] have integrated the control hardware and software needed to implement the PAT system. Integration of NIR with chemometric tools, real-time prediction tools, and PAT data management tools in a control platform for a pharmaceutical tablet manufacturing plant has been demonstrated by Muzzio et al.[312] The OLE process control (OPC) communication protocol has been widely used for efficient communication between databases and calculation-analysis tools. Also, we have not yet found commercial tools that are able to design the PAT system, which is described in detail in the next section.

5.8.1. Systematic Framework for PAT System Design. The design of a PAT system requires a stepwise procedure involving the selection of critical process variables, followed by the selection and placement of suitable monitoring and analysis equipment, and finally, the coupling of the monitoring and analysis tools to a control system to ensure that the selected critical process variables can be controlled, such that the process is kept within its design space.[274,313] Decisions need to be made taking into account the interaction between product quality specifications, process operational constraints, cost of the PAT system, and the time needed for analysis. The methodology for design of a PAT system is shown in Figure 35. It consists of a work-flow with nine hierarchical steps.[274] This figure also shows the supporting tools (knowledge base[314] and model library[275]) needed for each step and corresponding outcomes. The first step (product property specifications) is concerned with specifying the product properties that are desired (to be achieved) in the considered production process. The necessary process related information such as the raw materials, their composition, and the equipment used in the production process are provided through step 2 (process specifications). The information provided through steps 1−2 acts as input data for the design problem. On the basis of the input data and with the consultation of the knowledge base, step 3 (process analysis) of the methodology generates a list of process points (in general, the pieces of process equipment

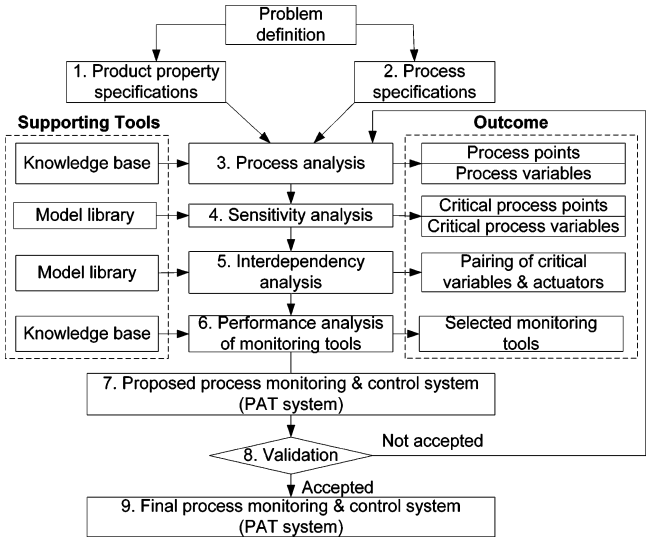

Figure 35. Overview of the PAT design methodology, including the use of the supporting tools and the outcome of the individual analysis steps. Reprinted with permission from ref 274. Copyright 2009 Elsevier.

are considered as the process points) and a list of the corresponding process variables. The outcome of step 3 serves as the basis for subsequent analysis steps. The critical process points where monitoring and analysis equipment need to be placed and the corresponding critical process variables that need to be monitored and controlled in order to achieve the desired end product quality are then identified through step 4 (sensitivity analysis). The identification of the appropriate actuators are made in step 5 (interdependency analysis) to successfully implement the control system for control of the critical process variables identified in step 4. Step 6 (performance analysis of monitoring tools) generates the list of the feasible measurement methods and tools for selected critical process variables. On the basis of the outcomes of steps 4−6, a PAT system (process monitoring and control system) is suggested in step 7. The proposed monitoring and control system consists of a list of critical process points, corresponding critical process variables, actuators, monitoring techniques, and monitoring tools. The proposed process monitoring and control system is validated in step 8, and finally step 9 identifies the final PAT system. Modeling tools, such as ICAS-MoT,[315] are employed for simulation of process models that are retrieved from the model library.

5.8.2. Data/Information Sources (Knowledge Base/Model Library). A knowledge base and a model library are important sources of information/data needed for design of any PAT system. The knowledge base provides the necessary information/data during the design of the PAT system while the model library generates additional or missing data needed for design and analysis. The ontological knowledge base consists of two sections. The first section stores the necessary process knowledge (type of processes, corresponding process points, process variables, and actuators), while the second section stores the knowledge/data on measurement methods and tools (type of variables, available monitoring techniques, and tools with specifications such as accuracy, precision, operating range, response time, resolution, sensitivity, drift, cost, etc.). The model library contains a set of mathematical models for different types of unit processes, sensors, and controllers. The details of knowledge base and model library have been previously reported.[275,314]

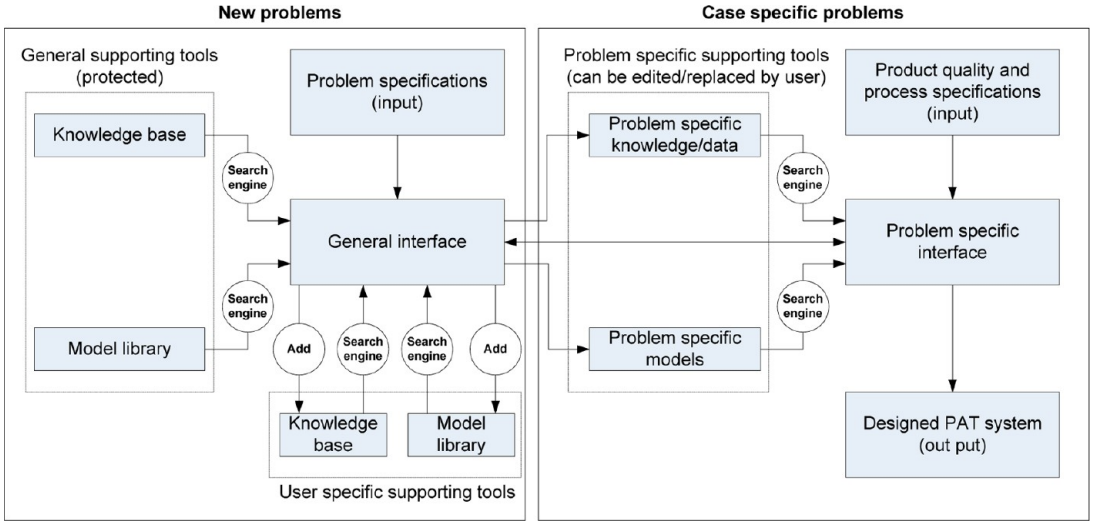

Figure 36. Overview of the software tool for PAT system design. Reprinted with permission from ref 275. Copyright 2010 Elsevier.

5.8.3. PAT Design and Implementation Platforms. Corresponding to the methodology shown in Figure 35, a software tool (ICAS-PAT) has been developed to design the PAT system.[275] An overview of the software tool is shown in Figure 36, where the general supporting tools (protected general knowledge base and model library) as well as the user specific supporting tools (specific knowledge base and model library developed by the user) are integrated within a general user interface. The system has built-in flexibility to either use the general supporting tools or the user specific supporting tools. The user specific supporting tools can be developed, extended, and managed according to the user's needs while administrator rights are needed to edit/replace the general supporting tools. In either case a problem specific supporting tool consisting of the problem specific knowledge and models is generated and used for design of a PAT system. As shown in Figure 36, the starting point for new problems is to provide the problem specifications, followed by the creation of problem specific supporting tools and then to design the PAT system according to the PAT design methodology proposed (see Figure 36). For already existing case specific problems (saved earlier) the design methodology is used directly to generate new solutions and/or analyze previous solutions to find improvements.

5.9. Hybrid Modelling for QbD and PAT. Process modelling is mostly done in two principally different ways.[1] Mechanistic, fundamental, or empirical models are developed from first-principles, considerations, and observations about the process by formulating mathematical equations, wherefore they can be referred to as parametric models. Alternatively, data-driven, chemometric, or multivariate data analysis models are developed utilizing mostly process data, such that they can be designated as nonparametric models. However, those modelling approaches are not mutually exclusive, and in fact by integrating them into hybrid semiparametric models (short: hybrid models), unique model properties can be obtained. For instance, the requirements on experimental data (both quality and quantity) for model development can decrease, the process description may improve, and they can increase process understanding.[316] This makes hybrid modelling a cost-effective approach for industrial applications,[316,317] particularly under the PAT framework.[318−321] Just recently the challenges and benefits of hybrid modelling for QbD and PAT have been carved out.[321] As one of the main points for fostering industrial PAT applications of hybrid modelling, the need for business relevant case studies that clearly highlight the benefits has been reported. However, hybrid models have been successfully applied in the past to model processes such as milling,[322] drying,[323,324] crystallization,[325] or cultivations of various cells (e.g., yeast,[326] bacteria,[327−329] or mammalian cells[330]). The backbone of the hybrid models is the parametric framework derived from first-principles or mechanistic considerations. In serial hybrid models, variables/parameters that vary with the process conditions are then typically described by nonparametric models; see Figure 37. In most parallel settings,

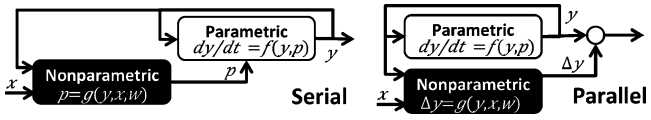

Figure 37. Schematic representation of serial and parallel hybrid modeling structures. y designates the state variables, x the on-line measurements, w the nonparametric model parameters, and p the parameters of the parametric model, which are estimated by the nonparametric model in case of the serial structure and fixed values in case of the parallel structure, Δy is the residual between the estimates/predictions and the true values, $f(\bullet)$ and $g(\bullet)$ designate some parametric and nonparametric functions, respectively.

the estimations of the parametric models are corrected by nonparametric models; see Figure 37. In both settings, the nonparametric models can be functions of the models' prediction and/or on-line measurements (frequently sampled and at-time available measurements).

In relation to PAT, hybrid models have been recognized as a possibility to bridge different knowledge sources[331] and more importantly as a possible method to establish correlations between (critical) process parameters and (critical) quality attributes, particular for biologics production.[320] For instance, Teixeira et al.[332] demonstrated that by integrating knowledge about the most eminent metabolic pathways into hybrid modelling framework, variations in the process that resulted from the process operation, i.e. batch or fed-batch, could be analyzed, see Figure 38.

Also the process monitoring performance can be improved by the integration of at-time measurements from process

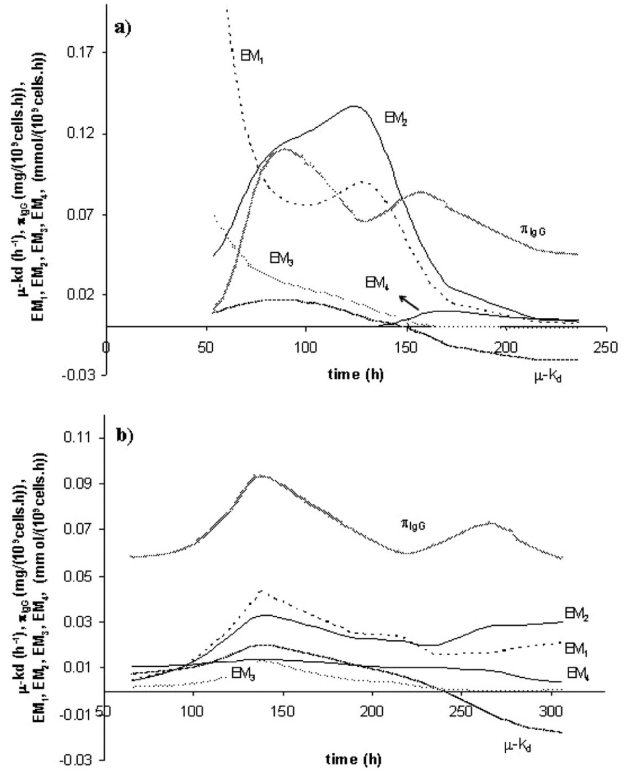

Figure 38. Kinetic rates over time for (a) a batch and (b) a fed-batch cultivation of BHK cells. μ-k_d are the specific biomass growth and death rate, respectively; π_{IgG} is the specific formation rate of glycoprotein; EM_i are rates of pathways that are involved in biomass growth or product formation. It can be seen that the product formation π_{IgG} is consistently more stable in the fed-batch culture than in the batch culture. It was suggested that this is due to the overflow metabolism in the batch experiments, which seems to be detrimental for product synthesis.[332] Adapted from Teixeira et al.[332]

analyzers into a hybrid model, as, e.g., reported by Aehle et al.[333] who compared different methods on the basis of on-line measurements of oxygen uptake rate, carbon dioxide production rate, and cumulative base addition or by von Stosch et al.[329] who compared hybrid models to partial least-squares models based on on-line measurements of near-infrared spectra, temperature, pH, and dissolved oxygen concentration. The integration of on-line measurements can also enable the hybrid modelling approach to account implicitly for concentration gradients in the reactor,[334] which are, e.g., observed in large-scale production.[335] Hybrid models should thus also support the knowledge transfer during scale-up, since the knowledge captured in the parametric model will typically remain valid across scales, while the influences on the scale-dependent variables (such as kinetic rates, which can depend on the reactor design and operation) can be captured through the nonparametric models.[336] Though experiments are necessary at both scales to derive the nonparametric models,[336,337] the number of experiments on both scales is typically much reduced as in comparison to strictly data-driven models. However, scale-up studies that would fully exploit this potential have not been reported to date. Successful hybrid modelling applications have been reported for process development[326] or optimization.[330] Recently, it was demonstrated that, in comparison to the methods that are routinely applied in optimization, e.g., response surface models, the number of experiments could be reduced by up to 70%.[338] In addition, it was shown that the typically intrinsic dynamic nature of the framework allows process variations to be assessed better, e.g., the impact of a pump failure on the product formation, shown in Figure 39, can be assessed. These insights can increase process understanding and hence can help to design quality into the process. The dynamic properties are also important for process control applications, though to date very few hybrid modelling approaches have been reported for closed-loop control.[316,321,332]

Hybrid modelling is clearly not always the best option, and each of the three modelling approaches has its merits.[321] However, the development of hybrid models provides a cost-efficient alternative when different knowledge sources exist, which can be linked and exploited in process operation and design through this approach. In order to foster the application of hybrid models in PAT, a spin-off company, HybPAT, has recently been formed, which provides hybrid modelling software solutions and modelling/consulting services.

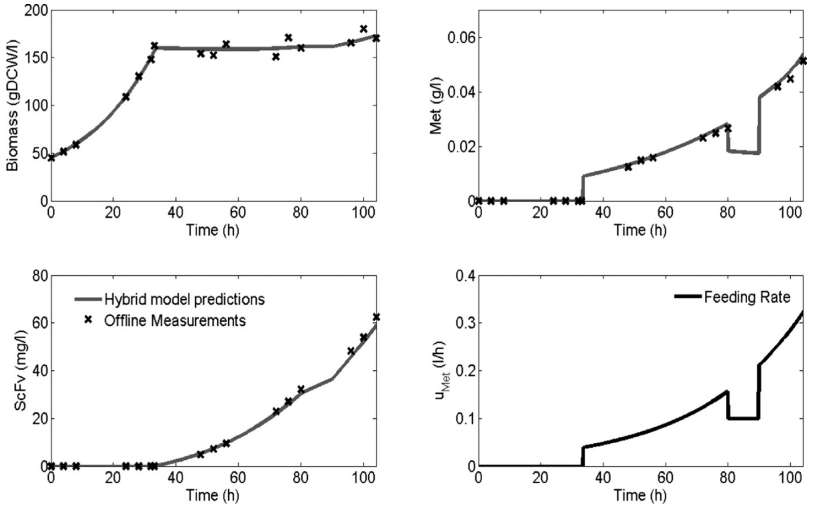

Figure 39. Plots of biomass, methanol, and product (ScFv) concentrations and the methanol feeding rate over time. The 10 h lasting pump failure at 80 h can be seen in methanol feeding rate profile. A direct impact of the pump failure on the methanol concentration can be observed, whereas only minor deviations in the biomass and product concentration profiles are visible.

