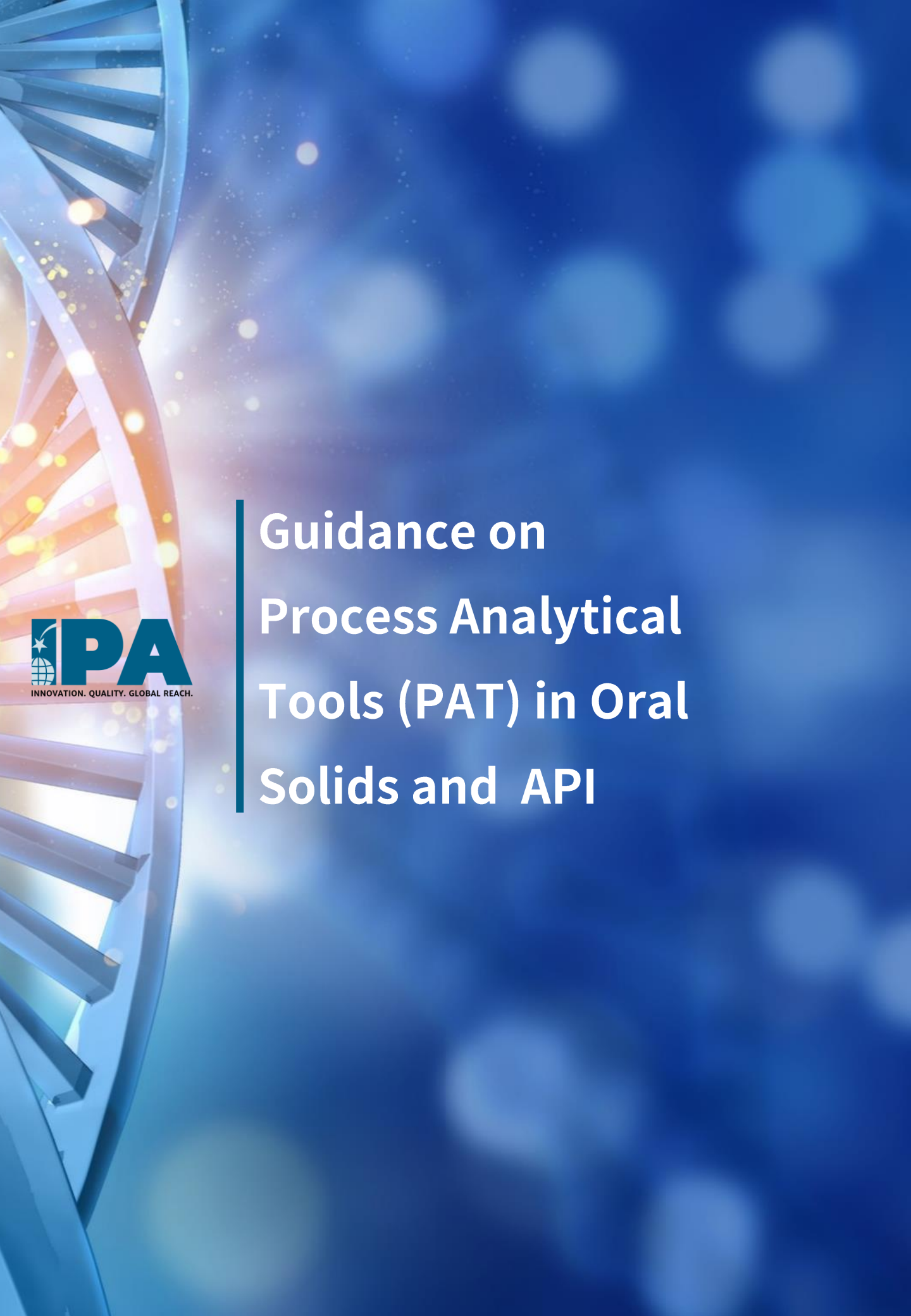
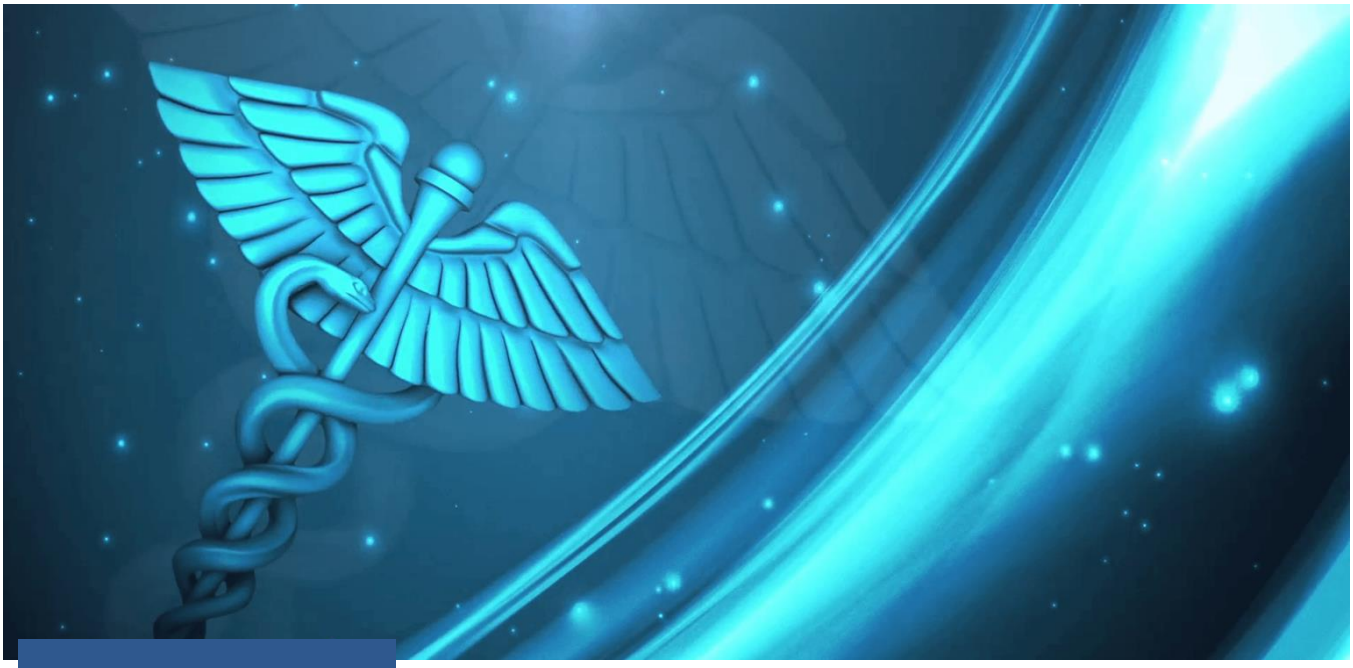


