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PROCESS ANALYTICS EXPERIENCES IN BIOPHARMACEUTICAL MANUFACTURING

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Process analytics play a key role in achieving the objectives towards control strategy per Quality by Design in biopharmaceutical process development and manufacturing. It also has the potential to enhance continued process verification and make it closer to real-time. While the common perception of process analytics could be more focused on the analysers or on-line assays, our approach in this paper is more towards a systems thinking which is aligned with regulatory guidelines. Experiences in multivariate tools for data analysis, process analysers, process control and continuous improvement and knowledge management tools are summarised. The role of multivariate statistical process monitoring in understanding the sources of variation and detecting weak signals is articulated with industrial examples.

A lot of data are generated during biopharmaceutical process development and during the commercial process runs within the product lifecycle. Effective management of these data and development of insightful control strategies are critical for ensuring process consistency and verification. Recent guidelines[1,2] from the agencies also promote the lifecycle concept linking product and process development with the commercial manufacturing process. Availability of the right data is critical to achieve this endeavour while at the same time having systems in place to effectively monitor and control the manufacturing process to obtain repeatable and reproducible runs. Process analytical technology (PAT) with its tools helps address the monitoring and control aspirations summarised above. These tools are summarised in the FDA's PAT guidance[3] as follows:

1. Multivariate tools for design, data acquisition and analysis
2. Process analysers and process chemistry tools
3. Process and end-point monitoring and control tools
4. Continuous improvement and knowledge management tools

We will summarise our approach in data management, storing and organising the vast amounts of data generated during commercial manufacturing, multivariate tools and monitoring technologies, some of the experiences with process analysers and other process chemistry tools combined with process control opportunities and a short discussion on the knowledge management tool in capturing the learning during commercial campaigns via advanced multivariate monitoring systems.

Systems thinking

A combined use of aforementioned technologies in the PAT toolbox provides an effective means towards understanding and controlling process variability as well as supporting continued process verification and process improvements. Managing the data is crucial to enable the PAT toolbox. Therefore, establishing robust data capture and management systems has been our preliminary focus on the journey to PAT-enabled manufacturing.

Data Management Approach

It is imperative to capture process and product data coming from various source systems. Different levels of data/information hierarchy are described in ISA S95 model in five levels. Level 0 being the I/O level where analysers and sensors are, level 1 above it is where the distributed control systems (DCS) typically are found, level 2 has manufacturing execution

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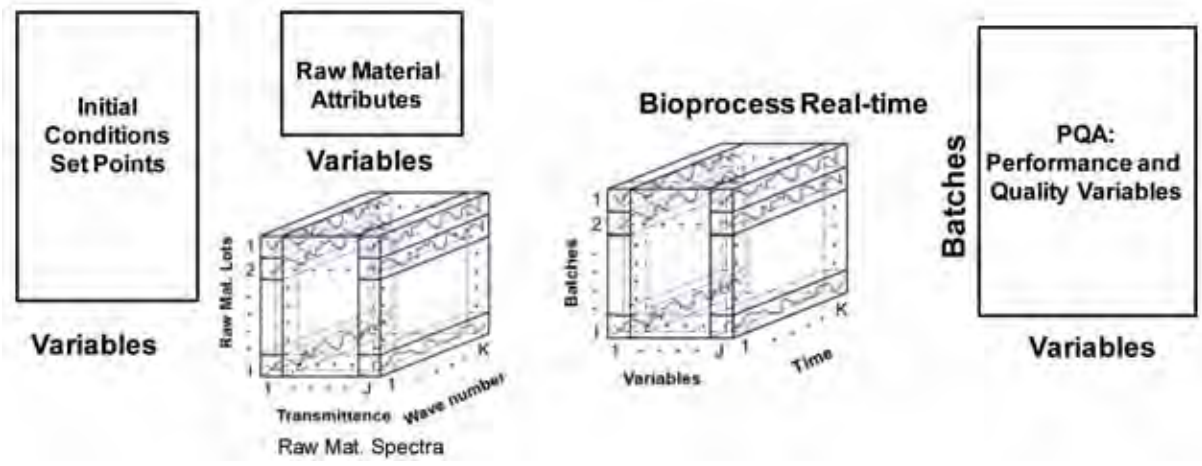

FIGURE 1 Multiple data blocks generated in a typical biopharmaceutical manufacturing process

systems (MES) and other batch data collection and Plant Data Historians, level 3 contains manufacturing operations and supervisory control systems and finally level 4 at the top has the business planning and logistics systems (such as enterprise planning). While we take data management as a lifecycle approach, even within the commercial manufacturing setting, there are various sources of data that require organisation and access in the cGMP environment. In a typical biopharmaceutical manufacturing process, these include operational parameters measured in real-time and made available in Plant Data Historians, and process parameters such as daily cell counts, metabolic indicators, other process set points and performance parameters captured in Manufacturing Execution Systems (MES) (e.g., electronic Batch Records) and lastly, product quality attributes that are usually tested by Quality Control and captured in Laboratory Information Management Systems (LIMS) (**Figure 1**). In addition, there might be raw materials-related data captured in other source databases. If we multiply these data sources with multiple plants, multiple molecules and multiple geographical areas, it quickly becomes a complicated task to manage and access the data.

We have successfully deployed a virtual Plant Data Warehouse (PDW) application that provides a single point of access to all of the data sources mentioned above for multiple plants and products[4]. PDW design is based on (but not limited to) the S88 physical and procedural models as outlined in **Figure 2**. For data management purposes, we have made some additions to the standard S88 models. For instance, an additional data element 'Product' has been incorporated into the Physical Model to accommodate multi-product facilities. We have also added an additional data element 'Step' to the Procedural Model for processes that require data management at a fine level of granularity.

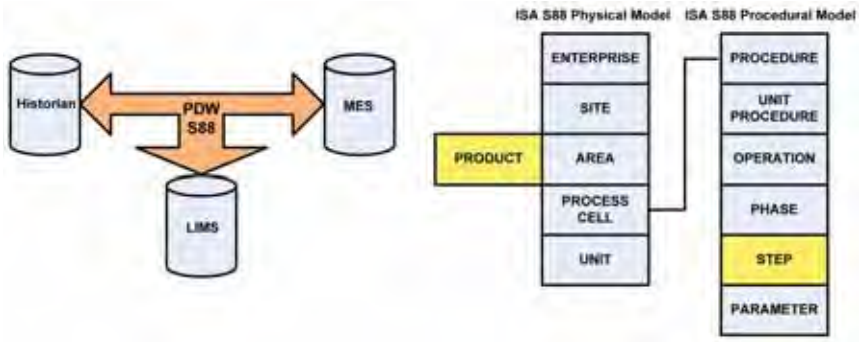

FIGURE 2 Manufacturing Data Management and use of S88 Model to tie the data together

This infrastructure is an important enabler for accessing historical data to support development of process models, generation of automated cGMP reports, and understanding of process variability via process monitoring. Furthermore, it supports the Lifecycle Data Management paradigm.