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6. APPLICATIONS OF PAT BASED PROCESS MONITORING AND CONTROL

6.1. Crystallization Process Development, Monitoring and Control.

6.1.1. Sensors for Crystallization Process Monitoring. Applications of PAT tools to monitor process variables in industrial crystallizations are extremely important to ensure that the product quality of the process remains within acceptable limits. In the past decade a large number of PAT tools have been proposed and analyzed. The qualification of such tools is not straightforward as the usability of a process monitoring tool is strongly dependent on the way the tool is applied in the process. In general, different strategies can be applied depending on the complexity of the control policy. The simplest one is to use the PAT sensor to monitor the evolution of one or more relevant process variables. The sensor can then for example be used to control the rate of supersaturation generation in a batch process to reproduce the profile of this variable from a so-called "golden" or optimized batch run. Unfortunately, the final product quality in a crystallization process is in most of the cases not easy to reproduce by enforcing a certain supersaturation profile. In fact a large number of not well understood phenomena influence the final product quality:

- The complicated interplay between the initially formed or added seed crystals;
- The formation of primary or secondary activated nuclei, which has a strong statistical nature;
- The growth of the crystals to produce the desired crystal mass and size;
- The attrition or breakage of the crystals due to the mechanical contacts of the crystals with each other or with the crystallizer hardware;
- The often not desired agglomeration of the formed crystals to form larger entities;
- Nucleation of the metastable polymorph possible followed by a transformation to the stable one.

All mentioned phenomena are controlled by the rate at which supersaturation is generated during the different phases in the process.

In general the PAT tools can be divided into two categories, determining the properties of the solution or of the solid phases, respectively. The solution concentration sensor systems aiming at the control of the supersaturation during the crystallization process are not new, and for instance, the in situ refractive index measurement systems have already been applied a long time especially in the sugar or related crystallization processes. Besides the refractive index systems, sensors are applied based on measurement of the conductivity, speed of sound, density, and the spectroscopic based techniques measuring the adsorption of part of the electromagnetic radiation spectrum (ultraviolet–visible (UV–vis), near-infrared, or mid-infrared) or Raman scattering.[27] For the selection, application, and interpretation of the concentration sensors, three important points should be taken into consideration:

- The measurement principle. Most of the concentration sensors determine a lumped solution property, such as the density, refractive index, or speed of sound, which is determined by all the species present in the solution phase, which might give erroneous results in multicomponent systems. Only the spectroscopic techniques and especially the mid-infrared sensors can give a fingerprint of the solution composition.
- Depending on the measurement principle, solids present in the solution will affect the measurement results (speed of sound, density, conductivity, Raman, UV–vis) and requires the correction algorithms or solid liquid separation systems. Refractive index measurement and FTIR measurement using a ATR probe are less sensitive for the presence of particles in the suspension.
- The calibration of the sensor in order to translate the sensor data into the solute concentration or the supersaturation requires in most cases extensive calibration experiments. Especially the FTIR technique often requires the application of chemometric techniques to develop a sensor model which is suitable to determine the solution concentration. In this respect also the translation from the lab measurements, where the calibration are done typically to the plant measurement, can sometimes be an issue.[339]

In the second category, the sensor is applied to determine the properties of the solid phase, such as the size distribution of the crystals, the crystal shape or the crystal form. Also here, a wide variety of measurement techniques can be used such as

- Total (back) scattering of the suspension, used to determine the total particle concentration;
- Forward light scattering measuring the angular diffraction pattern to estimate the crystal size distribution;
- FBRM, yielding a chord length distribution and also detecting nucleation events;
- Ultrasound attenuation measured at a number of frequencies, from which the CSD can be deconvoluted even at high crystal concentration;
- Imaging techniques which can deliver information on nucleation events, as well as information on the shape and size of the crystals in the suspension;
- Raman scattering, yielding information on the crystal structure and that can be used to determine the type of polymorphs or to quantify the relative amount of a particular polymorph in the suspension.

All mentioned phenomena are controlled by the rate at which supersaturation is generated during the different phases in the process.

For a more detailed overview of the characteristics of these sensors, see ref 27.

One of the main challenges for the application of PAT tools for the control and optimization of crystallization processes remains the interpretation of the limited information from the sensor. As outlined above, the concentration sensors deliver an estimate on the supersaturation when combined with knowledge on the solubility of the solute but do not provide any information on the amount and size distribution of the crystals in the suspension. On the other hand, a particle size distribution (PSD) or chord length distribution (CLD) sensor gives the latter information but lacks any information on the kinetic processes. For a proper optimization and control of the process, information on both the solid and the solution phase is essential. At the Delft University of Technology, a number of these issues concerning the application of PAT sensors have been studied and will be discussed in the following paragraphs.

In the first study, two spectroscopic sensors, a NIR and a MIR, were compared for four different crystallization systems, R-lactose monohydrate in water, ammonium sulfate in water, ibuprofen in hexane, and L-glutamic acid in water.[339] The two probes from Bruker Optics GmbH differed not only in the spectral range but also had different immersion probes (IN-350 F fiber optics probe for the MIR and the IN-271 P transflection probe for the NIR).

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It was found that both sensor systems can, in principle, be used to monitor the solute concentration in a crystallization process, although the NIR system was more limited in its application range (in at least one of the four tested systems the system was not suitable, while also the accuracy at which the solute concentration could be determined was much better for the MIR probe). In addition when applied under crystallizing conditions, the NIR signal is affected slightly by the presence of the crystals in the optical path and appeared to be more susceptible to fouling. Also in the determination of the PLS model the MIR has some advantages. The MIR spectrum contains a number of distinct peaks, while the NIR spectrum shows only the broad overtones and combinations of vibration bands. This makes the model development more complicated and chemometric techniques are required. In terms of robustness, however, the MIR was also susceptible to fouling of the diamant probe tip in batch cooling crystallization experiments, and care should be taken to create the proper hydrodynamic conditions to minimize this fouling. In addition the transmission through the fibre optics appeared to be sensitive for stresses and temperatures in the fibre optics. Small changes in the measurement setup or environment can therefore result in a shift in the spectrum.

In a second paper,[340] the application of the MIR probe in an 75 L evaporative crystallizer was studied. A number of problems were identified associated with the use of the PLS model developed at the laboratory scale on a semi-industrial scale setup for the same instrument. The lab scale model leads to a bias in the solution concentrations due to due to the differences in the curvature of fibre optics and the uneven thermal expansion of the probe. To avoid the encountered problems with the application on industrial scale an alternative method for the rapid on-line calibration has been introduced and demonstrated on the semi-industrial scale crystallizer; this allows the derivation of a robust calibration model without consuming significant industrial time. For this calibration an ultrasonic instrument, which can determine the solution density based on the speed of sound measured in a crystal-free medium, was used. It was shown that, although the calibration could only be used under crystal free conditions, very good approximation of the solute concentration could be obtained even in the presence of crystals.

Another relevant development on the application of PAT was reported by Kadam et al.[41] Four different PAT tools were assembled in an external measurement skid equipped with a circulation pump as well which facilitates the generation of an external loop in the analyzed crystallizer. The main advantages of such a configuration are that time and cost-intensive modifications in the crystallizer design can be avoided, rapid characterization of the thermodynamics and kinetics of the crystallization process can be achieved during operation, and rapid opportunities for the optimization and control of the process are created. Finally the combination of the different sensors measuring the same sample allows for the application of sensor fusion, improving the quality and the robustness of the measurement system. The authors also show rapid in situ calibration methods avoiding the above-mentioned problems. The preliminary results, however, show the robustness problems of especially the FTIR probe in an industrial environment.

In a large number of studies, CSD or CLD sensors have been applied to monitor the nucleation.[205,341−343] Although the application of laser diffraction was successfully applied to control the CSD and the growth rate in batch and continuously operated processes, industry has not adapted this approach due to the costs and robustness problems of the on-line dilution system. An alternative sensor, based on attenuation of ultrasound (the OPUS system of Sympatec GmbH) which in principle does not need dilution of the sample, also did not find many industrial applications. One of the drawbacks of the application of these CSD sensors, especially in batch operated processes, is that the sensitivity of these instruments towards changes in the number of crystals in the suspension is rather low. The resulting detection delay of changes in the process conditions poses severe problems for the control of the process.

In this respect a study has been performed[344] in which the growth rate was estimated using various nonlinear observers for output feedback model-based control of industrial batch crystallization processes. In this approach a process model is used to estimate the actual process states on the basis of the CSD measurements. It allows the estimation of the actual growth rate and the supersaturation level but also gives the prediction of the development of these variables in the future. In the paper the shortcomings of a number of observers in coping with the nonlinear dynamics of crystallization systems that are subject to large disturbances have been reviewed. The studied observers are the extended Luenberger technique, the extended Kalman filtering, the unscented Kalman filtering (UKF), and the ensemble Kalman filtering, used to develop nonlinear state observers for a semi-industrial batch crystallizer. In addition to open-loop tests, the nonlinear observers are embedded in an output feedback model-based control framework. This facilitates performance evaluation of the observers in terms of their closed-loop behaviour as well as their ability to cope with model imperfections and process uncertainties commonly encountered in industrial batch crystallizers. The process uncertainties include uncertain initial conditions, unmeasured process disturbances, and measurement errors. It is observed that the extended Luenberger observer cannot adequately suppress stochastic measurement noise, due to its deterministic framework.[340] On the other hand, the stochastic observers, in particular the unscented Kalman filter, provides accurate state estimations that ensure satisfactory closed-loop control performance. The better estimation accuracy of the UKF is due to its derivative-free Bayesian framework that circumvents the need to approximate the nonlinear model. It is tempting to apply this technology also to the in situ measurement techniques such as the FBRM and in situ microscope sensors, in which the interpretation of the sensor data is not so straightforward.

Although a successful application of state observers can improve the monitoring capability in a batch process, it is likely that the presence of sensors for both the solute concentration and the crystal properties give better information. This was suggested in the paper by Kadam et al.,[340] in which it was demonstrated that the solute concentration monitoring at pilot plant with ATR-FTIR in combination with process information from on-line CSD measurement (laser diffraction) can lead to better kinetic parameter estimates and enhanced process understanding.

Emerging fields for the application of PAT sensors are in the context of continuous crystallization monitoring and continuous manufacturing. As of today, FBRM implementations (Simon and Myerson (2011),[122] Ferguson et al. (2012)[345]) and on-line imaging (Borchert and Sundmacher, (2011)[346] have already been reported. Figure 40 shows the chord-length distributions recorded during the antisolvent precipitation of a drug in a plug-flow flow crystallizer.

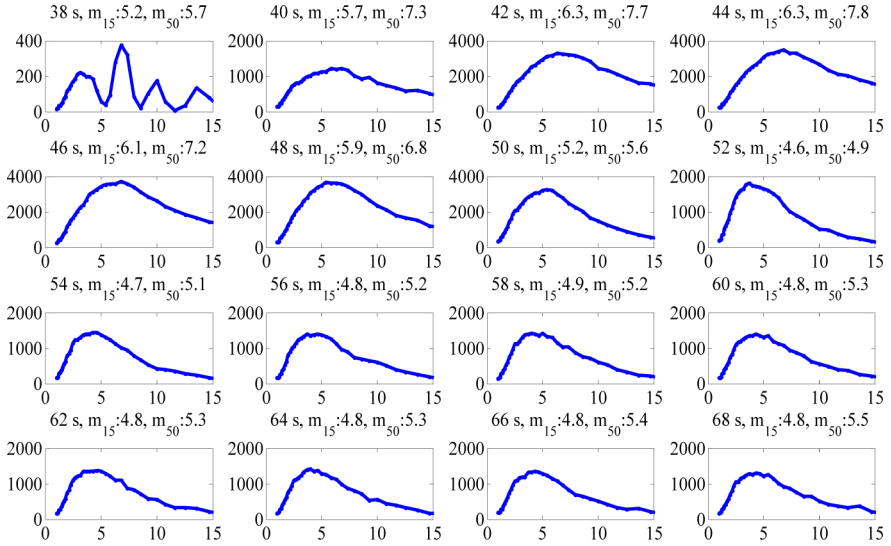

Figure 40. Chord-length distributions before and after nucleation in a continuous plug-flow crystallizer (Simon and Myerson, (2011)[122]); *x*: cld size, *y*: counts/s. Nucleation detected at 40 s. m_{15} is the unweighted mean CLD size on the 1−15 μm interval; m_{50} refers to the unweighted mean on the 1−50 μm range. Reprinted with permission from ref 12. Copyright 2013 Elsevier.

6.1.2. Temperature Cycling and Adaptive Direct Nucleation Control at AstraZeneca. Since the particle properties of active pharmaceutical ingredients can be of paramount importance in the manufacture of formulated medicines, the crystallization and isolation of APIs are arguably the most important steps in their production. However, crystallization is often problematic, since there are many, often competing, issues to be addressed, e.g., purity, yield, size distribution, correct polymorph, and crystal shape. It is well-known that any of these can affect further unit operations, e.g., filtration and drying and secondary processing (milling), and the formulation manufacture and performance of dosage forms.[347]

In order to gain a better understand the crystallization step, scientists and engineers now routinely use PAT for crystallization process understanding monitoring, and control both in the laboratory and in production.[42,348] PAT has provided unique insights into crystallization, particle engineering, and the polymorphism of compounds and enabled the robust production of high-quality API to be realized. Indeed, with the publication of ICH Q11 and the use of quality by design principles now well-embedded (at least in the larger pharmaceutical companies[349]), PAT tools are now considered to be essential for process development and API delivery.[350]

The production of AZD7009, a potential cardiovascular drug, provides a good example of the use of combined PAT techniques for process understanding, particle engineering, and process control. In early campaigns to manufacture this compound, it was observed to oil out from ethanol/water mixtures prior to crystallization. Oiling out of compounds is generally considered undesirable from a process development perspective, and hence the lead chemist screened over 100 solvents (and solvent mixtures) until a solvent system (di-iso-propyl ether/isopropyl alcohol) was found from which the compound could be directly crystallized.

At the time (2004) the literature on the oiling out (or liquid−liquid demixing) of small molecules was relatively scarce;[351] therefore, a retrospective investigation using multiple in-line PAT techniques (FBRM, particle vision and measurement (PVM), and ATR UV−vis) was undertaken to better understand the phenomenon. The data obtained from the PAT probes and the corresponding PVM images are shown in the annotated Figure 41 (AZD7009 is denoted compound A, since it could not at that time be identified for commercial reasons when first published by Deneau and Steele).[352]

The data obtained was clearly complex; however, by using the three PAT techniques in conjunction, it was shown that the time course of the oiling out/crystallization could be followed and additional information about its mechanism could be obtained. Overall the process consisted of oiling out, droplet coalescence, release of AZD7009 from the compound-rich droplets, and finally, crystallization. As with all cooling crystallizations, the determination of the temperature−solubility curve and metastable zone width are considered to be essential measurements, and hence the FBRM was used to measure the clear and cloud (oiling out) points (Figure 42). The measurements were performed in triplicate, since the convergence of the oiling out and solubility curves was, at that time, considered to be unusual. What was clear from these data is that below ∼35 °C there was a metastable zone that could possibly be utilized for seeding. A small experimental design was therefore devised to examine the effect of seed size, load, and (linear) cooling rate. The results showed that, by cooling the solution slowly (0.1 °C/min, linear cool), with a 5% (w/w) seed loading with seed size in the range 20—45 μm, the solution could be crystallized directly and oiling out avoided. These experiments showed that oiling out from a particular solvent system need not be impossible to overcome, and by using the PAT measurements along with crystallization knowledge, a workable system can be developed.