Guidance on Process Analytical Tools (PAT) in Oral Solids and API



PREFACE

In April 2015, The IPA launched its Quality Forum (QF) to help Indian pharmaceutical manufacturers to achieve parity with global benchmarks in quality. The QF made a commitment to a multi-year journey to address key issues facing the industry and develop best practices.

The QF focused on several priority areas in the last four years, namely, Data Reliability, Best Practices & Metrics, Culture & Capability, Investigations, etc. It took upon itself the challenge of developing a comprehensive set of Best Practices Documents for several of these topics. In this document, we focus on best practices for Guidance on Process Analytical Tools (PAT) in Oral Solids and API.

The six participating companies in the QF nominated senior managers to study the best practices and frame the guidelines. They are: Kalaiselvan Ramaraju (Sun Pharma); Pratik Patel (Torrent); Manish Parikh (Torrent); Aruna Khanolkar (Cipla); Sanjay R Sharma (Zydus Lifesciences); Amol Galande (Lupin); S Sri Rama Murty (Dr Reddy's Laboratories).

The IPA wishes to acknowledge their concerted effort over the last 12 months. They shared current practices, benchmarked these with the existing regulatory guidance from the USFDA and other regulatory bodies such as UK MHRA, WHO, etc., developed a robust draft document and got it vetted by a leading subject matter expert and regulatory agencies. The IPA acknowledges their hard work and commitment to quality.

The IPA also wishes to acknowledge the CEOs of six member-companies who have committed their personal time, human resources and provided funding for this initiative.

This document, to be released at the IPA's 9th Global Pharmaceutical Quality Summit 2024, will be hosted on the IPA website www.ipa-india.org to make it accessible to all manufacturers in India and abroad.

CONTENTS

1 Process Analytical Technology : Introduction and Implementation

Introduction :

The conventional understanding of pharmaceutical quality involves testing of a finished product in a quality control lab, and depending on the result, accepting or discarding the batch if the specifications are not met. The alternative approach is a concept of Process Analytical Technology (PAT) for real time monitoring of quality during the manufacturing process. There is a need of guidance for the implementation of PAT in a manufacturing site emphasizing the necessary pre-requisites, interpretation of the data, and selection of suitable tool(s).

Purpose :

The objective is to discuss the role of PAT and provide guidance for the implementation in key unit operations of solid oral pharma manufacturing.