Process analysers and process chemistry tools for end-point monitoring and control

There have been a lot of process analysers and chemistry tools proposed for use in biopharmaceutical process development and manufacturing[5-7]. While we will not be covering

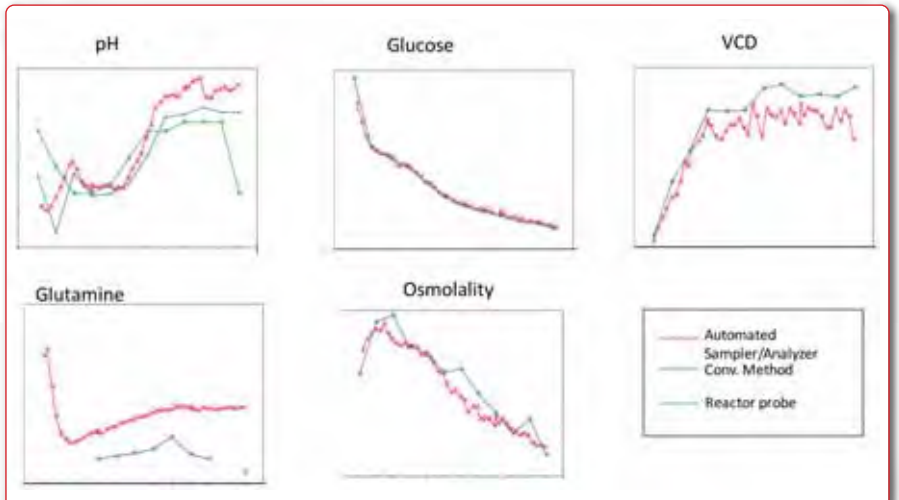

FIGURE 3 Comparison of sterile automated sampler and analyser and conventional offline methods for cell culture

FIGURE 4 Left – Processed NIR spectra data of different lots of the same raw material; Middle – Scores plot of a number of different lots of the same raw material; Right – Contribution plot of NIR spectra showing the differences of the raw materials lots highlighted in Red in the Scores plot vs. the rest of the lots

the entire domain here, it has been our experience that when implemented right, these tools can help achieve variability reduction and end-point monitoring / control goals. They also include automated sterile sampling capabilities to reduce the time required to take offline samples. For instance, in a typical cell culture bioreactor setting, offline samples are taken once or twice a day during many days of cultivation to monitor process performance. This involves sterile manual sampling and quickly analysing the samples using bench-top equipment and finally entering the results into batch records (and into MES). This could be fully automated by using compact on-line analysers that are available today (direct method). Another approach has been to use spectral probes (NIR and Raman are the most common) and developing calibration models to relate the spectra to the measurement of interest (indirect method). In our bench-top testing, automated sterile sampling and analysis has worked despite the refinement opportunities. Note that it has given us more frequent sampling and automation capabilities that otherwise required additional effort to collect the same amount of data manually.

While direct methods have their advantages and wide area of applicability, the indirect method has also shown a lot of promise and industrial applications especially in cell culture monitoring such as NIR and Raman-based optical probes which give real-time information about the culture[8-10]. Successful application of an NIR-based cell density probe has shown variability reduction in cell culture performance[8]. Another process chemistry tool that has found effective utility is on-line HPLC for detecting aggregate levels in chromatography operation to determine the stop of the elution phase to achieve consistent purity levels[11]. This application is also considered as end-point monitoring and control.

Furthermore, advances in Raman and NIR-based spectroscopy have made these technologies available in handheld units. One application of this development involves non-intrusive rapid identification and variance monitoring of raw materials. As processes advance and become more controlled, the impact of raw material variation becomes more pronounced. Due to the excellent functional group identification capability of the Raman and NIR spectroscopy methods, rapid identification can be used throughout the process for fast and reliable identification of critical materials. The unique spectra information for the raw material can also be fed into multivariate analysis (MVA) to monitor lot-to-lot variability and gain greater understanding of the incoming

raw material. **Figure 4** on page 5 shows how a few outlier lots of a raw material can be easily identified by using NIR spectroscopy.

Real-Time Multivariate Statistical Process Monitoring (RT-MSPM) used as a continuous improvement and knowledge management tool

RT-MSPM provides an effective means of monitoring many variables measured at many different unit operations across many batches in real-time. This data-driven technology has allowed us to monitor process consistency and identify weak signals about equipment issues and process trends early. This helps with quick process troubleshooting and prevents process failures and losses in product yield. Some of the benefits of this technology include:

- Prevention of process and equipment issues (e.g., during the process and after the process is complete)
- Process performance improvement (e.g., yield increase and impurity reduction)
- Operational excellence (e.g., faster troubleshooting, purposeful presence on the manufacturing floor)
- Predictive monitoring

The methodology of RT-MSPM involves data mining of historical batches that are representative of desired process performance and inherent process variability. Once the rational subgroup of historical batches is determined and data mined for the parameters monitored, various multivariate models are developed after appropriate data pretreatment (i.e., outlier detection / removal, scaling, etc.) is applied. Multivariate charts are constructed to monitor new batches. Further details of multivariate modelling and monitoring algorithms can be found in our other technical publications[5-7,12].

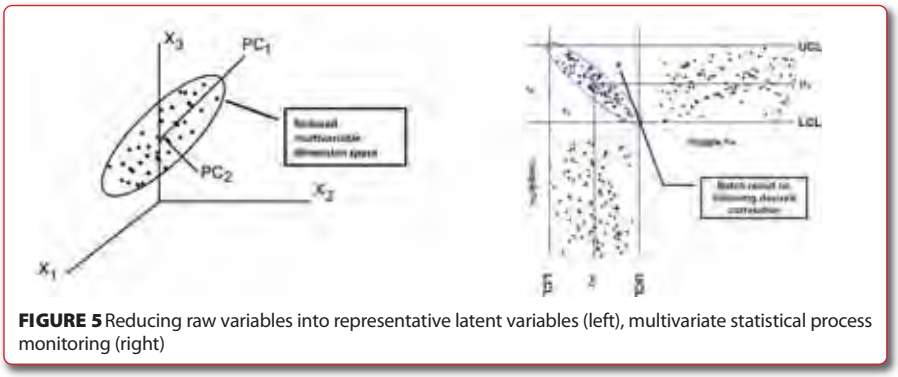

FIGURE 5 Reducing raw variables into representative latent variables (left), multivariate statistical process monitoring (right)

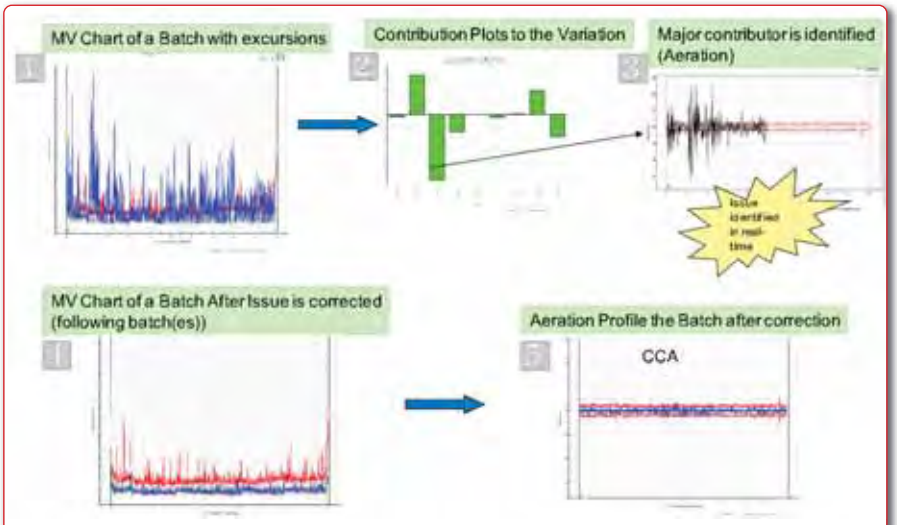

FIGURE 6 (1) A batch showed high degree of variation violating its multivariate chart limits, (2) Contribution plot indicates the major variability offender being aeration rate in the bioreactor, (3) inspecting on the raw data confirms the noisy signal, (4) after recalibrating the mass flow controller before the next batch, process noise is significantly reduced and (5) confirmed by inspecting the univariate chart

We also make use of high-level dashboards that are based on multivariate chart run rules to make issue identification effective for the manufacturing and other process support staff. Multivariate modelling technology helps by reducing large number of variables monitored to a few latent variables and establishes monitoring on those few latent variables. It also provides us with the ability to monitor the interactions between the variables.