As noted, these oiling out experiments were performed after the project had progressed to a direct crystallization process from a di-iso-propyl ether/isopropyl alcohol mixture (5:1), since this was the only solvent system that was found from which AZD7009 would crystallize. However, as initially developed, this procedure (an unseeded cooling crystallization) brought with it its own problems of agglomeration and a residual solvent smell of di-iso-propyl ether that could not be eliminated even with relatively aggressive drying. Both of these

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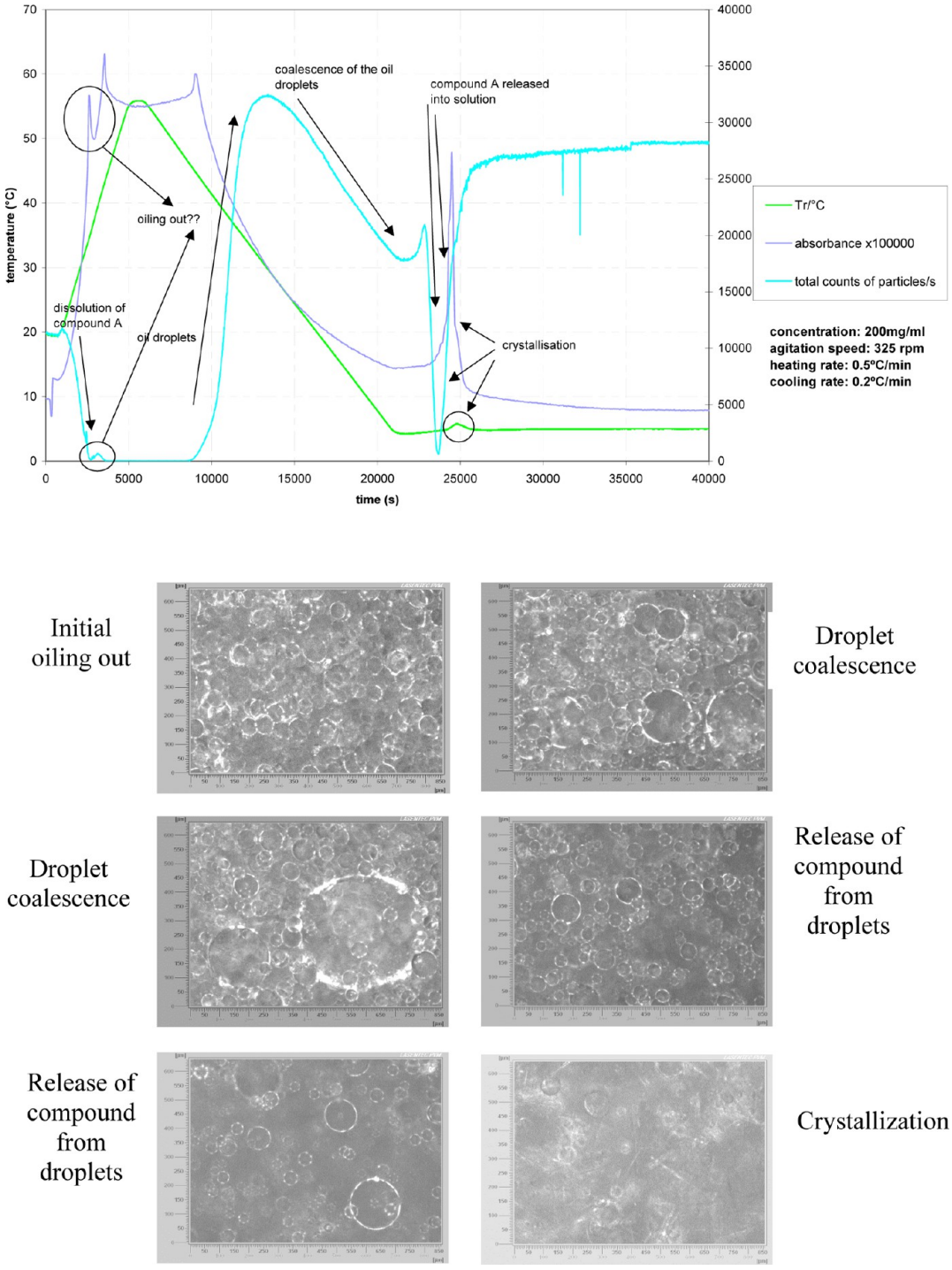

Figure 41. Annotated PAT data for the oiling-out and crystallization of AZD7009.[352]

characteristics were undesirable from a formulation point of view, and hence a program of work was undertaken, using PAT, to improve the crystals.

It was found that temperature cycling after crystallization could be used to both increase the size of the crystals as well as eliminate the agglomeration and residual ether smell.[353] Figure 43 shows the combined FBRM/UV−vis data for the temperature cycling post-crystallization and the corresponding PVM images. The increase and decrease in solution concentration with the temperature fluctuation are evident from the UV−vis data, and with each cycle a decrease in the fine particle count was observed along with a corresponding increase in the mean square weight of the larger particles.

Although the initial process was considered too long (18 h), after a program of experimental design and PAT this was reduced to a more acceptable 9 h. The process was eventually outsourced to a contractor, and eventually 750 kg of the compound was produced to fund the ongoing clinical trials. At the point of project termination, seeding was also being investigated as another method of improving the crystallization behaviour of the compound; however, this avenue was not further explored.

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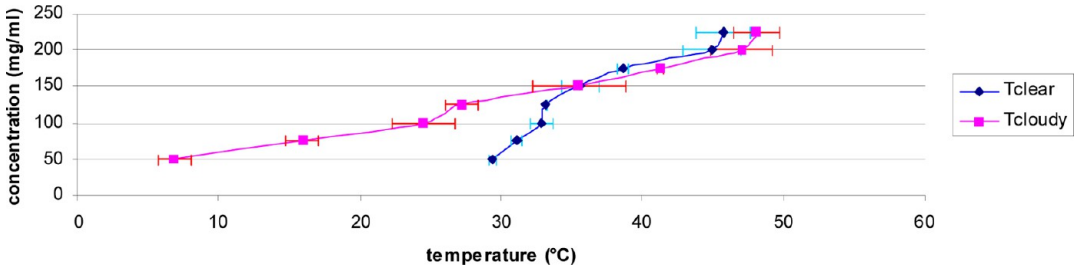

Figure 42. Clear and cloud point curves with respect to temperature for AZD7009 in water−ethanol.

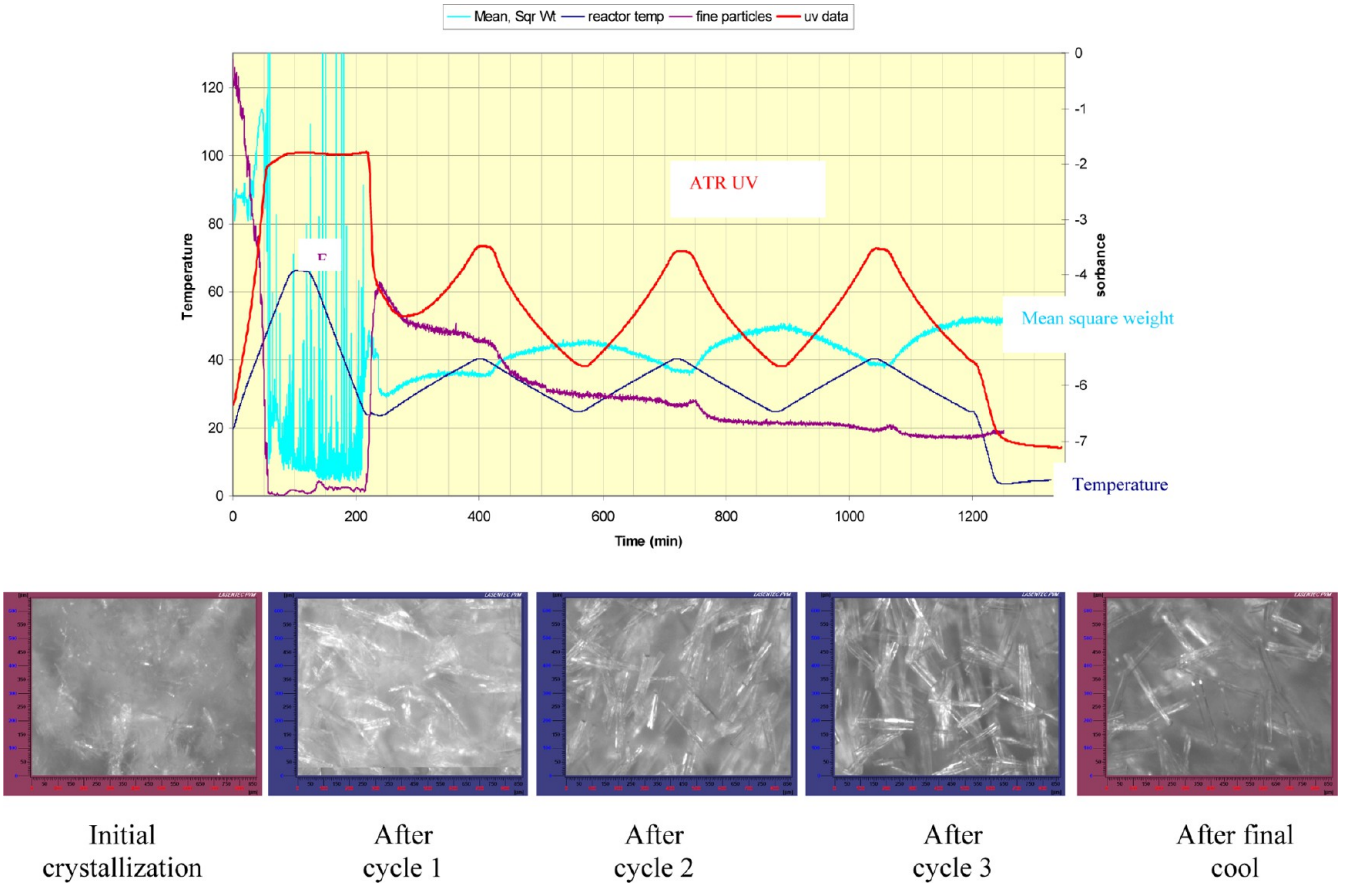

Figure 43. Combined FBRM/UV−vis data and PVM images for AZD7009 temperature cycling experiment.

The use of PAT for process control is now well-established, and the CryPRINS software developed by Prof. Zoltan Nagy (Loughborough and Purdue Universities) has used AZD7009 (in the diiso-propyl ether/isopropyl alcohol solvent) as a test substance in light of the work performed by AstraZeneca described above (Saleemi et al., 2012).[227] Known as adaptive direct nucleation control (ADNC), this technique is a model-free approach in which the number of counts measured by the FBRM is controlled using feedback control. Essentially, if the number of counts/s exceeds the desired set-point value, the excess particles are dissolved by an increase in temperature, which drives the process into the undersaturated zone. Once the set-point has been attained, the process then re-enters the supersaturated region by cooling the solution. During this phase the supersaturation generated by the preferential dissolution of the smaller particles is consumed by the larger crystals present in the slurry resulting in their growth. The ADNC approach has the benefit of automatically driving the crystallization process toward the optimal operating curve by automatically and adaptively by detecting the metastable zone limits (Abu Bakar et al., 2009).[199] Results showed that ADNC had the same net effect as the conventional temperature cycling carried out by AstraZeneca but combines in situ seeding and temperature cycling in real time and hence is a significant improvement on the former process.

6.1.3. Solvent Mediated Phase Transition Monitoring. PAT tools are particularly useful within the context of crystallization processes, specifically those processes for which multiple crystal forms (polymorphs, solvates, hydrates, salts, cocrystals) can appear. During these crystallization processes, phase transitions between metastable and stable phases often occur, characterized by changes in both solution composition as well as solid phase properties (form, particle size, particle shape). Metastable suspensions are responsive to external perturbations, and hence, controlling these processes by sampling and ex situ analysis is not recommended. However,

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as both solution and solid phase characteristics change, a large variety of PAT in situ tools become available (FTIR spectroscopy, video-monitoring, FBRM, Raman spectroscopy, viscosimetry[354]).

According to Ostwald's rule of stages, a metastable form often crystallizes out first, followed by a subsequent transition to the most stable form. To achieve a high quality end product containing a single solid form, it usually suffices to pinpoint the end of the phase transition, by following either solution composition (FTIR,[355] NIR[356]) or nature of the solid form (Raman,[47,242,357,358] FBRM,[359,360] video-monitoring[361]). Multiple examples can be found in the literature where a single PAT probe is used to control solution mediated phase transitions during crystallization processes.[362] Raman spectroscopy has been shown to be a suitable method for real-time monitoring of polymorphs[363] and for monitoring of solute concentrations in highly concentrated mother liquors.[364,365] Raman spectroscopy is also an appropriate tool to monitor the stability of metastable polymorphs or pseudopolymorphs in various solvents.[366−368]

From an academic point of view, one wants to go beyond mere process control, aiming for fundamental process understanding during the phase transition. Such understanding requires studying crystal growth, dissolution, and nucleation kinetics of all solid forms involved in the phase transition. In this case, the use of a single PAT tool is no longer sufficient as no current analytical technique yields both quantitative information on the solution composition, as well as qualitative information on the nature of the solid form. By combining two or more PAT tools, one can gain valuable process insight.[369−373] The monitoring of citric acid anhydrate to monohydrate transformation was investigated by Simon et al.[119] using FBRM, FT-NIR, FT-Raman, turbidity, and endoscopy.

Within the context of solution mediated polymorphic transitions, two different process scenarios can occur depending on nucleation, crystal growth, and dissolution kinetics of both polymorphs.[362,374] In all cases, the transformation of a metastable towards a stable polymorph is driven by the supersaturation of the latter. When the growth and/or nucleation of the stable phase occurs more rapidly than dissolution of the metastable phase (scenario a), one deals with a "dissolution controlled polymorphic transformation". Typically, the solution concentration drops to the solubility of the stable polymorph, as soon as this latter is present in solution. In a second scenario, the dissolution rate of the metastable form is more important than the combined crystal growth/nucleation kinetics of the stable phase, with the solubility concentration remaining at the solubility limit of the metastable state during the transformation process. Such a transformation is coined "growth controlled polymorphic transformation". Depending on the time required for the stable phase to nucleate, some subscenarios can exist.[375]

In 2006, Schöll et al.[376] investigated the solvent-mediated polymorphic transformation of L-glutamic acid in water, combining four PAT tools (PVM, FBRM, ATR-FTIR, and Raman). Whereas the FBRM probe gives information on the evolution of CLD and hence number and size of crystals, the Raman probe yields valuable insight into the nature of the solid form present. In parallel, the solution concentration is followed using the FTIR technology after appropriate calibration. The α and β polymorphs of the L-glutamic amino acid were shown to be monotropically related with the β form being the most stable at all temperatures. According to Ostwald's rule, the α form appears first and then subsequently undergoes a growth controlled polymorphic transformation, characterized by a rapid dissolution of the metastable α form and slow nucleation/crystal growth of the β form. For this process a combined PAT tool approach was shown viable at a pilot-scale level.[377] In a similar setup, Herman et al. investigated the polymorphic transformation of etiracetam in methanol.[378] Etiracetam is a racemic drug intermediate for which two enantiotropically related polymorphs have been characterized.[379] On the basis of the scrupulous analysis of the data from three probes, the full process was completely characterized. During cooling, form II spontaneously nucleates. As this form nucleates above the transition temperature[380] of 30.5 °C, this nucleation process is opposite to Ostwald's rule of thumb. Further cooling is characterized by secondary nucleation and crystal growth of this form. During the final isothermal hold, the transformation of Form II (which became metastable below 30.5 °C) to form I occurs. Although the polymorphic transition occurs spontaneously typical induction times of around 10 h are observed. The polymorphic transformation involves three phases: In a first phase, FTIR data show a constant etiracetam concentration in solution equal to the form II solubility (0.24 g/g_{sol} at 10 °C) and in supersaturation with respect to form I. The Raman probe does not detect any form I crystals. This first phase ends when form I nuclei appear in suspension. The Raman probe detects form I and form II crystals and will continue doing so for the entire duration of the second phase (φ 2). FTIR analysis shows the solution concentration to drop only slightly and to remain constant just below form II solubility, indicating the global dissolution of form II crystals to occur more rapidly compared to the overall mass increase of form I crystals. Such a behaviour is characteristic for a "growth controlled" transformation process. During this phase, nucleation and crystal growth of form I crystals are driven by the form I supersaturation and form II dissolution by the slightly undersaturated solution with respect to this form. A third phase starts when the Raman probe no longer detects any form II crystals in suspension. As form II dissolution no longer delivers compound to the solution, form I crystal growth consumes the remaining supersaturation with respect to this form as illustrated by the decrease of etiracetam solution concentration. FBRM chord length analysis shows the consumption of the supersaturation to be mainly due to crystal growth. As illustrated by these two examples, to fully understand solution mediated polymorphic transformations from a fundamental point of view, a combined use of in situ Raman, FBRM, and ATR-FTIR PAT tools is required.