Scope :

- This document is applicable for process analytical tools in key unit operations of pharmaceutical solid oral dosage form and API manufacture.
- This document is focused on the benefits to the pharma industries planning to implement PAT tools for real time monitoring of a manufacturing process, and to train the PAT team involved in implementation and operation.
- It does not discuss the installation and maintenance support provided by the vendor.
- The brands and models specified in this document are examples of products in the market, and are not recommendations.

PAT in a Regulatory Perspective :

PAT is defined by US FDA (PAT guideline 2004) as *"A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality". As per ICH Q8 - R2 (2009), Quality by Design (QbD) is "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and Quality Risk Management"*

The US FDA (PAT guideline 2004) states that "Quality cannot be tested into products. It should be built-in by design". "A desired goal of the PAT framework is to design and develop well understood processes that will consistently ensure a predefined quality at the end of the manufacturing process". Thus, PAT is part of QbD. PAT is also an investment in the process economy for real time batch release and reducing QC load apart from ensuring product quality. It is a recommendation, not yet a regulatory demand.

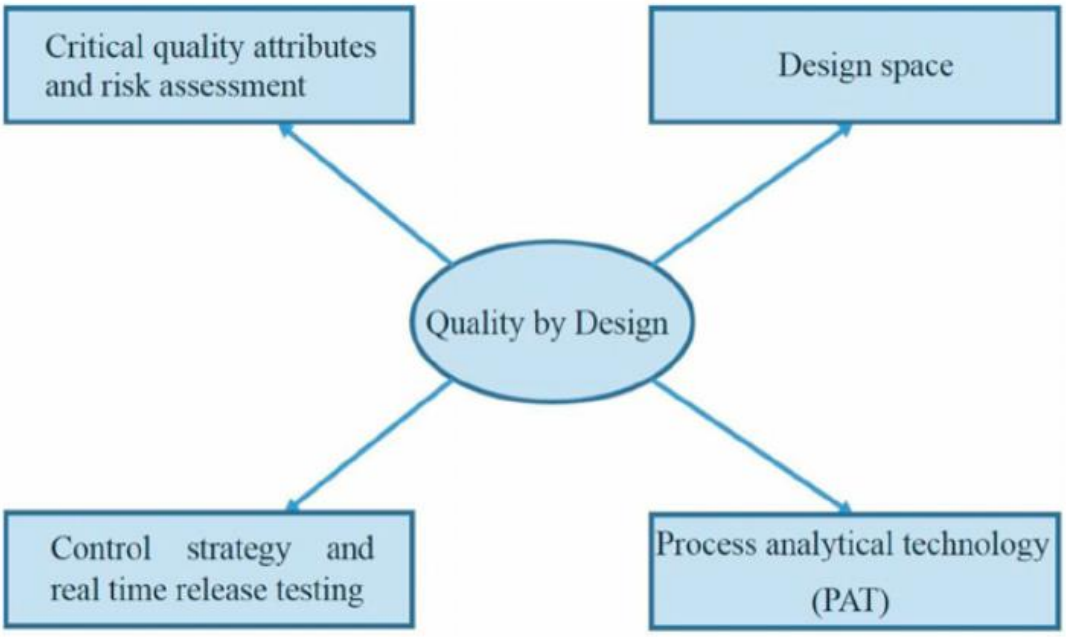


Figure 1 : PAT as part of QbD

"Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach (FDA cGMP guidance 2004)" and "*Innovation and Continuous Improvement in the Pharmaceutical Industry* (book chapter in 'Pharmaceutical process scale-up' 2005) highlight the support of FDA for continuous improvement in pharmaceutical manufacturing. As a direct consequence of the "cGMPs for the 21st Century" initiative, the pharmaceutical industry is experiencing pressure from the regulator to address concerns around limited process understanding, process inefficiencies and continuous process improvement through the adoption of PAT.

PAT for Ensuring Consistent Quality :

In absence of PAT, the manufacturer is bound to work in a narrow limit of a process parameter, for example, blending or kneading for 10 minutes. However, the process end point should not be dependent on a clock; rather, it should vary based on the input material attributes to get the consistent output quality. With the support of PAT, it is possible to set a range for the process time (for example, 10 to 20 minutes).

As per the US FDA (PAT guideline 2004), *"a process end point is not a fixed time; rather it is the achievement of the desired material attribute. This, however, does not mean that process time is not considered. A range of acceptable process times (process window) is likely to be achieved during the manufacturing phase and should be evaluated, and considerations for addressing significant deviations from acceptable process times should be developed".*

It further states that *"Currently, most pharmaceutical processes are based on time-defined end points. However, in some cases, these time-defined end points do not consider the effects of physical differences in raw materials. Processing difficulties can arise that result in the failure of a product to meet specifications, even if certain raw materials conform to established pharmacopeial specifications".*

Input raw materials, machine and environmental factors may vary within the defined limits, yet cumulatively these factors may impact the output consistency. A PAT based process monitoring ensures the consistency in output quality by allowing a range of parameter or variable process time.