An example of equipment issue identification and batch-to-batch correction is provided in **Figure 6**. This is a representative case of how this technology is used on the manufacturing floor by the operators. It helps by identifying variability in real-time and quickly brings the staff's attention to the issue. The staff can then triage it and take the appropriate action (by following cGMP procedures).

Another means of using the tool is to prevent issues by anticipating the potential process or equipment issues. In **Figure 7**, a case where a salient increase across batches in chromatography differential pressure is presented. The RT-MSPM tool allowed staff to quickly identify across-batch trend that was

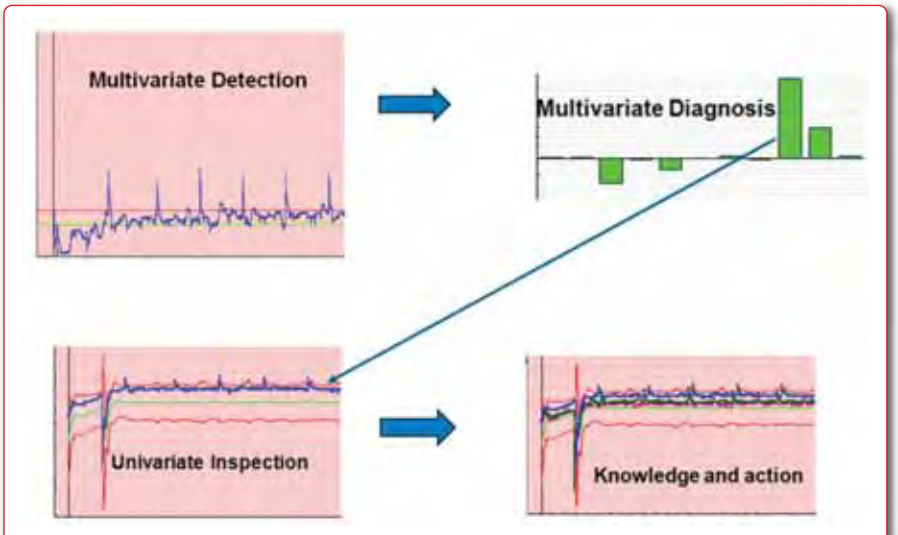

FIGURE 7 Real-time detection of a developing trend followed by across-batch analysis to anticipate a long-term trend to prevent further issues in chromatography column operations

developing (bottom right chart in **Figure 7**) and in a timely manner to allow re-packing of the column before any further issues. Trends identified via RT-MSPM can be weak signals which, if not checked, may develop into real process problems.

Figure 8 demonstrates this on a signal that was picked up using the multivariate charts and helped identify the potential root cause of a transmembrane control issue in an ultra-filtration skid which was addressed in real-time. Notice that the process TMP was well within the defined quality alarm ranges for subsequent duration of the batch after the issue was corrected in real time.

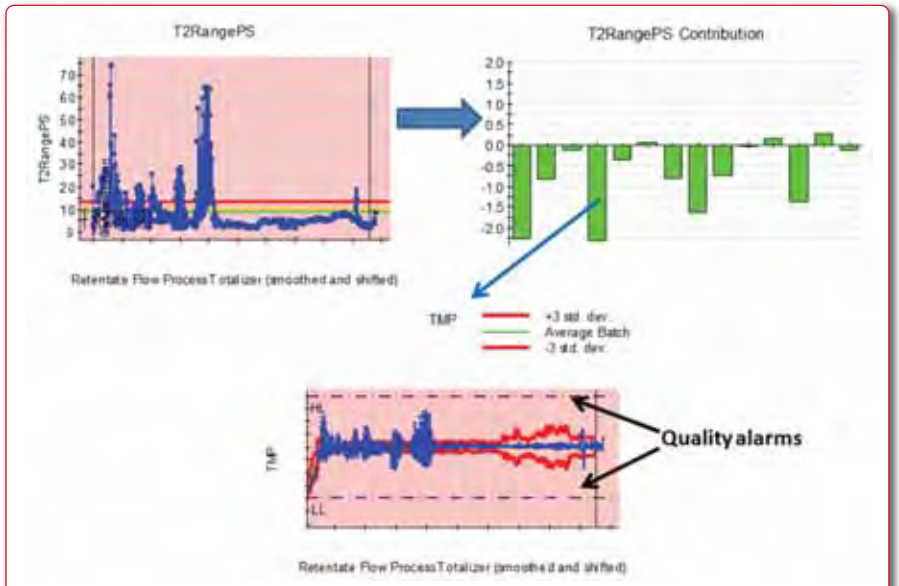

FIGURE 8 Monitoring of an ultrafiltration unit indicated oscillatory behavior and higher than usual noise in transmembrane pressure (TMP). While the TMP is still within its quality alarms (normal operating ranges in this case) RT-MSPM, picks up this weak signal before it develops into a bigger issue

Visual factory and knowledge management

RT-MSPM has also made use of Visual Factory principles to improve the end user interaction with the multivariate tool. To that end, it was not only made available in client desktops/laptops, it was also made available in large touchscreen displays and iPads that are accessible on the manufacturing floor (**Figure 9**, page 8).

In order to capture the key trends identified during production campaigns, we have also developed a knowledge management tool. Once the trends are reviewed and triaged (**Figure 10**, page 8), the key findings are entered and catalogued using this tool (**Figure 11**, page 8). It is designed in such a way to allow advanced filtering to quickly find related information. For instance, one can quickly get a summary of all the observed trends in a given unit operation, (including a given phase) across campaigns and products to get any systemic trends or cyclic events. This then allows systems analysis, review of the equipment and event process holistically. **Figures 10 and 11** (page 8) are representative views from the system, though it has more information and links to the relevant reports to enrich the knowledge management experience.

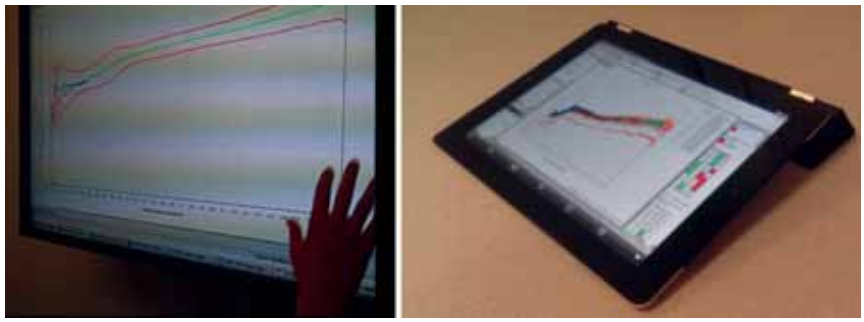

FIGURE 9 Large touchscreen display used on the manufacturing floor (on the left), iPad for remote and mobile access (on the right)

Predictive monitoring

Multivariate predictions using RT-MSPM adds value across many aspects of processing from efficiency to yield savings and improvements. and scheduling future activities which are dependent on time, performance and / or batch size. In one example, a bioreactor is required to meet certain viable cell density (VCD) levels in order to inoculate the next step (Lower Acceptance Limit, LAL in this example). For improved process consistency and higher capability, statistical control limits are also followed (Lower Control Limit, LCL in the example). The top left chart in **Figure 12** (page 9) illustrates a low growth situation in a bioreactor where two final samples were required as the first was below the LCL. The culture was extended to meet the LCL resulting in additional time spent sampling, analysing and re-scheduling manufacturing activities. The top right chart in **Figure 11** demonstrates this new batch was in the lower growth quadrant of the batch level model on the second to last day. Evaluating the associated prediction (bottom bar chart in **Figure 11**) shows the Final VCD prediction was slightly lower than the LCL for the target culture duration. Efficiency and improved