From an academic point of view, combining different PAT tools can thus be very useful, especially within the context of fundamental process understanding, and in particular for those compounds which suffer from phase transitions.

6.1.4. Co-crystallization Process Development. Co-crystals have become increasingly important over the past decade as alternative solid forms, especially for those active pharmaceutical ingredients that do not or not easily form salts.[381,382] This new class of compounds offers opportunities from a pharmacological point of view, as they can not only prolong patents but also lead to improved biophysical properties of the final drug. Co-crystals are frequently identified via solid-state grinding of both components, with, so far, very little efforts placed in trying to develop solution crystallization processes. The fairly complicated thermodynamic characteristics of these systems (cocrystal components often show strong solubility differences with respect to the same solvent, leading to incongruent solution behavior[383]) likely explain the limited number of

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crystallization studies. Besides incongruent behavior, cocrystal systems can furthermore be subject to polymorphism[384] and stoichiometrical diversity.[362] Gagnière et al. were the first to study cocrystallization kinetics of the carbamazepine−nicotinamide (CBZ/NCT) system.[385] Within this context they emphasized the complementary use of sensing PAT technologies for process understanding, combining data from video-monitoring, FBRM, and FTIR. Although the FBRM data brings additional insight, the sole use of such a probe would not have been straightforward, as needle-shaped crystals are involved.[386] Mainly based on in situ FTIR data, they were able to split the typical cocrystal phase diagram into six thermodynamic and 11 kinetic domains[385] as shown in Figure 44.

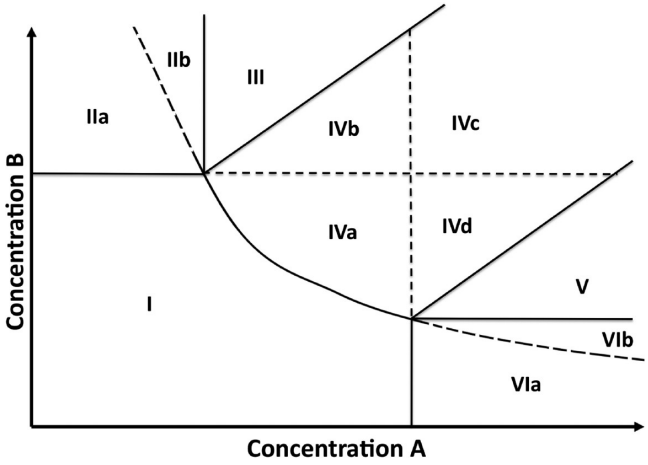

Figure 44. Co-crystal phase diagram.

In domain II, carbamazepine is the thermodynamically stable phase. However, the CBZ-NCT cocrystal is kinetically accessible in the IIb subdomain. As both components have different IR spectra, cocrystal formation is easily identified by stoichiometric solution consumption of both components. Their in situ data furthermore illustrate how starting in zone III a CBZ-NCT cocrystal phase is formed, and cocrystallization continues until the metastable solubility of the cocrystal is reached inside zone IIb. At this stage, a solution-mediated transition occurs by simultaneous dissolution of the CBZ-NCT cocrystal and crystallization of the pure CBZ compound. As for the polymorphic transitions discussed above, this process is limited by the growth of the novel crystal form. Bringing their work to the next level, they showed how on-line PAT analyzers can be used to control the phase transitions occurring during a cocrystallization process, leading to a robust final process yielding a single cocrystal solid phase.[387]

6.1.4.1. Construction and Interpretation of the Phase Diagram. Eutectic points in the phase diagram of a solution cocrystallization system represent a boundary within which pure cocrystal only, instead of a mixture of cocrystal and single component crystal, can crystallize out. It is necessary to locate these points to construct a complete phase diagram for process development. Childs et al.[388] and Good and Rodriguez-Hornedo[389] located eutectic points by analyzing solid samples from a slurry experiment using off-line Raman spectroscopy and X-ray powder diffraction techniques, respectively. In a more efficient manner, Yu et al.[390] exploited the phenomenon of solution-mediated phase transformation to drive solution composition towards eutectic points. During the process, ATR-FTIR was employed to monitor and record equilibrium concentrations of constituent components at various points in a phase diagram including eutectic points. There was no need to analyze solid samples. The phase diagram of caffeine−glutaric acid cocrystals in acetonitrile is presented in Figure 45.[390]

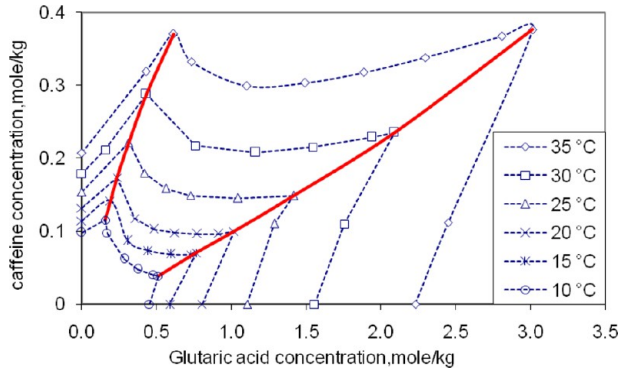

Figure 45. Phase diagram of caffeine−glutaric acid cocrystal in acetonitrile. Note that different scales are adopted by *x*-axis and *y*-axis, Yu et al.[390]

The *X*-axis and *Y*-axis represent the molality of glutaric acid and caffeine, respectively. Equilibrium concentration curves of glutaric acid and caffeine at different temperatures are marked by different legends. Taking the equilibrium concentration curve at 35 °C as an example, the solubility of caffeine is around 0.2 mol/kg in pure acetonitrile. Its solubility increases when an increasing amount of glutaric acid is added to the solution until a eutectic point is reached. At this eutectic point, cocrystals appear and coexist with caffeine crystals in suspension (three-phase equilibrium). After this eutectic point, the concentration of caffeine goes through a minima with increasing concentration of glutaric acid until a glutaric acid/cocrystals eutectic point is reached. Between these two eutectic points, the liquid phase is in equilibrium with cocrystals (two-phase equilibrium). Eutectic points for caffeine/cocrystals and for glutaric acid/cocrystals at various temperatures are connected by two bold red lines in Figure 45. The region sandwiched by these two boundaries is where pure cocrystal can be produced. Its implication for process development of cocrystallization is that the composition of starting solution and final temperature must be chosen in such a way that the cocrystallization path should not cross the boundaries. Otherwise, cocrystal product may be contaminated by crystals of single components. Zhang and Rasmuson[391] demonstrated that polymorphism in constituent components will change the position of corresponding eutectic points and thus the operating region of cocrystallization.

6.1.4.2. Feedback Control of Supersaturation. Rodríguez-Hornedo et al.[392] defined the supersaturation of a 1:1 cocrystal as a ratio, eq 5:

$$\sigma = \left(\frac{C_1 C_2}{K_{SP}}\right)^{1/2} \tag{5}$$

where K_{SP} is the solubility product and C_1 and C_2 are the concentrations of components 1 and 2, respectively. This definition works well for ideal solutions wherein K_{SP} is a constant at fixed temperatures. In real solutions K_{SP} also changes with solute concentrations, which causes difficulty in supersaturation calculation. Yu et al.[393] adopted a new definition of supersaturation that is suitable for PAT monitoring and control of

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real systems. In this new definition, a cocrystal is imagined to be a single chemical entity with a molecular weight equal to the sum of respective molecular weights of its components. It dissolves or crystallizes just like a single component. Its solubility, C_{co}*, can be calculated from its phase diagram. Supersaturation, S, in cocrystallization is then calculated as a concentration difference between actual concentration of cocrystal, C_{co}, and solubility, eq 6:

$$S = C_{co} - C_{co}^{*} \tag{6}$$

This new definition was used successfully in feedback control of supersaturation to produce the stable form of caffeine–glutaric acid cocrystal from acetonitrile by cooling. The metastable form will crystallize out when supersaturation is relatively high. Therefore, seeding with the stable form and supersaturation control are keys to producing the stable form consistently. ATR-FTIR was used as a sensor to construct the feedback loop. The trajectories of supersaturation and temperature are shown in Figure 46.[393] The starting and final

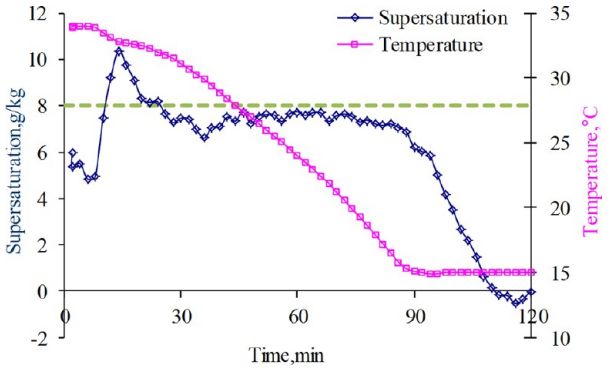

Figure 46. Supersaturation and temperature trajectories in feedback control of caffeine–glutaric acid cocrystallization. The bold dashed line is the set point for supersaturation. Seeds were introduced at the beginning as indicated by the arrow—Yu et al.[393]

temperatures were 35 and 10 °C, respectively. The set point of supersaturation was 8 g/kg, which was found sufficiently low to suppress the appearance of the metastable form. Seeds of the stable form were applied when the solution became slightly supersaturated at the beginning and the feedback control loop was immediately activated. Supersaturation rose to around 10 g/kg in a short time and then decreased to its set point due to cocrystal growth. Supersaturation stayed there for most of the batch time. After the final temperature was reached, supersaturation could not remain at its set point anymore and eventually dropped to zero. PVM images showed that metastable form did not appear throughout the batch.

6.1.5. Filter Cake Washing Monitoring. Crystallization influences the downstream operations such as filtration of crystals from mother liquor. The topic was studied by Häkkinen et al.,[394,395] who investigated the filterability of crystallized sulfathiazole products with a pressure filter. The results showed that, by using appropriate crystallization conditions, the filtration can be influenced significantly. The filter cake washing with the aid of in-line Raman spectroscopy has been studied by Louhi-Kultanen et al.[396] Raman spectroscopy can be used to obtain washing curves, leading to optimized filter cake washing (to minimize wash liquor volumes, to increase washing capacity, etc.).

6.2. Melt Extrusion and Electrostatic Spinning Monitoring Using Raman Spectroscopy. Many of the recently developed drugs have poor water solubility that makes it difficult to create an effective dosage form. Some formulation techniques (e.g., spray drying, melt extrusion) can be used to increase drug dissolution. Further development lead to the adaptation of an innovative continuous process, electrostatic spinning, to the pharmaceutical area.[397−402]

Real-time Raman spectroscopy could be successfully used to investigate drug morphology during pharmaceutical extrusion[403,404] and other drug formulation processes;[405] however, electrostatic spinning proved to be a more challenging technology in this respect as it produces superfine polymer/drug fibers of 50−1000 nm diameter. The solution or melt of the polymer, drug, and solvent connecting with an electrode is charged into high voltage (∼10−35 kV), while the counter electrode is usually grounded as a collector. Fibers are formed by electrostatic forces between the two electrodes, and the solvent evaporates, resulting in solid nanofibers. In a former study, Stephens et al.[406] performed in-line noninvasive Raman monitoring to analyze the solvent−polymer ratio and polymer orientation during electrostatic spinning of polystyrene. Use of real-time Raman spectroscopy for identifying the morphology of a drug in drug−polymer fibers has been reported recently.[407] The detection was performed during the continuous formation of the nanofibrous web structure. The drug morphology was identified as a function of the thickness of nanofibrous web. The real-time Raman monitoring technique was transferred to larger scale experiments as well. Figure 47 shows the in-line Raman spectra of the nanofibrous web in the case of 165(±10) μm thickness of web together with the reference spectrum of polymer (polyvinylpyrrolidone) matrix, reference spectrum of drug (carvedilol), and that of the polypropylene used as carrier textile. The drug was preserved in amorphous form as is emphasized with red rectangles in the Raman spectra. The calibration of Raman intensity values as a function of nanofibrous web structure's thickness provides another possibility for process classification.

These recent results highlighted the advantages of the use of Raman spectroscopy as a method to predict morphological changes during drug crystallization or other continuous processes (melt extrusion, electrostatic spinning). Thus, real-time Raman analysis can be considered as a suitable PAT tool not only for monitoring but also for controlling the product quality extending the capabilities of other in-line analytical techniques (e.g., ATR-FTIR, ATR-UV/vis, FBRM). Real-time application of chemometric evaluation of spectra offers even more accurate Raman-based process control than the univariate approach.

6.3. Bioreactor Monitoring. Small-molecule (MW < 1000) drug substances (APIs, NCEs) have traditionally been produced via organic synthesis. Antibiotics, which can be small molecules as well, form an exception and have for many decades been produced by fermentation. Penicillin, the first antibiotic that was discovered, is a well-known example. Following its discovery, production was developed and introduced in industry during the 1940s. In the decades that followed, the penicillin production has been optimized, and today penicillin is produced at industrial scale by fed-batch fermentation of *P. chysogenum*.[408] However, large-molecular (MW > 1000) drug substances—also known as biopharmaceuticals—have become increasingly important in recent years. Examples are monoclonal antibodies and therapeutic proteins.

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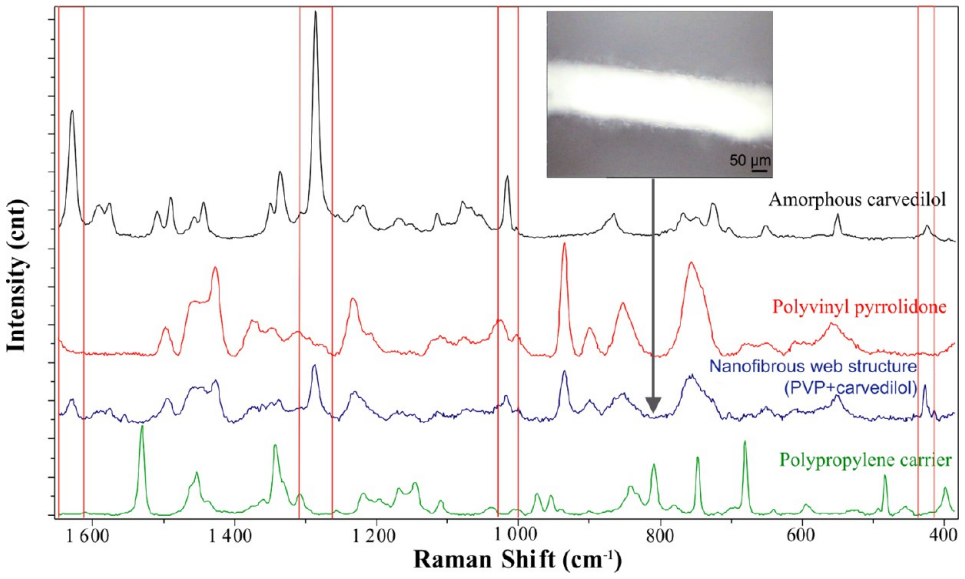

Figure 47. Raman spectrum of nanofibrous web structure with other reference spectra.

The former are mainly produced using mammalian cells, and details about cell line development and production process development were reviewed by Li et al.[409] The latter can be produced by fermentation using production hosts such as *Escherichia coli*, *Saccharomyces cerevisiae* (baker's yeast), and filamentous fungi, or by cultivation of mammalian cells, plant cells, or insect cells.[410]

Aerobic fermentations with mammalian cells or insect cells are usually operated with moderate aeration and agitation.[411] However, the focus of this contribution is on fermentation processes and more specifically on some of the tools that are available for the monitoring of such fermentation processes. Monitoring fermentation processes can be extremely challenging, all depending on which type of fermentation is to be monitored. Fermentation processes are traditionally performed in stirred bioreactors and can be classified into two different categories:[411] (1) anaerobic fermentations where the gas phase cannot disturb measurements; (2) aerobic processes with vigorous aeration and agitation. The former category usually yields the easiest processes from a process monitoring point of view, whereas the latter category—most often used in practice—poses a clear monitoring challenge. The host organism itself can cause additional monitoring challenges: filamentous fungi are especially known to be rather problematic due to their hyphal growth, where cells start growing from a germination point and branch into different macroscopic structures that can be observed under a microscope as stringy filaments, interwoven clumps, or pellets.[412]

The size of the bioreactor poses a clear monitoring challenge: the larger the scale of a bioreactor, the more challenging it will be to maintain the content of the bioreactor homogeneous. For industrial fermentation processes, the scale of operation can vary from a few hundreds of liters to several hundred m^3, depending on the product. The larger the fermenter, the more difficult it will be to rely on a single measurement as being representative for the processes taking place in the fermenter, especially in case of a filamentous fermentation broth. Typical substrate gradients in a large fermenter (22 m^3) were documented by Larsson et al.[413] The spatial heterogeneity in large-scale fermentation processes is indeed important, and gradients in the reactor will result in variation of the physiological state of the organisms throughout the reactor.[414] The impact of spatial heterogeneity on the microorganisms as well as how to quantify heterogeneity in a population of microorganisms has been reviewed recently.[415] Important for fermentation process monitoring, most traditional sensors will measure one "average" value and will not take any population heterogeneity into account.

6.3.1. A Basic Fermentation Process Monitoring Setup. Considering a modern aerobic fermentation process at industrial scale, the standard instrumentation will usually include equipment for monitoring the tank weight, the air flow rate, the agitator speed, the power consumption of the motor driving the agitator, the temperature, the pH, the dissolved oxygen concentration, and the off gas composition (CO_2 and oxygen). Some of these measurements generate data that serve as an input for basic single loop feedback controllers for pH control, temperature control, etc. Since many fermentation processes are operated in fed-batch mode, a suitable controller regulating the feeding rate is usually also present.[416]

6.3.2. Advanced Measurements—Biomass. Interestingly, an important variable such as the biomass concentration in the bioreactor is usually measured off-line as cell dry weight.[417] In this respect, Olsson and Nielsen[417] wrote "Despite the availability of a large number of experimental techniques for measuring biomass, there is, however, no method that is generally applicable for on-line monitoring of the biomass concentration in a process environment". Several reviews have been published on the topic of on-line biomass measurement in fermentation[417−419] describing methods such as optical density measurements, multiwavelength fluorescence, capacitance measurements, and soft sensors.

One could, of course, wonder why development of improved methods and tools for in situ biomass concentration monitoring is still an important research topic.[419,420] A plausible explanation is the fact that the appearance of the fermentation broth can be very different, depending on the host organism,[412] and therefore the development of a universal in situ method for biomass concentration determination is extremely difficult.

Research into methods that also allow the characterization of the heterogeneity in a population of microorganisms in situ is a significant recent trend in the field of on-line biomass characterization. Characterization of particle properties has

been in focus for quite a while now and became possible by development of in situ microscopy,[421] which can be coupled to image analysis for processing of the acquired data. Methods such as FBRM have been evaluated for fermentation monitoring as well. Pearson et al.[422] published a study on characterization of filamentous fermentation broth using FBRM. Nowadays, on-line characterization of the heterogeneity of populations of microorganisms using automated flow cytometry is an important research topic in the area of biomass monitoring.[423] However, instruments for particle/biomass characterization are typically found in a research lab or pilot plant lab, not in full-scale production.

6.3.3. Advanced Measurements—Spectroscopy. Spectroscopic methods have been tested extensively on fermentation processes. Multiwavelength fluorescence (MWF) has been evaluated on various production hosts, mostly in lab-scale[424,425] for the determination of variables such as the biomass concentration, the protein (product) concentration and the substrate concentration.[424] Despite the obvious potential, MWF is only rarely used in industry for the monitoring of fermentation processes in stirred aerated bioreactors. Techniques such as mid-infrared spectroscopy and Raman spectroscopy have been applied sporadically, typically in lab-scale fermentations, either in an at-line configuration[426] or in situ.[427]

Near-infrared (NIR) spectroscopy has been researched intensively for the monitoring of substrates, the biomass concentration, and intermediate metabolites. The main challenge with NIR spectroscopy is the large water interference and the limited sensitivity. Both Scarff et al.[411] and Cervera et al.[428] have published detailed reviews on the topic. Specifically on NIR spectroscopy, Cervera et al.[428] concluded that "many of the publications which are available in the literature are related to at-line NIR measurements or on-line measurements using relatively simple fermentation matrices. For NIR spectroscopy to be accepted as a standard monitoring tool by the pharmaceutical and biotechnological industry, more on-line studies using highly challenging fermentation conditions are required demonstrating reliability and simplicity".

In conclusion, specifically for industrial scale bioreactors, spectroscopic measurements cannot yet be considered as standard measurement equipment, especially not for in situ measurements, i.e., in most work that is published the probe has been inserted in the fermentation broth at-line or has been inserted in a pretreated—typically filtered—particle free sample. It seems more likely that NIR spectroscopy and related methods can be successful when applied in a particle-free sample matrix (see below), or when used in the downstream processing part of the production process.

6.3.4. Future Trends. The harsh process conditions—sensor equipment has to be able to withstand sterilization/autoclaving in addition to presence of gas bubbles and particles—form a major explanation for the limited success of in situ spectroscopy in industrial fermentation.[411,428]

An important future trend could be introduction of more advanced sensors measuring on a particle-free sample that is taken out automatically from the bioreactor under sterile conditions. Research efforts on automated sampling of fermentation processes have started several decades ago.[429] Automatic operation of at-line flow injection analysis (FIA) and high-pressure liquid chromatography (HPLC) on a sample taken from a lab-scale high density fermentation bioreactor has been demonstrated in 15 L scale fermentation.[430] However, such systems are definitely not part of the standard equipment used at industrial scale. Nowadays, robust automated sterile sample ports are becoming available[431] and can for example be combined with on-line HPLC analysis of substrate and metabolites, or on-line near-infrared spectroscopy of the filtered fermentation broth. When performed in a particle-free sample, the use of spectroscopic methods will suddenly become a lot easier at the industrial scale. Another method of performing advanced particle-free on-line measurements is by performing mass spectrometry on the offgas, thus extending the range of measured components far beyond traditional O_2 and CO_2 off-gas measurements.[432] Online MS is increasingly applied on the off-gas in fermentation laboratories and will probably also become more popular in industry in the forthcoming years.

Another important future trend within bioreactor monitoring could be the increased use of soft sensors. A soft sensor or a software sensor is a virtual sensor consisting of an algorithm implemented in a computer program that will process several measurements in order to predict other variables of interest which are for example difficult to measure otherwise. The prediction of biomass concentration using software sensors is a relevant example.[419] A recent expert report by Luttmann et al.[433] concluded that the fermentation industry has in general not been too keen on using soft sensors, despite their obvious potential and frequent use in other industries, because there are doubts about the amount of work involved, their reliability, and the need for maintenance of the soft sensor algorithms. Luttmann et al.[433] therefore suggested that "a number of case studies based on industrial data should be carried out and documented with the purpose of benchmarking soft sensors", such that the benefits and the pitfalls could be clearly documented in order to promote future use of soft sensors in industry.

6.4. Continuous Distillation Control Using Near-Infrared Spectroscopy. PAT has successfully been developed and implemented at GSK laboratories and plant scale to control a continuous distillation operation performed at atmospheric pressure. The input solution from the previous continuous unit operation (continuous extraction) is of variable quality (solvent composition and API concentration). The output from the distillation needs to be controlled within tight ranges for these parameters, as they can affect resulting API particle size and form. A quantitative in-line NIR method was developed using a transmission probe that could measure both the API concentration and solvent composition in real-time. The predictions from the PLS model were fed back into the distillation control system to automatically adjust the distillation temperature and reflux ratio of the column every 30 s, ensuring that the output was well-controlled. This approach was compared to a traditional approach where the distillation temperature was used to control the process. The NIR control was far superior as it provided tighter control and was not impacted by external atmospheric conditions. The application has been demonstrated to be robust and has run for extended periods of time on several products. Figure 48 shows the comparison of temperature control with NIR process control, clearly demonstrating the improved control using NIR.

6.5. Oil/Water Emulsion Monitoring in the Petrochemical Industry Using FBRM. The PAT framework offers pharmaceutical companies the opportunity to implement innovative development, manufacturing, and quality assurance protocols within a prescribed regulatory environment. However, in many industries, less stringent regulatory conditions mean that innovation in these areas has been ongoing for many

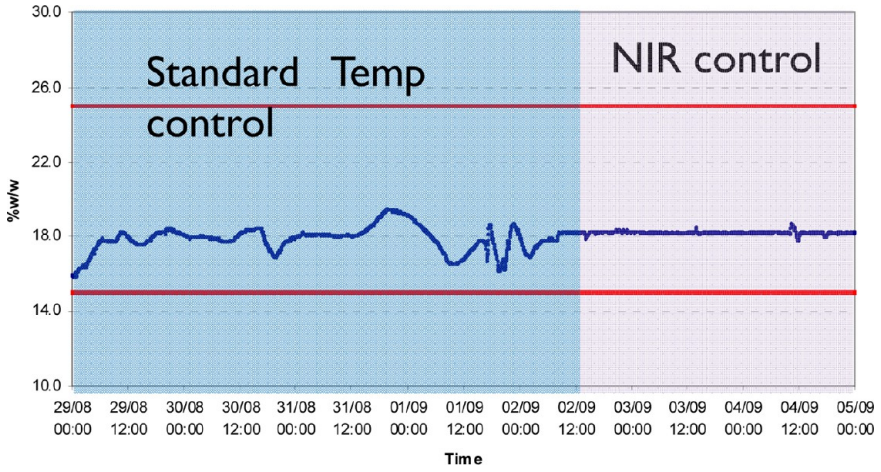

Figure 48. Comparison of temperature control to NIR control for continuous distillation. The red lines indicate the control limits for the process.

years. In the petrochemical industry the use of inline tools to monitor process streams is common due to the often hazardous nature of the material under investigation as well as the difficulty associated with sampling multiphase and viscous streams at elevated temperatures and pressures.[434,435] Since the production of petrochemicals is largely driven by the supply and demand of key commodities, the ability to ensure consistent product quality while targeting the desired throughput is critical. Timely measurements of in process materials and processes are necessary to achieve this goal. This contribution will provide recent examples of how in process particle characterization tools, regularly applied in the pharmaceutical industry as part of a PAT program, are implemented for similar purposes in a separate field, namely, upstream and downstream petrochemical development and production.

6.5.1. Separating Oil/Water Emulsions. The methods used to extract and recover oil change over the lifespan of an oil well.[436] Primary recovery methods rely on inherent underground pressure to drive oil to the surface. As the reservoir becomes depleted and internal pressure drops, secondary recovery methods are employed that typically rely on injecting water or gas into the well to drive production.[437] Tertiary methods are used to increase the mobility of the oil reducing its viscosity either through steam injection or sometimes the addition of surfactants. Methods of recovery also vary depending on the location and quality of the reservoir with primary recovery methods becoming less feasible as less productive oil fields are exploited.[438] These various recovery methods often mean that oil is rarely extracted in a pure form and is more often extracted as a multiphase flow composed of oil, water, sand, and insoluble inorganic particles. It is therefore necessary to introduce a separation step downstream from the well whereby pure oil can be recovered for refining. The separation of oil/water emulsions is particularly important and the control of droplet size is critical to ensure efficient separation.

Much research has been conducted into increasing droplet size to improve separation efficiency, and one area of interest is in the use of an inline electrostatic coalescer (IEC). An IEC causes frequent collisions between water droplets and an electrical field, which destabilizes the film between droplets which have collided, thereby increasing the probability for coalescence.

In this study, an oil/water emulsion (oil characteristics given in Table 1) was fed through a pipeline containing the IEC (FBM Technologies) with a ParticleTrack instrument (Mettler Toledo) just downstream. The real time droplet chord length distribution, measured using ParticleTrack, was used to study how changing electrical field strength influenced droplet size and count. Incoming water cut, flow rate, and pressure drop were adjusted to simulate varying production conditions. The electrical field strength that produced the largest droplets (and most efficient separation) was identified for each condition.

Table 1. Oil properties

crude oil density	825 kg/m^3
crude oil viscosity	5.1 cP
crude oil density	825 kg/m^3
crude oil viscosity	5.1 cP

Figure 49 shows how the application of an electrical field across the pipeline using the IEC increases median droplet

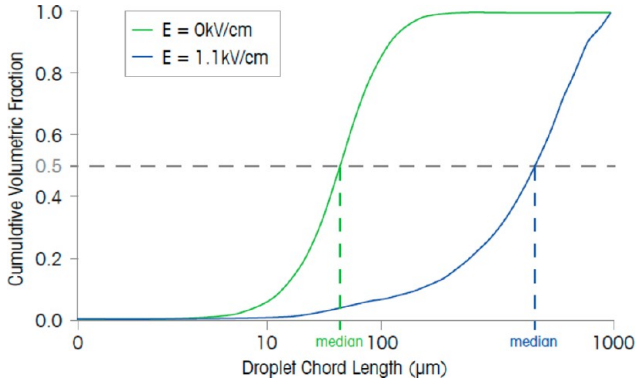

Figure 49. Droplet chord length distributions with the IEC switched on and off. Flow rate = 20 m^3/h; pressure drop = 0.2 bar; water cut = 20%.

chord length by an order of magnitude for a set of standard conditions. With initial feasibility demonstrated, it was possible to study a set of operating conditions. The influence of electrical field strength on droplet chord length for varying water cuts is shown in Figure 50. As expected, with increasing water cut droplet chord length increases, due to the increased contact probability between droplets and subsequent coalescence. In Figure 51, the influence of varying electrical field strength for two different water cuts is shown. A strong relationship between electrical field strength and droplet chord

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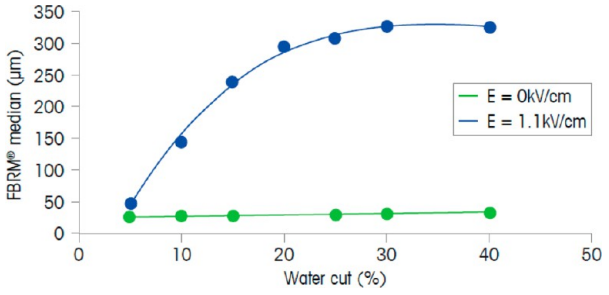

Figure 50. Water cut (w/w%) vs droplet chord length (μm) with and without electric field applied.