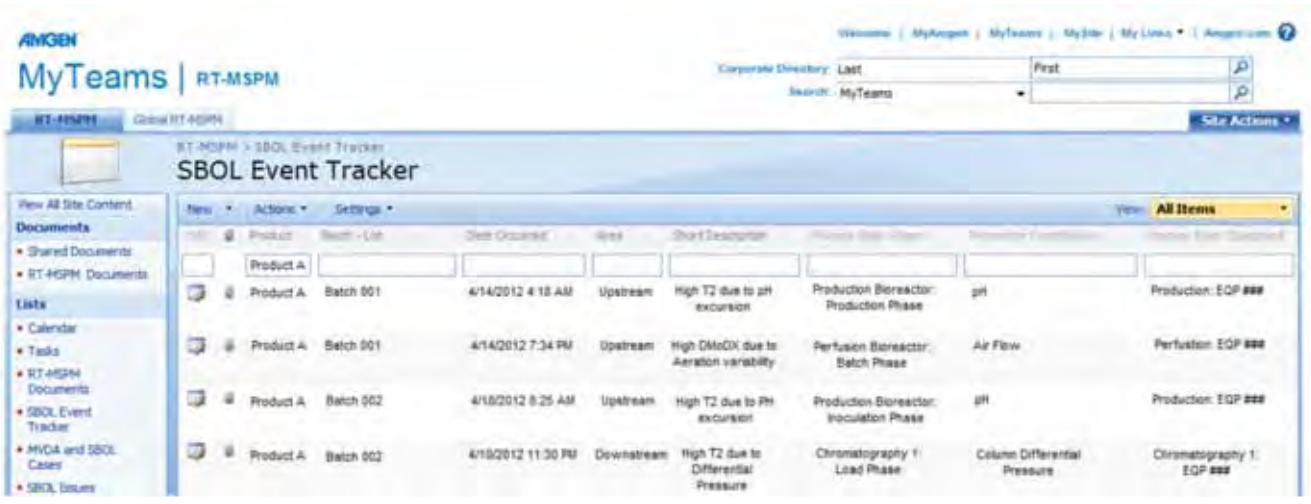

FIGURE 10 RT-MSPM Knowledge Management tool displaying multivariate event summary information with example filter by product

Having early knowledge of process performance lends itself to opportunities such as shifting the process operating space within validated limits seeding can be achieved through accurate predictions of the final process performance by adjusting the schedule and process duration,

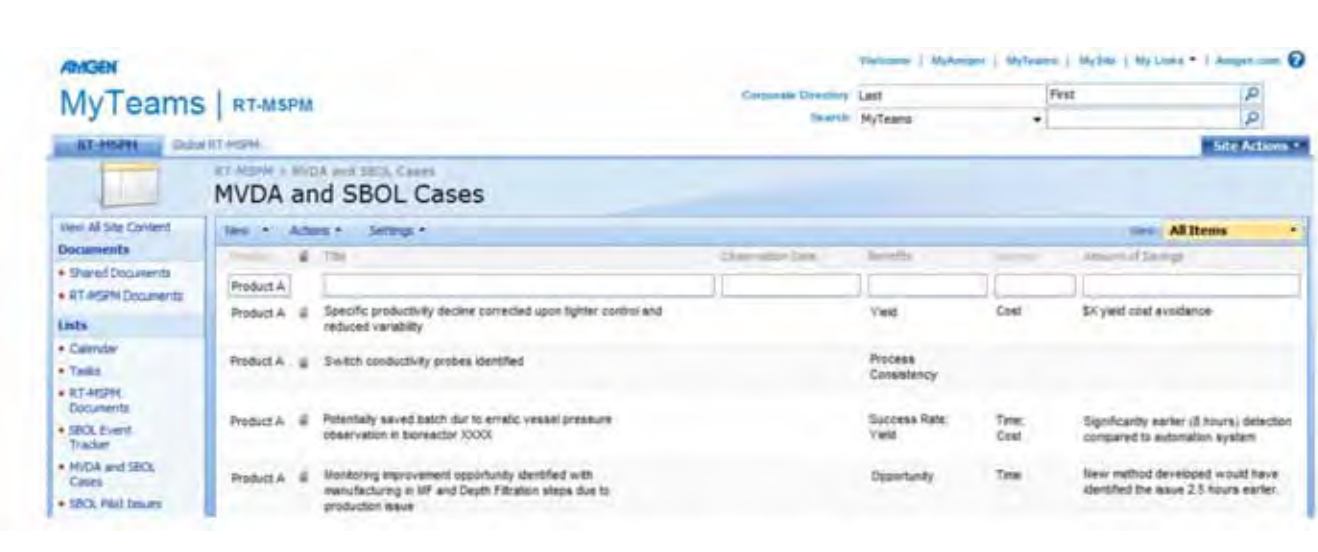

FIGURE 11 RT-MSPM Knowledge Management tool example for capturing solutions and benefits for triaged events

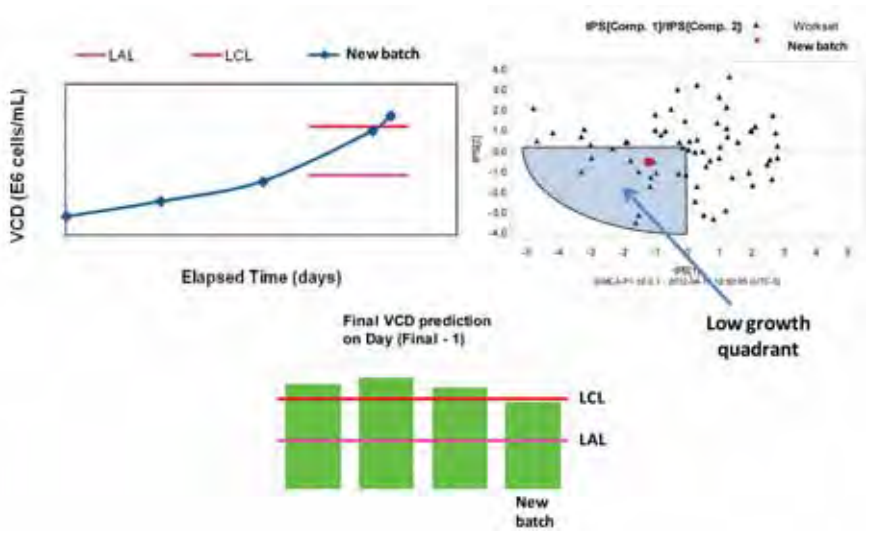

FIGURE 12 Sampling points for VCD across the culture duration (top left), batch level model for VCD prediction indicating a new batch associated with lower growth historical batches (top right), Final VCD predictions indicating a new batch will be lower than the LCL at the target duration (bottom)

within validated limits, before the process reaches the sampling time.

In summary, applying process analytics, RT-MSPM technology in particular, has provided notable business benefits. It also supports the paradigm shift towards enhanced continued process verification and establishes the necessary platform to bring process and product data together for process end-point monitoring and control. The use of RT-MSPM technology in preventing process or equipment issues has proven successful. While the initial use of RT-MSPM was limited to monitoring the consistency of the process and the equipment, with the advent of process analysers and process analytical chemistry tools the monitoring capability can evolve into a predictive end-point monitoring and control tool and used as a continued process verification tool.

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BIOGRAPHY

Cenk Undey, PhD, is a Director of Process Development in Process and Product Engineering at Amgen. He leads the Process and Systems Analysis group within the Network Process Engineering, advancing the Process Analytical Technologies, implementation of real-time multivariate statistical process monitoring and control for biopharmaceutical manufacturing processes as well as applications in formulation and finish, and in monitoring and control of variation in raw materials including primary containers and media. He has a BS, MS and PhD all in Chemical Engineering from Istanbul University in Turkey.

BIOGRAPHY

Bryan Looze is a Senior Engineer in Process and Product Engineering at Amgen. His responsibilities in Process Analytical Technologies include implementing real-time multivariate statistical process monitoring, multivariate data analysis, and raw material information management and analysis. He obtained his BSc in Chemical Engineering from the University of Massachusetts and is currently pursuing his MS in Chemical Engineering from the Illinois Institute of Technology.