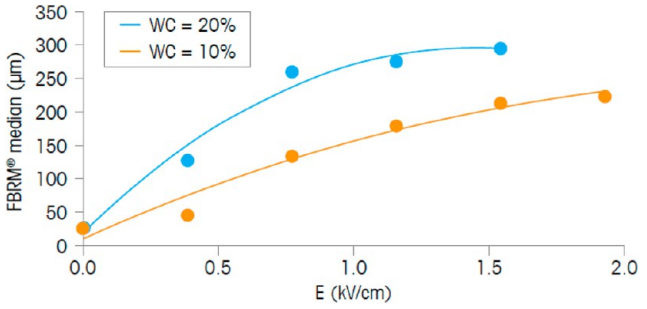

Figure 51. Electric field strength vs droplet chord length (μm) at two water cuts (10% and 20%).

length is shown; however, at higher electric field strengths, droplet chord length does not increase as dramatically. The influence of flow rate was also studied. As flow rate increases, the residence time in the electrical field decreases so droplet chord length should be expected to decrease, and this is shown in Figure 52. Finally the effect of shear rate on the droplet

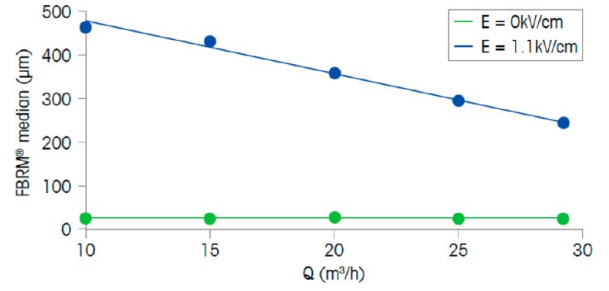

Figure 52. Flow rate vs droplet chord length with and without electric field applied.

chord length was studied by adjusting pressure drop across the pipeline. As the pressure drop increases, the droplet chord length decreases due to the increased shear and degree of droplet breakage (Figure 53).

It has been shown that the application of in-process particle and droplet characterization tools has broad applicability in the petrochemical industry to deliver products of the desired quality efficiently. In many cases applying in-process measurement is necessary to acquire the information needed to optimize and monitor petrochemical processes specifically in cases where sampling is unsafe or impossible. Information gathered using these techniques allows for innovative methods for development, manufacture, and quality assurance to be developed and applied.

6.6. Studying the Effect of Inhibitors on Gas Hydrate Formation Using FBRM. Hydrocarbon streams are subject to

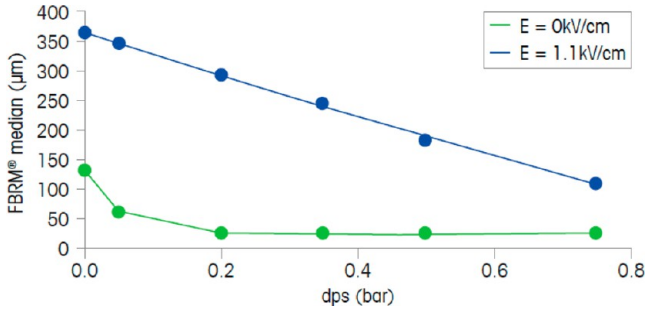

Figure 53. Pressure drop vs droplet chord length with and without electric field applied.

a wide variety of temperature and pressure conditions as they are transported from deep sea reservoirs to the refinery. The complex interaction between oil, gas, and water under high pressure and low temperature can result in the formation of solid hydrates.[439] These hydrates can inhibit flow rates or even plug pipelines resulting in safety issues or refinery shutdowns. The study of hydrate formation and how it may be inhibited is critical to ensure good pipeline flow. Thermodynamic inhibitors are industry standards for hydrate prevention despite high cost, environmental concerns, and high operating costs. Low dose hydrate inhibitors (LDHI) are a new class of chemicals being developed as an alternative to expensive thermodynamic inhibitors.

In this study ParticleTrack and PVM probes were inserted into a 3″ pipeline flow loop. The flow loop was charged with kerosene, 30% brine, and natural gas. After charging, the loop was cooled from 21 to 5 °C, and the loop pressure was maintained at an average of 103 bar. Hydrate formation was studied with no inhibitors present and with LDHI.

In Figure 54, real time ParticleTrack data illustrate the stages at which hydrate formation occurs and when a steady-state is

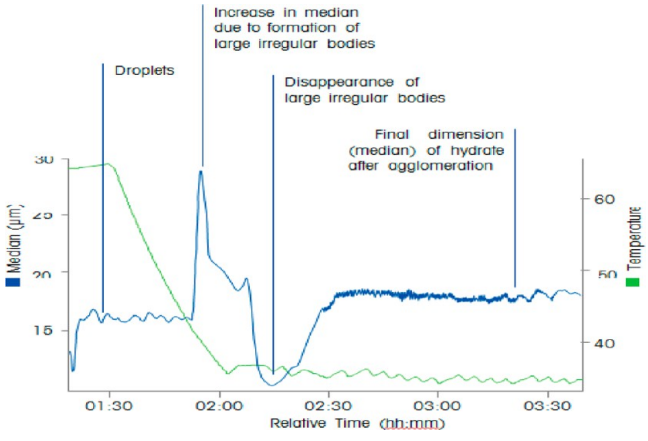

Figure 54. Median chord length vs time is used to identify the various stages of hydrate formation in the absence of LDHI.

achieved. In Figure 55, PVM images visualize hydrate formation and shows that, while LDHI does not inhibit hydrate formation completely, it ensures that a flowable hydrate suspension occurs rather than a large agglomerated mass that will be more likely to cause pipeline blockage.

6.7. Polymer Particle Size Distribution Monitoring Using FBRM and PVM. In polymerization reactions, the final polymer particle size distribution and the changes in the particle and droplet size distribution over time are important

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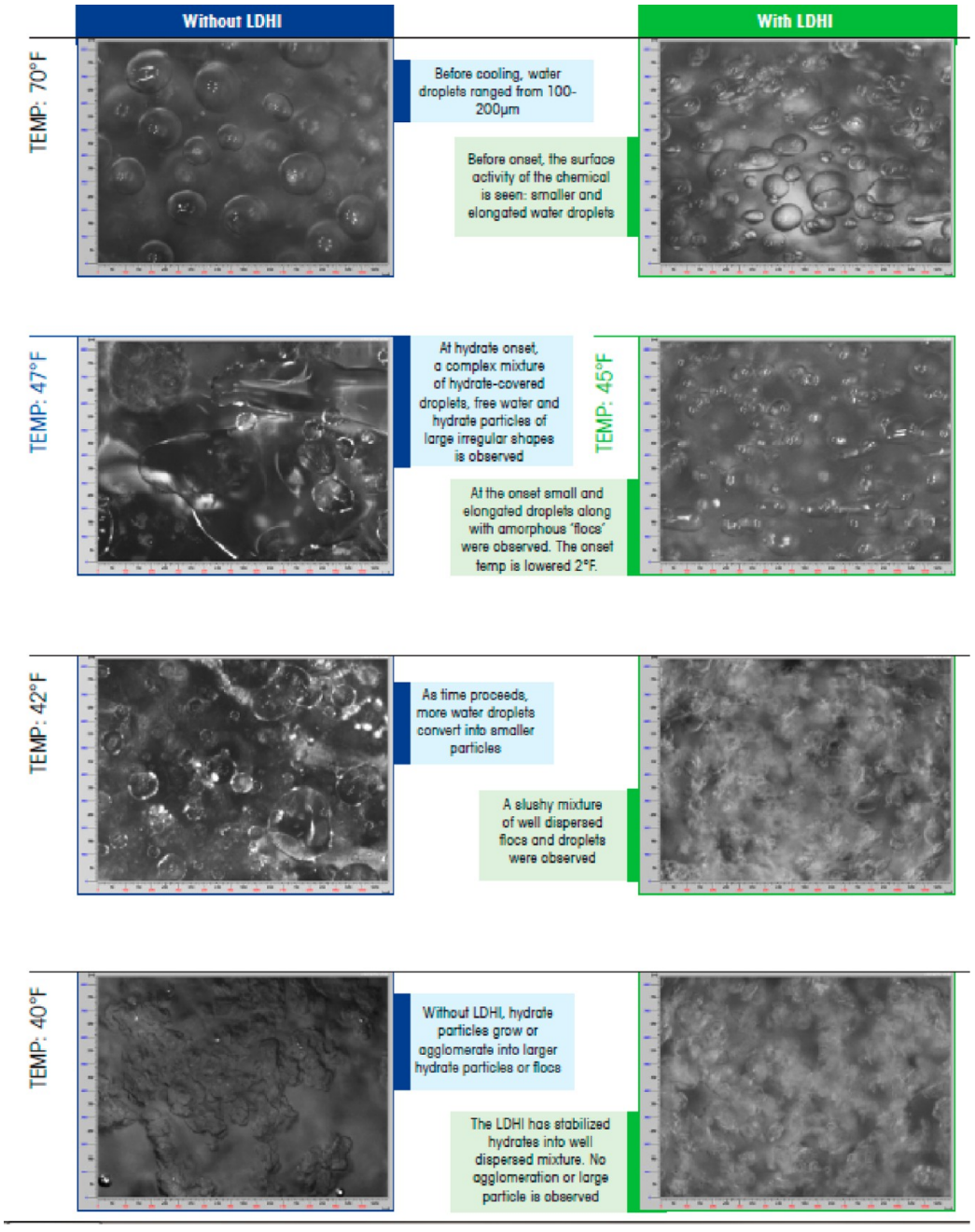

Figure 55. PVM images comparing hydrate formation at varying temperature with and without LDHI.

factors to consider.[440] Traditionally polymerization kinetics have been estimated using off-line methods, however, such an approach can be difficult due to poor sample stability at room temperature and pressure, high sample viscosity making sample preparation difficult and a fast rate of reaction meaning off-line measurements do not capture kinetics with a high enough resolution. In addition, safety is a major concern as polymerization reactions are highly exothermic and the materials are often toxic. Therefore, off-line sampling of a polymerization process can be difficult and sometimes unsafe. A deeper understanding of the polymerization kinetics can help scientists improve many areas of polymerization development and production, in particular safety, reaction kinetics, post processing and final product specification. The use of in situ instruments can facilitate the elucidation of polymerization kinetics with no need for sampling. Real-time measurements ensure a high degree of resolution and also allow operators to act decisively in the plant environment to ensure product specifications are met.

This case study highlights how FBRM and PVM can be used to rapidly understand the impact of changing process parameters on a polymerization process. Agitation speed is a critical process parameter that needs to be controlled to ensure the correct droplet distribution is achieved prior to initiation. In this case study, PVM images reveal how reducing agitation leads to extensive coalescence. Reincreasing the agitation rate results in disintegration of the coalesced droplets. However, PVM images (Figure 56) clearly reveal that varying the agitation rate has significantly altered the starting material. This indicates that the coalescence process is nonreversible and close attention should be paid to agitation rate especially during scale-up and manufacture where a changing initial droplet distribution

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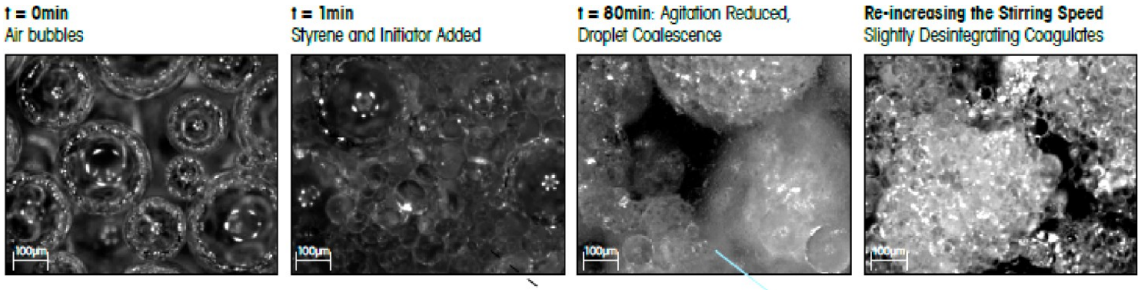

Figure 56. PVM images visualizing emulsification and polymerization at various stages in the process.

can have a serious impact on final polymer quality and overall process efficiency.

Where PVM images immediately reveal particle and droplet mechanisms, FBRM provides real-time quantitative information vital for process optimization. Figure 57 shows mean droplet

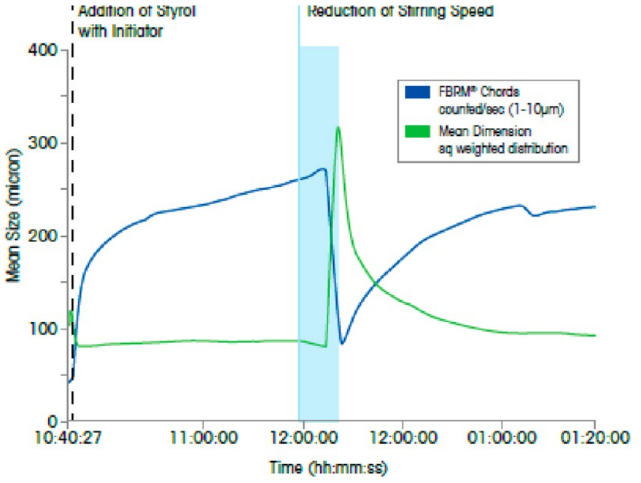

Figure 57. Mean chord length vs time for the polymerization process.

dimension and droplet counts between 1 and 10 μm vs time. Here we see the initial styrol addition takes over 1 h to reach steady state (blue trend flat-lines). When the agitation is reduced, droplet coalescence is very rapid with the mean dimension increasing from 80 to 320 μm in a matter of minutes. The reverse process, when agitation is reincreased, takes much longer—the mean drops from 320 to 100 μm over 1 h. Kinetic information obtained, without the need for sampling, provides a sound scientific basis for polymerization design scale-up and manufacture.

7. PAT IN INDUSTRIAL MANUFACTURING

7.1. Reaction Monitoring Using Mid-Infrared and Ultraviolet Spectroscopy at GlaxoSmithKline. The application of PAT within GSK has been primarily focused within R&D as part of the development process for new chemical entities (NCEs). PAT has been used to support the development lifecycle of the asset, initially to provide process understanding followed by application as part of the control strategy. PAT has also been employed within GSKs commercial manufacturing environment to assist in process understanding of mature assets as part of continuous improvement post file. The retrospective introduction of PAT to assist or supplement the control strategy of commercial products has not been carried out extensively due to the expected significant regulatory burden required to implement these changes. More recently, several regulatory files for NCEs have included PAT applications as either part of process development or for control of attributes; however, the number of applications have been limited in comparison to the potential opportunities across the drug substance and drug product manufacturing processes.

The development of PAT applications for measurement of CQAs (critical quality attributes) is driven by risk assessments performed by project teams assessing impact of process parameters on CQAs. For a PAT method to be developed and fully implemented, there needs to be a quality/control requirement. Furthermore, it is needed that methods and instrumentation being suitable in the manufacturing environment are available. Whereas in development the benefit-to-cost ratio may be high for developing and optimizing the manufacturing processes, in development a substantial amount of information can be gained in a short time using a nonvalidated method. As the product progresses from laboratory through to manufacturing, the cost of validation and implementation of the PAT method increases significantly and could become prohibitive to use in routine manufacturing. This is often a barrier to the wide deployment of PAT in commercial, traditionally batch, pharmaceutical manufacturing.

7.1.1. Reaction Monitoring Using MID-IR: Why Do We Do in Situ On-Line Sampling? Sampling in PAT is the key to success or failure. The following example showcases why in situ, on-line, sampling is important to generate in depth process understanding. This example relates to a step in the synthesis of an API. Traditional sampling was performed after the catalyst was added to the reaction to ensure that the reaction was proceeding as expected. The results from off-line analysis supported that the reaction was initiated by the catalyst. Later, the reaction was monitored using a mid-infrared system by inserting a silver halide (AgX) probe into the reactor.

The reaction can be followed using mid-infrared as shown in Figure 58. Beginning with the reagent addition, it can be seen that reagent bands grow as the reagent dissolves into the solvent. Then the catalyst was added. Shortly after this point is when the process would be sampled for the off-line HPLC. The spectra show that there is no change upon the addition of the catalyst. The next step in the process was water addition to quench the reaction. After the water was added, several absorbance bands (in addition to the water band seen at about 1640 cm^{-1}) can be seen in the spectra that are associated with an aldehyde that is formed in this reaction. In this case the HPLC method was a reverse phase method that included water as a solvent. As soon as the off-line sample is prepared for HPLC analysis, it interacts with the water in the solvent, and the catalyst is activated by the water to form the aldehyde. This leads to erroneous results that the reaction has proceeded from the

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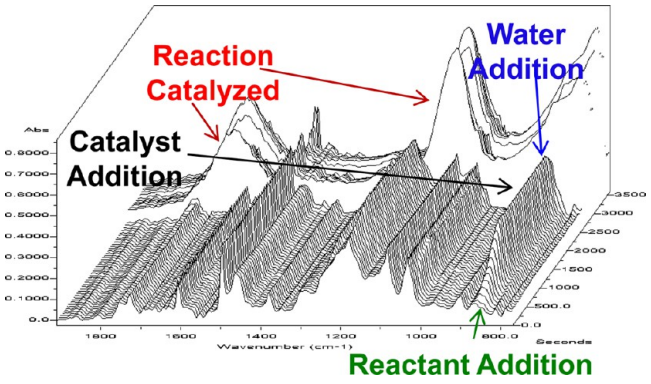

Figure 58. 3D plot of IR spectra to follow the catalyzed reaction.

addition of the catalyst alone. It was not until the reaction was monitored in situ that the reaction sequence was truly understood, demonstrating clearly that the catalyst is activated by the addition of water.

This is a simple example of why in situ monitoring of processes is recommended rather than relying on off-line sampling from the process. There are many reasons why process samples can dramatically change such as proceeding to react, precipitating components, or even reacting with air once the samples are removed from the process solution. In situ monitoring provides the real time picture of the in-process material in the environment where the change is happening.

7.1.2. Demonstrating Process Equivalence from Laboratory through Pilot Plant to Manufacturing. In PAT the ability to develop calibration samples that conform to the ranges for quantitative analysis suggested by ICH guidance (75−125% of target) is challenging at scale due to cost. It is much easier to produce the calibration samples for the calibrations at a smaller scale and then transfer the calibrations to larger scale equipment. PAT can be invaluable to demonstrate that there can be minimal impact on scale-up. Having a method that can show equivalence of manufacturing processes at different scales can facilitate site-to-site manufacturing transfers more easily, thus easing process validation after transfer. Reaction kinetics can be very sensitive to process parameters and are usually a good measure of the equivalence of one production facility to another.

In the example shown below, a quantitative model was developed using UV spectroscopy to determine reaction kinetics. The UV instrument was first calibrated with an independent set of samples. Figure 59 shows the agreement of referee data

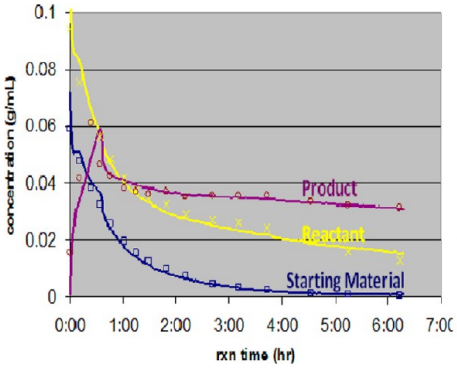

Figure 59. Agreement of validation set (individual points) with the quantitative in situ UV models.

quantitated by off-line HPLC (circles, X's, squares) with the quantitative UV kinetic trend models of the starting material, the key reactant, and the product. The agreement of this validation set is excellent.

The model for the consumption of the starting material was transferred from the laboratory to the pilot plant and ultimately to the manufacturing facility. The model was used to monitor both the pilot plant and manufacturing production. Figure 60 shows that there is good agreement between the

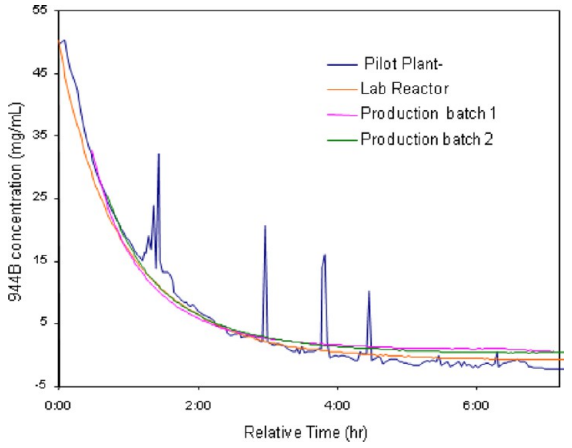

Figure 60. Agreement between kinetics for the consumption of reaction starting material.

kinetics for reaction material consumed as measured in the smaller scale lab reactor (orange), the pilot plant (blue), and the two production batches (pink and green). The spikes seen in the pilot plant (blue) trend occurred due to sampling of the reaction to verify the model.

In this way equivalence can be demonstrated for quantitative kinetic models developed at smaller scales, which can be transferred as the process is scaled up. When the process is run under kinetically controlled conditions, we have demonstrated that the agreement of the different scales can be used to ease our process validation. For example, when changing production facilities as the market for the product grows, or the rework strategy changes, monitoring the kinetics of the new process scale and showing process equivalence adds data to simplify the validation for the process facility or rework change.

7.1.3. Working with a Contract Manufacturing Organization To Implement PAT. In the current economic environment, many companies are using contract manufacturing organizations (CMOs) to accomplish various tasks such as the manufacturing of drug substance starting materials. In this application, the synthetic reaction was complex. The starting material in this stage can undergo degradation. When that happens, there is less than a stoichiometric amount of the starting material available to react, which can cause stalling of the reaction, and leave unreacted starting material which is difficult to purge and can become an impurity. If the reactant is overcharged, it is difficult to remove and produces a color problem as well as high impurity levels. If the reaction proceeds for too long, it can produce a thiocarbonate that will interfere with the subsequent stage of the synthesis. All of these circumstances result in unwanted impurities. A Raman spectrometer was shipped to the CMO and was used to monitor this reaction. By monitoring the rate of consumption of the starting material, the Raman was used to detect the end point of the reaction as seen in Figure 61.

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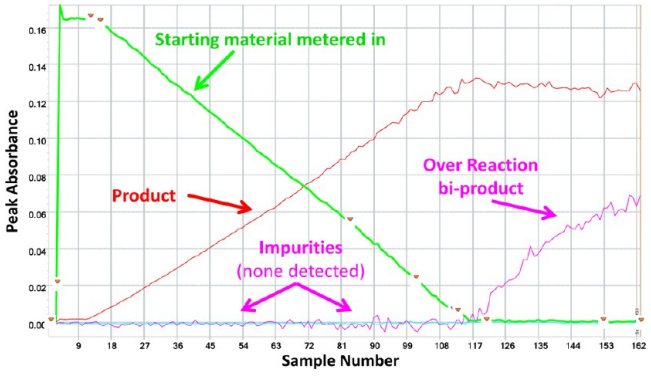

Figure 61. Raman spectral trends used to control end point of reaction.

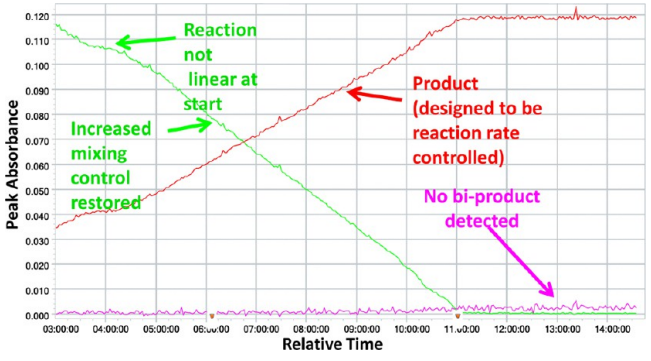

Figure 62. Raman spectral trend of first production batch at CMO.

The implementation in the plant was very successful. In Figure 62 we see that the rate of consumption of the starting material during the first 5 min was not following the expected rate of reaction seen during development and was not a linear decline. This was pointed out to the plant operators, and they realized that the agitation speed was set too low. After this parameter was corrected, the rate of consumption proceeded to match the expected rate. The corrected batch was right on the quality specification. The Raman monitoring saved the first batch of material, which more than paid for the entire effort. Subsequent batches that were made also met the quality specification.

7.2. Scale-up of an Exothermic Reaction at Roche: From Lab to Production. During the last 25 years, Roche Ireland has employed PAT tools in operations such as crystallization, solvent recovery, substance identification, and in process chemistry monitoring. This example describes the use of mid-IR spectroscopy for the safe scale-up and operation of a sodium borohydride reduction. The chemistry shown in Figure 63 is used in the manufacture of the anticancer drug Xeloda and involves the reductive cleavage of a tosyloxy group from a thermally labile tosylfuranoside in NMP, in the presence

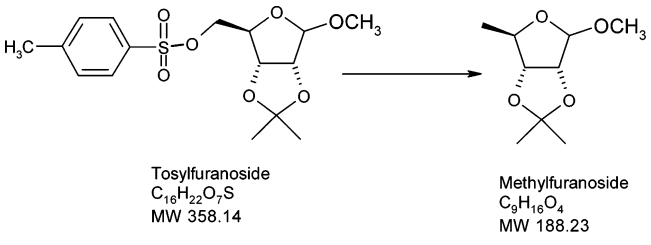

Figure 63. Synthesis of methylfuranoside.

of triethylamine (TEA) at about 80 °C. The reaction occurs with vigorous evolution of hydrogen gas, foaming, and the precipitation of tosylate salts. Unreacted sodium borohydride (up to 20%) can accumulate during the reaction.

The solid sodium borohydride is added in 15 kg amounts to reduce the risk of excess borohydride accumulation, the reaction being confirmed by the heat-kick/temperature rise. The next aliquot is only added when the reaction temperature has fallen to a predetermined level. Because, in the original process for the previous step, the isolation of the tosylfuranoside was hazardous and labour-intensive, a process improvement to eliminate it was developed and tested. However, in this revised process, the heat kick, the main method of safety control, was small and unreliable and sometimes absent altogether, possibly owing to the additional presence of isopropanol and water in the new process.

Mid-IR spectroscopy had been used in the laboroatory in the development of both the original and the new process, since the reaction could be followed by watching the disappearance of unreacted borohydride peaks, appearance of the borohydride–TEA complex, and reduction of the tosylfuranoside (Figure 64). Using a Mettler Toledo ReactIR, the system was installed in the manufacturing unit in October 2012 and has been operating successfully since then.

The Sentinel probe of the ATEX-rated, purged, 45P Mid IR ReactIR is interfaced to the process through a port near the bottom outlet valve via a K4 light guide (Figure 65). The instrument is permanently on and integrated with the manufacturing DCS system, acquiring data continuously, and is used to evaluate and confirm the operational status. The probe does not require cleaning between batches, and after 10 months (160 batches) the probe was in the same condition as when it was first installed. The spectral quality from the ReactIR was consistent over the 10 months with no measurable loss in peak resolution, sensitivity, or signal-to-noise.

During the new process, the reaction is aged at 85 °C after the last aliquot of borohydride has been added but shows a decrease in the unreacted borohydride and release of free TEA as well as hydrogen evolution and foaming. This was attributed to reaction between residual isopropanol and borhydride. Whilst this was a problem on the early batches, the use of the ReactIR helped to understand the process, and subsequent batches were well-controlled.

From a HAZOP viewpoint, the lack of frequency of failure data for the instrument is a serious issue—"How do we know it is working before we add the borohydride?" was the question. It was considered unrealistic to empower manufacturing technicains through training alone and unacceptable to use a chemometric approach, so an in process data "virtual" sample from the mid-IR analyser via the existing IT infrastructure is acquired and checked by QC remotely. The analysis requires the qualitative and quantitative comparison of the real time spectrum with a reference spectrum to verify the correct operation of the instrument. The remote analytical bridge between QC and manufacturing is called QC-PAT.

The process HAZOP also identified that insufficient TEA would lead to excessive accumulation of borohydride and a possible subsequent thermal excursion and uncontrolled hydrogen evolution. Originally verification of addition of TEA required time-consuming sampling and analysis, but it was subsequently shown that the ReactIR spectra could provide the same assurance of safety with the reduction in risk associated with manual sampling. The QC-PAT analysis is thus carried out

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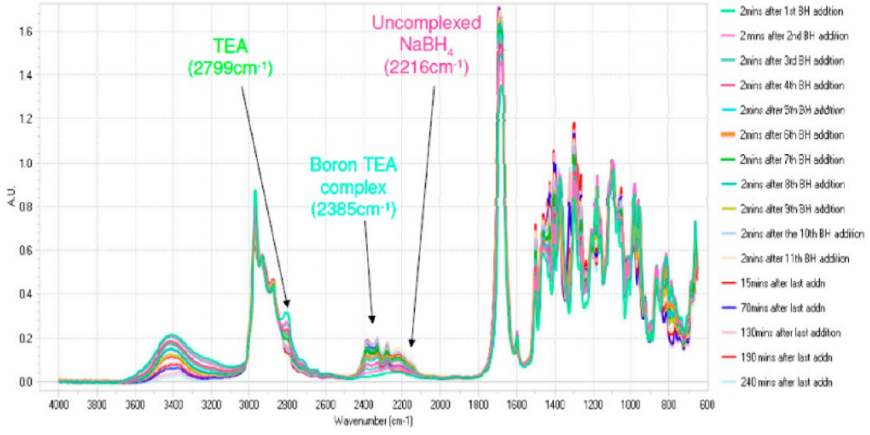

Figure 64. Mid-IR spectra observed following the additions of sodium borohydride in a laboratory reduction experiment.

Figure 65. Installation of the Mettler Toledo 45P mid-IR at the bottom of the tosylfuranoside reduction reactor.

remotely from manufactuiring and in principle could be carried out off-site if necessary.

In future it is anticipated that the mid-IR data could be used to establish process kinetics and that the adherence of the chemistry to the desired reaction path (a real time process quality parameter, PQ) may be used to eliminate downstream analysis of the product quality and facilitate real time release.

7.2.1. SIPAT: The Siemens Industrial PAT Data Acquisition, Management, and Control Platform. Recently PAT and QbD are finding more and more implementations into the pharmaceutical industry. While the focus of a PAT implementation is often on finding and integrating new analyser techniques, the impact on the data landscape, automation, and control strategies should not be underestimated. This section will elaborate on this aspect in order to increase the success factors of a PAT and QbD project.

7.2.2. It Is All about Data: "In God we trust. All others must bring data" (W. Edwards Deming). The basis for all PAT and QbD actions is core data. Secondary manufacturing, being tablet manufacturing, is taken as an example (although the same principles are valid also for other branches in the pharma industry). The obtained process knowledge on a specific unit operation (e.g., blending, granulation, drying, milling, compressing, or coating) is determined by the amount of data and the quality of the data that is available. Different data sources can be observed, as outlined in the following paragraphs.

7.2.2.1. Real-Time Data. Real-time data are collected during the process. Distinction can be made between multivariate or complex data and univariate or simple data. Typically, multivariate data are captured from PAT instruments, measuring the product in-line or at-line, like near infrared) devices, Raman instruments, or particle size instruments. Simple data include process data that are used to monitor the unit operation, like temperature, pressure, or rotation speed. Different analysers and data sources can be used, monitoring the same unit operation, each instrument having its own measurement rate. Moreover, all of these data must not just be captured but also contextualised and aligned to each other, to relate the correct pieces of information. Also calibrations or background measurements are important matter. Before starting a batch preparatory steps might be necessary, so integrating this information in a PAT application is smoothening this process. Standardisation in communication protocols for PAT analysers is a recent step forward, where the object linking and embedding for process control—unified architecture—analyser data integration standard is the most recent example.

7.2.2.2. Off-Line Data. Raw materials are controlled upon arrival and characterisation assays are performed to reveal the quality of the batches. This information is available in the company's LIMS (laboratory information management system) and has an impact on the consecutive process steps. So it is smart to capture also these data in line with the real time data discussed in the previous section, as the batch quality is impacted by the raw material quality. Samples are also taken during the runs, where the results might be available only hours or even days after a batch has been processed. Nevertheless, this information is relevant when working on process knowledge and QbD. A PAT system should be able to query the data from a LIMS database, or any other data source, and align the sample results with the real time data that were obtained earlier. This is key when building up process knowledge and creating new mathematical models.