BIOGRAPHY

Sinem Oruklu is an Engineer in the Process and Product Engineering at Amgen. She earned her BS in Chemical Engineering from Middle East Technical University, Turkey and MS in Chemical Engineering from Illinois Institute of Technology, Chicago, USA. Her expertise is in the area of multivariate data analysis, real-time multivariate statistical process monitoring. Her current responsibilities include advanced process monitoring and troubleshooting support to biopharmaceuticals manufacturing at the Rhode Island facility.

BIOGRAPHY

Tony Wang is a Senior Engineer in the Process and Product Engineering at Amgen. He is responsible for multivariate data analysis and advancing Process Analytical Technologies, including Raman, NIR applications in raw materials and cell culture monitoring, as well as model predictive control. Previously he has worked in cell culture within Process Development and also as a process engineer within Facility Engineering at Amgen. Tony earned his BS degree in Chemical Engineering and MS degree in Biomedical Engineering both from University of Calgary in Canada. He is a licensed Professional Engineer within APEGGA.

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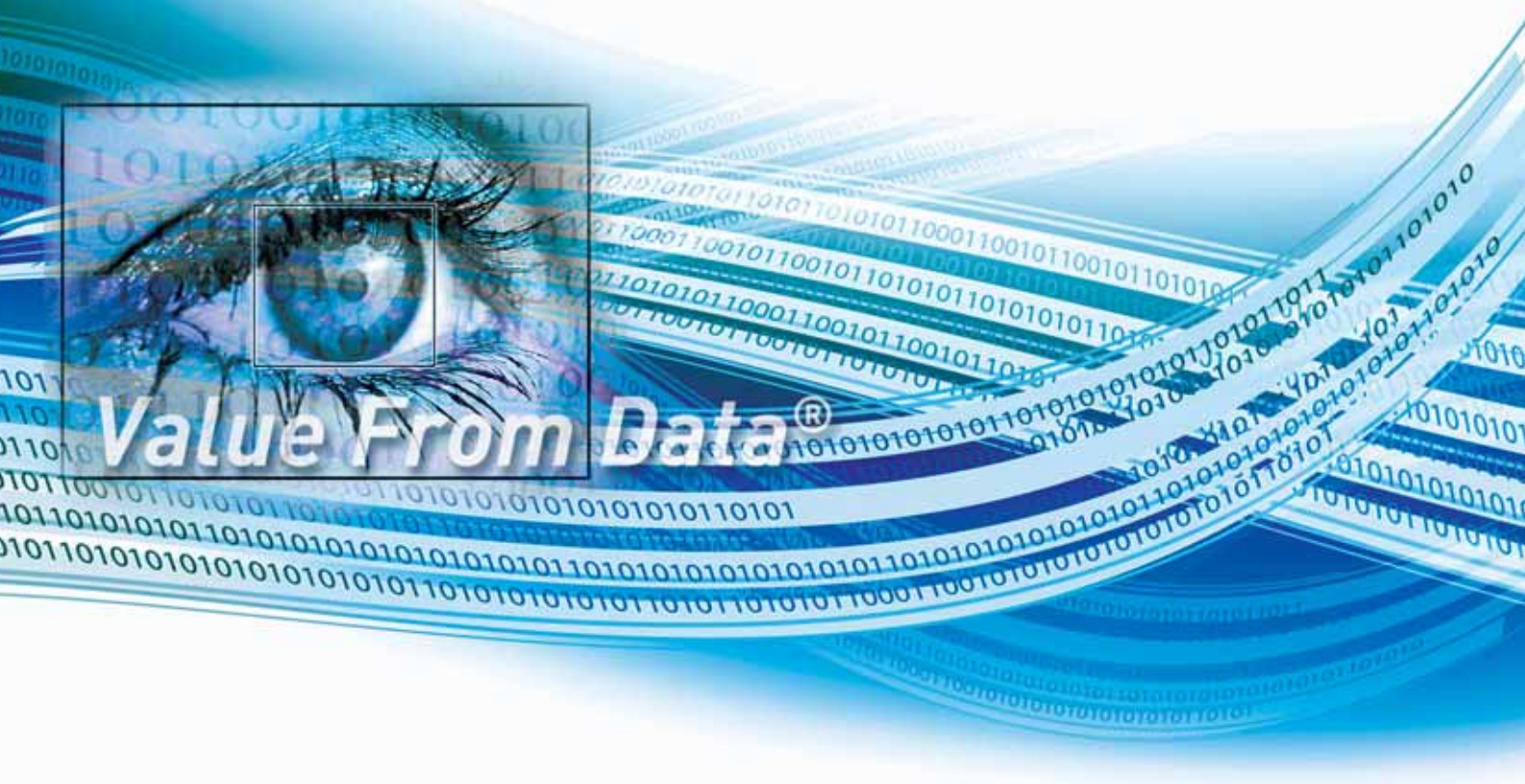

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CORRELATION BETWEEN POWDER RHEOLOGY DATA AND PROCESSABILITY IN SOLID DOSAGE FORM MANUFACTURING

Erik Skibsted
Principal Scientist, Oral Protein Formulation, Novo Nordisk

The Quality by Design (QbD) paradigm is being introduced to more and more R&D and manufacturing units in the pharmaceutical industry. There are many good reasons for this, e.g. clear scientific development routes, high product quality, focus on safety and efficacy, economy and increased process and product knowledge. Most often, there is a large focus on identifying the critical process parameters (CPP) that influence the product quality and should be controlled to consistently produce the same quality, but just as important a component in a QbD development strategy is characterisation of raw materials and to understand how variations in raw materials influence the manufacturing process and the critical quality attributes (CQA) of the drug product.

This article will show some preliminary results from powder characterisation and how the data correlates to process performance and drug product quality in solid dosage form development projects. Data from two development studies will be shown. The development and manufacturing of solid dosage forms relies heavily on powder material. API and tablet excipients are most often handled as a granular material. The powders are mixed and compressed to form a tablet. It is essential to characterise the mixing, flow and compression properties of the powders in order to be able to produce a high quality drug product. Traditional powder characterisation relies on static methods e.g. angle of repose, density and tapped density, but new techniques are emerging in the pharmaceutical R&D laboratory, for example, quasi- and dynamic techniques like compression methods and flowability tests performed under different conditions e.g. compression or aeration. By subjecting the powders to different environments during testing, the test results are more relevant when correlating them to process observations.

> **“ Key to understanding powder flowability is characterising the forces acting upon and between the particles ”**

Key to understanding powder flowability is characterising the forces acting upon and between the particles. A generalised depiction is shown in **Figure 1** on page 12. Each particle is affected by the gravity and the cohesive forces between the particles. The cohesive forces are Van der Waal forces. If particle one should be able to flow away from particle two and three, the gravity acting on particle one needs to exceed the cohesive forces between the particle and the neighbouring particles.

$$m_1 g > f_{coh\,a} + f_{coh\,c}$$

Study 1: investigating optimal mixing times for powders with different cohesiveness

A very important unit operation in solid dosage form is powder mixing. This process can be performed in many different types of equipment and controlled by various factors like speed and duration. In order to obtain a homogeneous blend, the powder must have sufficient flowability. The flow properties are highly dependent on the cohesive forces acting between the particles. In this study, the mixing

behaviour of three powders with different flow and cohesiveness was investigated.

The flow properties were measured by using a FT4 Powder Rheometer (Freeman technology, UK). With the FT4 instrument, a 25 millilitre powder sample was placed in a glass cylinder. A specially engineered blade is forced through the sample in a downward spiral movement with a constant tip speed. The energy required to move the blade from the top to the bottom of the sample was recorded. As the blade is moving, a stress transmission zone is created in front of the blade (**Figure 2**). For a cohesive powder, the stress transmission zone is small and transcends only a short distance in front of the blade. This is because a cohesive powder contains a lot of entrapped air that is removed when the blade is moved downwards. A small stress transmission zone means that a small amount of energy is required to move the blade at a constant speed to the bottom. For the non-cohesive powder, a large stress transmission zone is established during blade movement and a higher amount of energy is required. The non-cohesive powder has a small amount of air entrapped.

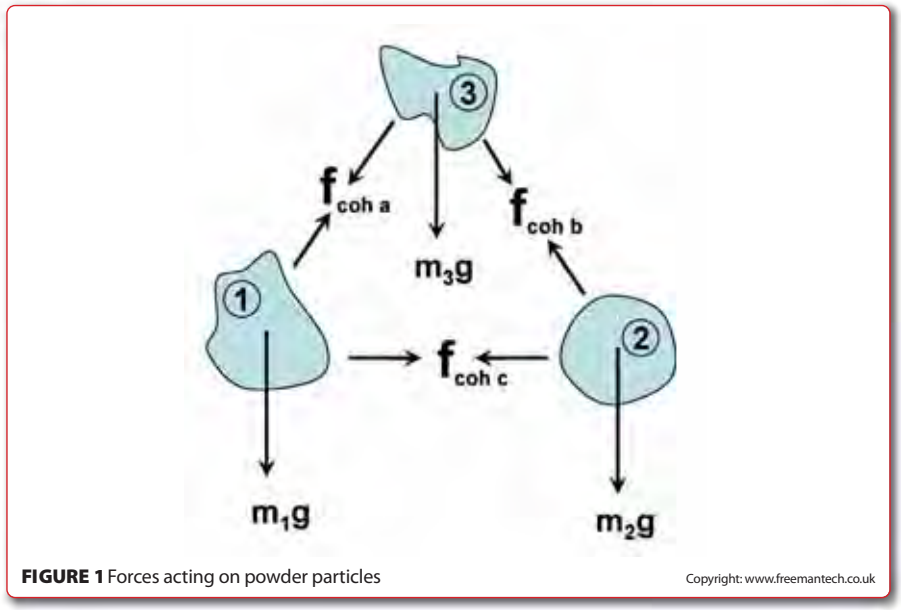

FIGURE 1 Forces acting on powder particles

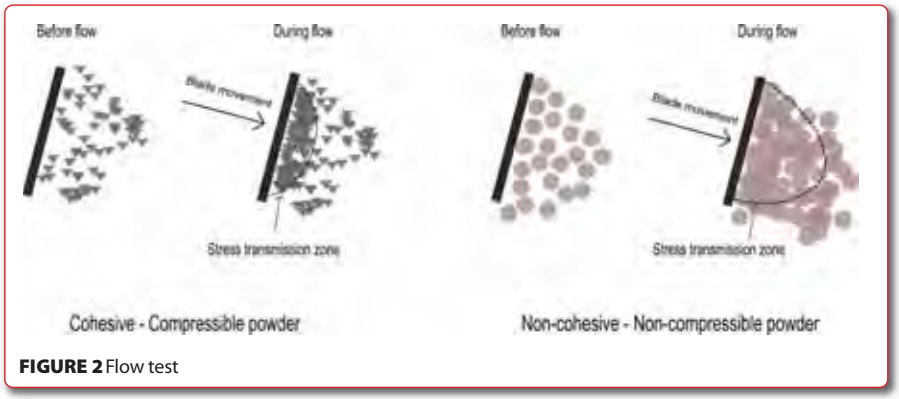

FIGURE 2 Flow test

In this study, the flow properties of three commonly used pharmaceutical excipients were characterised, i.e. micro-crystalline cellulose (MCC), hydroxypropyl methyl cellulose (Methocel) and Lactose. The test was carried out seven times using a constant tip speed of 100 mm/second (stability test). Then the test was performed four times using different tip speed i.e. 100, 70, 40 and 10 mm/second (variable flow rate test). MCC and Methocel were tested in triplicate and Methocel was tested once. The test results are depicted in **Figure 3**. It was clear that Lactose was the most cohesive powder followed by MCC and finally Methocel as the least cohesive powder.

> **“ A small stress transmission zone means that a small amount of energy is required to move the blade at a constant speed to the bottom ”**

To investigate the mixing performance, three different experiments were performed. Experiment A: 16.8 w/w % Lactose (high cohesiveness) mixed in MCC (middle cohesiveness), Experiment B: 16.8 w/w % Lactose (high cohesiveness) mixed in Methocel (low cohesiveness) and C: 16.8 w/w % Methocel (low cohesiveness) mixed in MCC (middle cohesiveness). Each experiment was performed in triplicate. The mixing experiments were carried out in small glass vials that were fixated in a rotary laboratory mixer. The vials completed 120 rotations and at 20 different time points (number of rotations), the mixer stopped, the vials were removed and placed on a near-

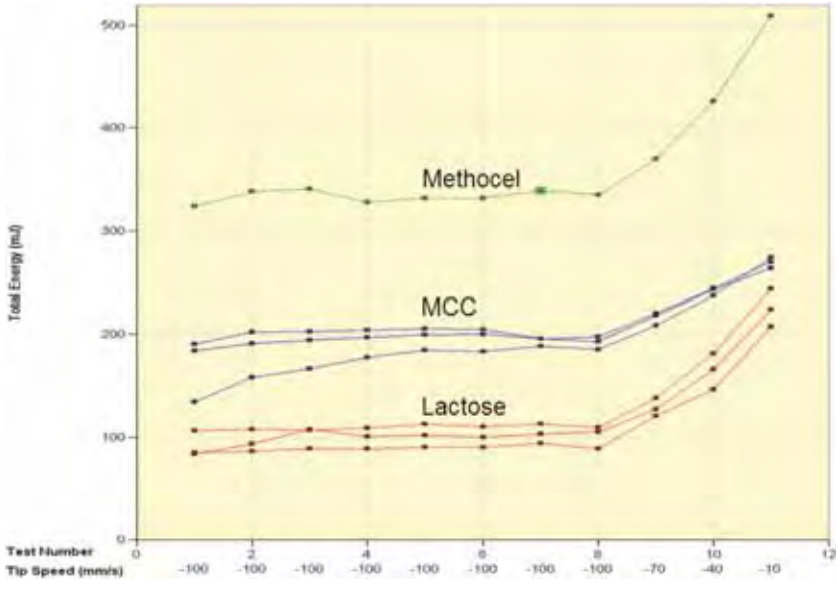

FIGURE 3 Results of stability and variable flow rate test. Test number 1 to 7 shows the stability test and test number 8 to 11 shows the variable flow rate part

infrared reflectance measurement module (Bruker, FT-NIR MPA analyser) and a reflectance spectrum was measured through the bottom of the vial. Using built-in calibration models, the w/w % concentration of the minor component in the blend was predicted. By plotting the percentage versus number of rotations, mixing curves for each experiment were generated. When the mixing curve is stabilised on the target value, the blend is homogeneous. The average and standard deviation (N=3) for each of the experiment types is plotted in **Figure 4** on page 14. When mixing high cohesive Lactose in medium cohesive MCC, the blend was first homogeneous after 80 rotations. When mixing high cohesive lactose in low cohesive Methocel, the blend was homogeneous after 40 rotations. In the last experiment, low cohesive Methocel was mixed in medium cohesive

> **“ Samples of formulation excipients and formulation blends were characterised by five different tests using a FT4 Powder Rheometer ”**

MCC and this blend was homogeneous after 18 rotations. The mixing curves for Methocel in MCC was also much more stable compared to the two other experiments, indicating that it was truly homogeneous. The study shows how the cohesiveness of the powder components has a high impact on the mixing performance. Increasing cohesiveness requires longer mixing times in order to obtain a homogeneous blend.