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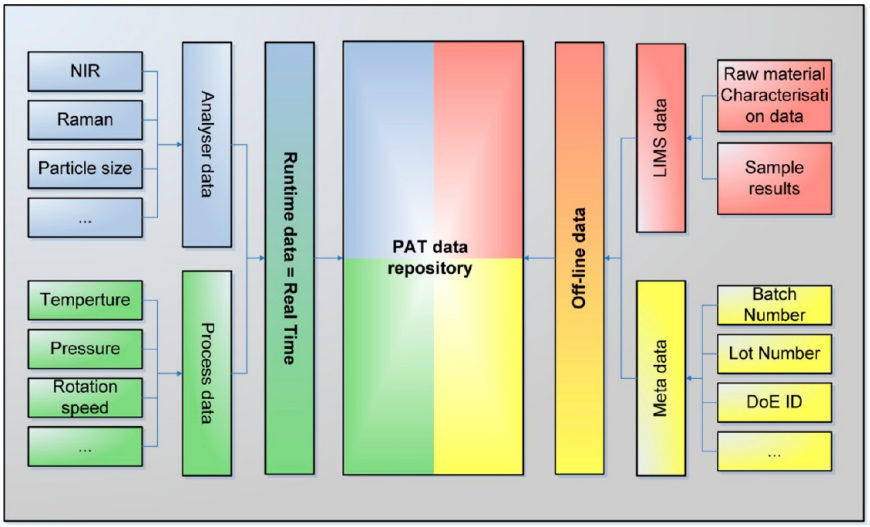

Figure 66. Aggregation of different PAT related data sources.

7.2.2.3. Metadata. A last level of data can be considered as the identifiers of the different data layers. Data must be tagged with batch numbers, lot numbers, DoE IDs, or sample IDs, to be able to contextualize the data afterwards. These data can be supplied manually at the beginning of a (test) run, but a more secure method is to capture this data on-line from the manufacturing execution system, the automation system, or the batch engine.

7.2.2.4. Integrated PAT Data. The goal of a PAT system is to integrate all PAT data (real-time data, off-line data, and metadata) to a single data platform (Figure 66). This means that the PAT platform is communicating with the used process equipment and in line analysers, synchronising the data acquisition, and also capturing the relevant meta data like measurement settings and used backgrounds or reference measurements for each data point. These data are available for real time trending, quality predictions, or advanced process control. In the longer run, this data repository, built up over several batches as described in the DoE (design of experiments), is to be explored and should lead to increased process knowledge and understanding.

7.2.2.5. Turning Data into Knowledge. In a next step, MVDA (multivariate data analysis) techniques can be applied to turn the collected data into process knowledge. The link between the different critical process parameters and the product's critical quality attributes is to be investigated and captured in mathematical models. Several techniques can be applied in this modelling area, from the commonly used PCA and PLS (to more advanced techniques like neural networks and hybrid models).

Key is that these models can be applied in real time on the collected data. Therefore, integration between the PAT application and the chemometrical calculations engine is essential. Having data collected in real time is a good start, drawing the right conclusions is essential! It is important that the collected information can be presented to the operators and line supervisors in an intuitive and flexible way. This is done by building a dedicated user-friendly graphical user interface (Figure 67) or by embedding the information in the unit operations' system control and data acquisition screens.

Also the right conclusions must be drawn from the observations. By integrating decision protocols and evaluation rules into the data management layer, unambiguous decisions can be taken by the software. Examples of implementations are the Western electrical rules applied as evaluation in control charts. Out-of-specs can be directly related to the control of diverting systems in the production line.

7.2.2.6. Validation and Data Integrity. Working in a highly regulated environment as the pharmaceutical industry puts also the necessary requirements on the level of software validation and data integrity. This means that the classical V-model must be applied when implementing a PAT data management layer.

Several guidelines are available in the area of software validation. The FDA issued the "General Principles of Software Validation; Final Guidance for Industry and FDA Staff", and there is the 21CFR Part 11 guideline on electronic records and electronic signatures. The most commonly used standard applied in the industry might be the GAMP 5 (Good Automated Manufacturing Practice, Version 5), issued by the International Society for Pharmaceutical Engineering. A PAT data management system must ensure the application of these standards. Important focus areas here will be the integration between the PAT central data layer and the different external data sources such as analysers or external databases. Ensuring the data integrity is one of the key elements of a centralised data system as it avoids mistakes of manually integrating and merging different data sources by custom applications.

7.2.2.7. Control—The Next Step in the PAT Journey. The integration of PAT and QbD into production—and as a consequence the increased understanding of the process monitored—is having two main benefits: it is opening the door for real time release as you can monitor critical quality attributes in real time, and it enables advanced process control based on multivariate real time data and process understanding.

A continuous tabletting line is used as an example (Figure 68), dealing with a series of unit operations that are continuously (or sometimes semicontinuously) following-up to each other. The levels of control are hence 2-fold: the first level is the control of the independent unit operation, while the second level of control is the control of another unit operation in the continuous train, which can be a previous step (feedback control) or a next step (feed forward control).

The crucial part is to integrate a PAT application into the company's production and automation software layer.

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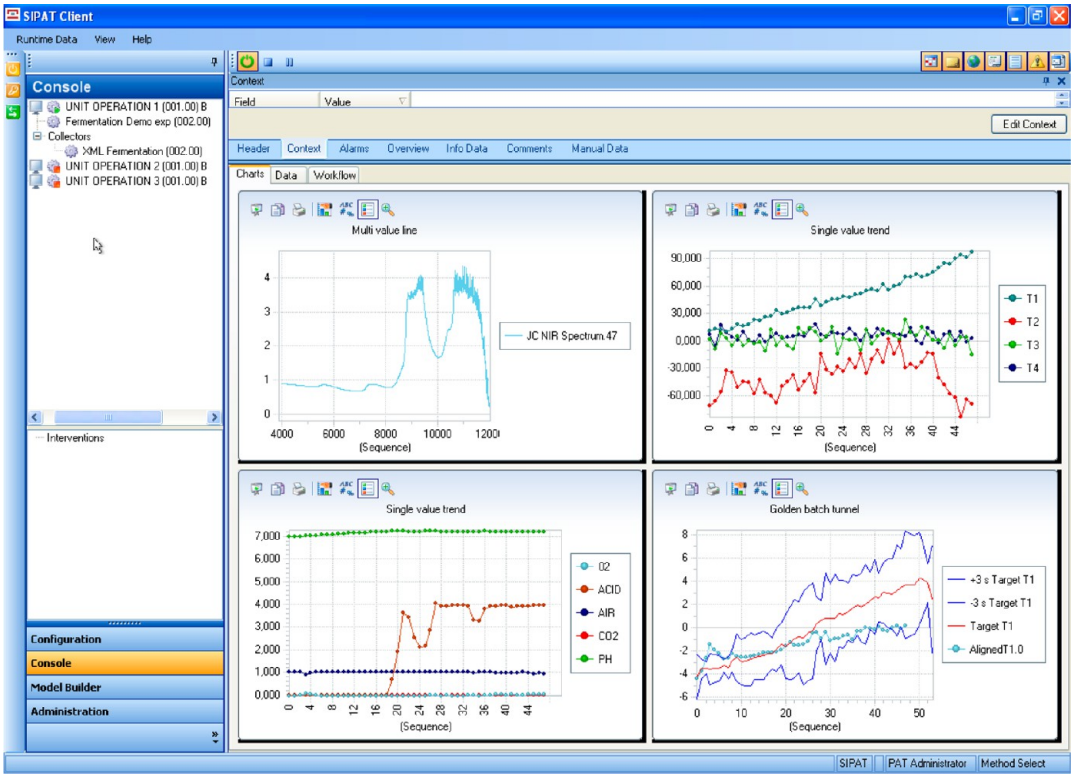

Figure 67. Runtime screen from a PAT application, including spectral NIR data (upper left), process data (lower left), calculated parameters (upper right), and a golden batch trajectory (lower right).

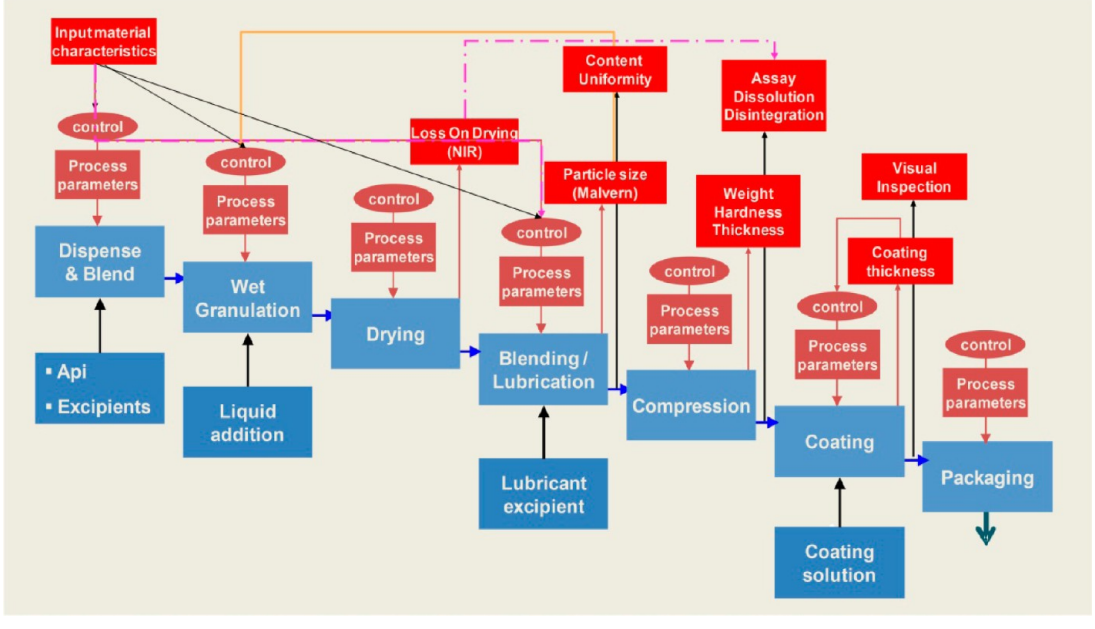

Figure 68. Example of control loops in a continuous manufacturing line based on PAT data management.

Data collection commands should be launched from the batch engine, analyser calibrations should be performed using the usual SCADA screens, and PAT feedback or alarms should be visualised in the regular operator's window. At this stage PAT should be a background process, monitoring the batch quality in real time and supporting the crucial product-related decisions. Especially feedback from the PAT data management layer to the process layer will be a crucial element, mainly when implementing advanced process control. At this stage the PAT layer is not just an aggregating layer but plays an active role in controlling the unit operations.

It is obvious that implementing PAT in an oral solid dosage plant is not an easy task. But with the right focus it can leverage the company's knowledge to a higher level. Starting from a sound data collection in an integrated PAT environment, data can be turned into knowledge, condensed in mathematical models. The PAT platform can apply these models in real time to support the crucial production related decisions.

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Integrating PAT in the company's information and technology framework is smoothing the operational use, while a global PAT approach is enabling data and knowledge transfer on a high level.

8. SUMMARY

This multiauthor review paper presented an overview of some of the methodological developments and applications in the field of PAT. The examples provided in this paper demonstrate the benefits derived from the application of PAT, which can be realized during process development as well as during commercial manufacturing. Typical advantages of using PAT include: increased process understanding, faster process optimization (e.g., feedback control to develop crystallization), removal of the need for off-line sampling (e.g., for safety control or unstable chemistry), understanding and predicting the impact of scale-up, and the ability to control/correct processes before isolation of intermediates or product, leading to improved quality.

Often in development, these benefits can be difficult to quantify from a financial perspective. In manufacturing the return on investment can be more easily estimated in particular when PAT is deployed to improve an existing manufacturing process, where the manufacturing costs are well-understood. When PAT applications are used in commercial manufacturing, the additional benefits may include: reduction in cost, time (off-line analysis), cycle time reductions allowing greater plant throughput, green metrics (energy, solvent usage, carbon footprint), safety (off-line sampling of hazardous materials), further verification on the effect of scale up on the process, and process variation monitoring as part of continuous verification during product lifecycle.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

ADNC - automated direct nucleation control
API - active pharmaceutical ingredient
ATEX - Appareils destinés à être utilisés en ATmosphères EXplosibles
ATR-FTIR - attenuated total reflection−Fourier transform infrared spectroscopy
BCS - Biopharmaceutics Classification System
B2B - batch-to-batch
CBZ/NCT - carbamazepine/nicotinamide
CCD - charge-coupled device
C-control - concentration-control
CD - cinchonidine
CDER - Center for Drug Evaluation and Research
CFC - concentration feedback control
CFR - Code of Federal Regulations
cGMPs - current good manufacturing practices
CLD - chord length distribution
CLS - classical least squares
CMC - chemistry manufacturing and control
CMOs - contract manufacturing organizations
CPPs - critical process parameters
CQAs - critical quality attributes
CSA - Canadian Standards Association
CSD - crystal size distribution
DCS - distributed control system
DLS - dynamic light scattering
DoE - Design of Experiments
DWS - diffusing wave spectroscopy
ELSS - extended loading space standardization
EPSAC - extended predictive self-adaptive control
EWMA - exponentially weighed moving average
FBRM - focused beam reflectance measurement
FDA - Food and Drug Administration
FIA - flow injection analysis
FT-NIR spectroscopy - Fourier transform near infrared spectroscopy
FT-Raman spectroscopy - Fourier transform Raman spectroscopy
GAMP 5 - Good Automated Manufacturing Practice, Version 5
GDCs - growth and dissolution cycle
GSDM - grey scale difference matrix
GSK - GlaxoSmithKline
GUI - graphical user interface
HAZOP - hazard and operability study
HPLC - high-performance liquid chromatography
ICF - intensity correlation function
ICH - International Conference on Harmonization
IEC - inline electrostatic coalescer
IQ - installation qualification
IRE - internal reflection elements
JITL - just-in-time learning
LDHI - low dose hydrate inhibitors
LIMS - laboratory information management systems
LSS - loading space standardization
MEMS - microelectromechanical system
MIR or MID-IR - mid-infrared
MPC - model predictive control
MPLS - multiway partial least squares
MSD - means square displacement
MZW - metastable zone width

MVDA - multivariate data analysis
MW - molecular weight
MWF - multiwavelength fluorescence
NCEs - new chemical entities
NCO - necessary conditions of optimality
NMPC - nonlinear model predictive control
OPC - OLE for process control (object linking and embedding for process control)
OPC UA ADI - object linking and embedding for process control—unified architecture—analyzer data integration
OPLEC - optical path length estimation and correction
PAT - process analytical technology
PCA - principal component analysis
PCR - principal component regression
PCS - process control system
PDS - piecewise direct standardization
PID - proportional integral derivative
PK/PD - pharmacokinetics/pharmacodynamics
PLC - programmable logic controller
PLS - partial least squares
PQ - process quality
PSD - particle size distribution
PVM - particle vision and measurement
QC - quality control
QbD - quality by design
R&D - research and design/development
RMSEP - root-mean-square error of prediction
SBC - slope and bias correction
S/N - signal noise ratio
SOP - standard operating procedures
SPEC - systematic prediction error correction
SPM - statistical process monitoring
SSC - supersaturation feedback control
SST - spectral space standardization
SynTQ - synchronised total quality
TEA - triethylamine
TFAP - trifluoroacetophenone
UCM - ultrasonic crystallization monitoring
UKF - unscented Kalman filter
UL - Underwriters Laboratories
URT - ultrasonic resonator technology
UV—vis spectroscopy - ultraviolet—visible spectroscopy
XRD - X-ray diffraction

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