Study 2: Characterisation of formulation blends and process performance

When the powder blend is mixed homogeneously and ready to be applied in the tableting process, it is important that the powder can flow in a consistent manner from the hopper and into the dies in the tableting machine. This is important as non-optimal flow will affect the dose uniformity and up-scaling will be difficult.

In this study were two different formulations showing distinct different behaviour during tableting in pilot scale manufacturing. Formulation A showed bad flow properties during tableting as the blend was not flowing out of the hopper in a steady flow but was creating a ‘rat hole’ in the centre of the powder bed (**Figure 5C**, page 14). Formulation B showed nice flowability in the hopper during tableting (**Figure 5B**, page 14).

Samples of formulation excipients and formulation blends were characterised by five different tests using a FT4 Powder Rheometer. From each test, the software calculated parameters that summarised the test results. In total, 33 parameters were calculated from the four tests. Seven blends with formulation A, seven blends with formulation B and six excipients were characterised by the tests creating a data matrix of 20x33 data points, each row representing a powder sample. The data matrix was imported into a software program for calculating multivariate statistical models (SIMCA 13, Umetrics). A principal component analysis (PCA) model was fitted to the data. Four principal components could describe 89 per cent of the original variation in the 33 parameters. When the score values for principal component 1 (PC1) and 2 (PC2) were plotted in a 2D score plot (**Figure 6**, page 14) it was clear that excipient samples 1, 2 and 3 that were used in Formulation A, and the formulation A blend

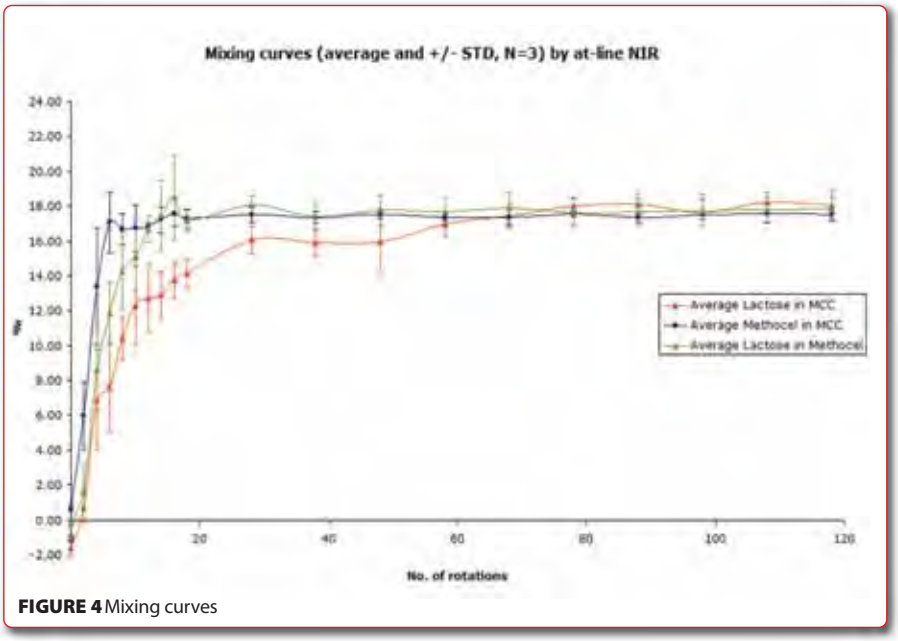

FIGURE 4 Mixing curves

samples were all grouped in a cluster in the lower part of the plot. Excipient 4 and 5, used in formulation B together with formulation B blend samples, were all clustered in the upper part of the plot. Excipient 6 was clearly completely different from all other powder samples. Excipient 6 was magnesium stearate which is an extremely fine and highly cohesive powder that has very bad flow properties. By investigating the loading plots from the PCA model, it was found that it was the parameters from three of the five tests that discriminated the two formulation types i.e. a shear test, a flowability test and an aeration test.

> "The PCA model approach seems to be a useful tool to evaluate many characterisation parameters at the same time"

The PCA model approach seems to be a useful tool to evaluate many characterisation parameters at the same time. If more test parameters can be used to discriminate between good performing and bad performing powders, the combination of numerous test parameters and PCA modelling could have a higher discrimination power compared to using only one parameter from one test. When the PCA model is established, future samples can be analysed and their test parameter results can be projected onto the score plot. The relative position to the two clusters in the plot can be used to assess the process behaviour of the sample.

Summary

When a QbD development strategy is being used it important to identify and control process factors that control drug product quality. But it is also as important to characterise material parameters and understand how their variability influences the processability of the materials as well as the drug product quality. In the two examples, presented powder characterisation with a modern rheometer was used to understand mixing performance as well as flow properties in two solid dosage form manufacturing studies

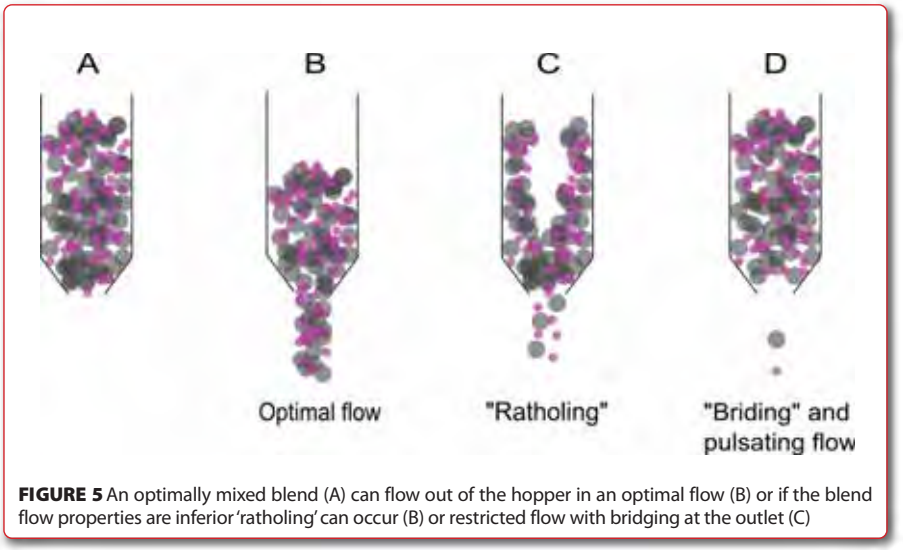

FIGURE 5 An optimally mixed blend (A) can flow out of the hopper in an optimal flow (B) or if the blend flow properties are inferior 'ratholing' can occur (B) or restricted flow with bridging at the outlet (C)

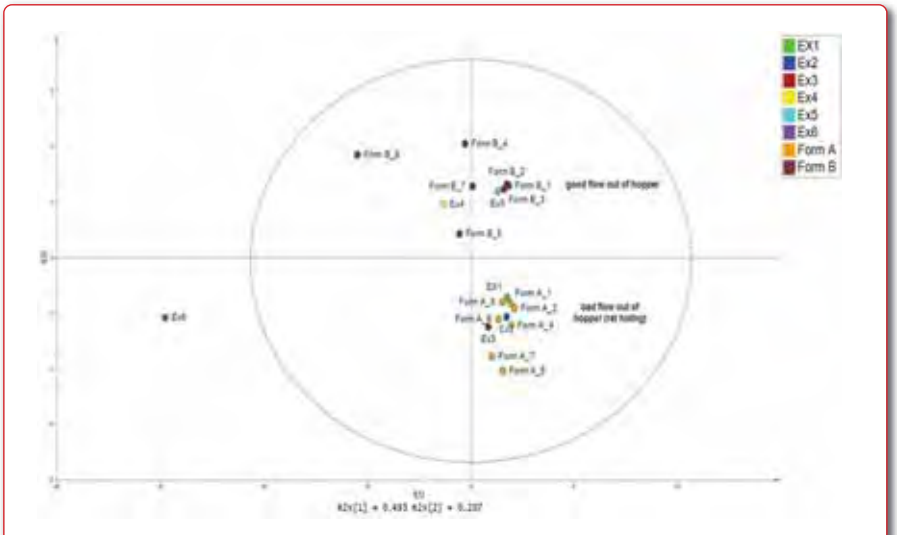

FIGURE 6 Score plot of PC1 versus PC2. The dotted ellipse shows the 95 per cent confidence interval

BIOGRAPHY

Erik Skibsted graduated with a Masters in chemistry from the Technical University of Denmark. In 2005, he joined Novo Nordisk as a research scientist working with spectroscopy, chemometrics and advanced trouble-shooting. After being appointed principal scientist in 2007, Erik became responsible for spectroscopy, chemometrics, quality by design and risk assessment in Oral Protein Formulation in 2009.

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To get the best out of process analytical technology tools, vendors and clients should discuss the needs and abilities of both sides to develop and discover what can be achieved. Four expert industry users of process analytical technologies for pharmaceuticals pose one pressing question each for four leading vendor experts of process analytical technology.

David Littlejohn
Associate Deputy Principal, Research and Knowledge Exchange, University of Strathclyde

Q Process analysers are in most instances quite large and expensive; what approaches will instrument manufacturers take to make process analysers smaller, less expensive and smarter, so that they are accessible to a larger number of users and applications, particularly SMEs, but without compromising performance in terms of spectral resolution and sensitivity?

Robert Mattes
Applications Scientist, Foss NIRSystems, Inc.

A The FOSS XDS Process analyser line has already been redesigned to a smaller integral package with a footprint approximately 19"x 14" and remains the low cost solution to in-line analysis. NIR is well suited for process real-time analysis because it can be utilised with no sample preparation, used with multiplexed fibre optic probes, and is robust in industrial environments. Process NIR instruments are designed to be used in-line to measure multiple parameters from each spectrum. There is a range of different process analysers available depending on the need of the customer's application. Dedicated process analysers can be made smaller and less expensive, but with the disadvantage that they are limited in their spectral range and sensitivity. FOSS is continually advancing the technology to improve process performance and sensitivity while at the same time reducing the process analyser size. This in combination with continued chemometric software and process communication development will make the analysers not only smaller, but also more user-friendly and 'smarter'. The major advancement in NIR technology is the improvement of signal-to-noise in these modern instruments. High resolution is not useful in the NIR region because the bands are naturally broad (10 nanometres or more). Signal-to-noise determines reproducibility and quantitative detection limit. Global companies around the world share calibration models making instrument matching and model transferability critical. FOSS process instruments and software are designed to meet these transferability requirements.

Julian Morris
Emeritus Processor, Technical Director Centre for Process Analytics and Control Technology, University of Newcastle

Q The use of multivariate statistical process control software for batch processes often raises questions as to the way the data is manipulated and the impact that this may, or may not, have on the performance of the process monitoring task. Different vendor companies such as UMETRICS, CAMO, PROSENSUS, etc. adopt different approaches, as witnessed in some recent discussions on LinkedIn. What are software vendor companies doing to make sure that non-expert users, particularly in SMEs, are able to understand and reliably use such software without potentially compromising the detection and diagnosis of subtle process malfunctions?

Petter Moree
Director, GPM, UMETRICS

A Misleading results from software can come from errors/bugs in the software or incorrect use of the software. Umetrics tries to avoid bugs in the software by adopting good programming standards and a large investment in testing and validation.

Incorrect use of the software usually comes from a lack of understanding of the methodology and thereby use of a technique that by itself can be perfectly okay but does not fit the problem. One example is multiple linear regression (MLR), which is a very useful technique for data that comes from Design of Experiments but can be very misleading when used on highly correlated X data.

Umetrics has had from the start a strong focus on publishing papers, giving seminars, providing comprehensive documentation, running formal training courses and has, during the last few years, had a large number of one-to-one webinars with customers all with the goal to increase knowledge and understanding for our customers.

The final responsibility to ensure proper use must be with the user rather than the vendor.

The responsibility the vendor has is to provide reliable software tools as well as ways to learn how to use the tools.

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Mario Hellings
Senior Scientist at Janssen, Johnson & Johnson

Q Are Bruker looking for improvements for more automated lab analyses (more than just a sample wheel) and also in being able to tackle more thick tablets in transmission mode as these two items are currently limiting once related to e.g. the Bruker MPA. Additionally, are Bruker looking at increased spot sizes to be able to cover more of the tablet during a uniformity measurement?

Holger Lutz
Intern. Manager Chemistry & Pharma, NIR & Process Technology Division, Bruker Optik GmbH

A For tablet transmission measurements with NIR, Bruker offers the MPA for method development and lab analysis as well as the TANDEM for online measurements of weight, thickness, diameter, hardness and NIR (mostly content uniformity and moisture content). For Bruker, it is very important that calibrations are exchangeable between these systems to optimise the calibration work starting at the development phase of a tablet up to the online process control.

Tablet handling and tablet positioning is always a great challenge – individual holders are necessary to avoid light leakage and the orientation of the tablet to the light beam is very important, too. The 30 position sample wheel with individual sample nests is already a good option to ease the daily lab work. Fully automated sample handling systems for the lab have not yet been requested, but are something we might have a look at in the future.

In general, the feasibility of NIR transmission measurements of a tablet needs to be tested for each and every type individually. For thick or dense tablets, Bruker offers the MPA with a high intensity option enhancing the NIR light throughput. Unfortunately, there might be some cases where a tablet can be too thick or too dense. A further increase in light intensity is however very dangerous in regards to heating up the sample and therefore not recommended.

Bruker's MPA offers one fixed spot size to be able to measure all sizes of tablets – from very small up to very big ones. Bear in mind that the NIR light does not cross the tablet in a direct way. The light is scattered inside the tablet covering a great amount of the volume before it is collected by the large collimator lens above the sample. Therefore, we see no need for larger spot sizes.

Steve Doherty
Process Analytical Scientist, Eli Lilly

Q The PAT guidance was issued in 2004, and the FDA subsequently advocated the use of both quality by design (QbD) principles and continuous manufacturing. Besides the regulatory oversight that occurs for pharmaceutical manufacturers, what other differences do you encounter between your pharmaceutical customers and those in other manufacturing areas that you think account for the slow uptake of these proven, enabling processes? Is your experience that the nature of the constraints is principally cultural, economic, or resource limitations (appropriate technologies and experienced personnel)?

Jan Verelst
Business Development Manager – SIPAT / PAT-QbD / Pharma, Siemens

A One might say a combination of different aspects could play a role in the slow uptake of PAT and QbD by the life sciences industry, for example, the conservative attitude towards the introduction of new technologies in the pharmaceutical industry, the reduced availability of PAT resources and technologies within the Pharma companies or the limited budgets released by upper management to invest in these initiatives. However, the fact is that it requires a change of mind set with regards to the validation aspect of this technology compared to the past, which does not mean it's not happening.

As the validation impact will be significant when bringing PAT into existing processes, the introduction of PAT happens at the Process Development stage for newly developed processes where often the visibility of the projects is lower or certainly less desired. Siemens' SIPAT solution for PAT Data Management has been largely introduced into R&D environments of the top five Pharma companies.

But also in the production area, PAT initiatives are taking off, certainly when applying it in continuous manufacturing initiatives, both in new lines as well as in converted existing processes. Slow uptake here was due to the availability of suitable technologies to allow for continuous processing in Pharma, now it's there for OSD application as a starter and the added value of PAT on top of these lines is obvious. SIPAT acts as a single front end solution for all PAT related activities, going from PAT-data collection, real-time PAT-data processing and Advanced Process Control to finally put the basis in place to come to Real Time Product Release.

Both in Process Development and in (continuous) manufacturing SIPAT is proving today its added value at multiple pharmaceutical companies worldwide, implementing QbD in their current processes.