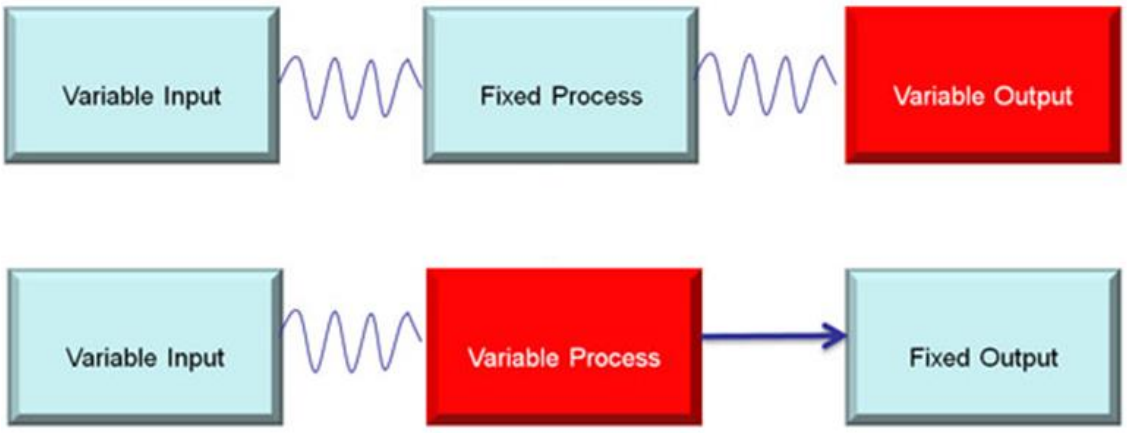


Figure 2 : Variable process giving consistent quality

Pre-requisites :

- Process understanding is a mandatory requirement.

- A thorough research on the underlying scientific principles behind the pharmaceutical process is necessary, in order to correlate the critical process parameter (CPP) or in-process critical material attribute (CMA) with the final product critical quality attribute (CQA).

- Design of experiments are necessary, ultimately developing a multivariate model that defines how variability of the CPPs affects the CQAs, and the boundaries where the CPPs can operate and produce a quality product.

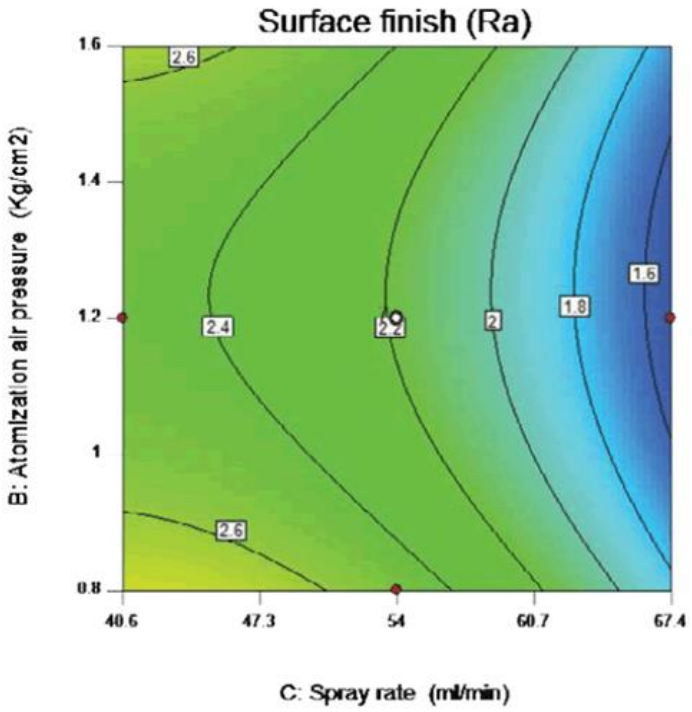


Figure 3 : Typical design space for the process parameters

Various Modes of Measurement :

Off-line : Sample analysis away from the process stream (e.g., QC lab).

At-line : Analysis close to the process stream (CU test by NIR tool next to the tablet press).

On-line : Analysis by diverting sample to the side stream in parallel to the main stream manufacturing process. The sample may be returned to the main stream after analysis (e.g., measurement of cell density in an anaerobic fermentation process using flow through cell).

In-line : Analysis within the process stream, without removing sample (e.g., NIR tool attached to a blender for scanning powder through a glass window).

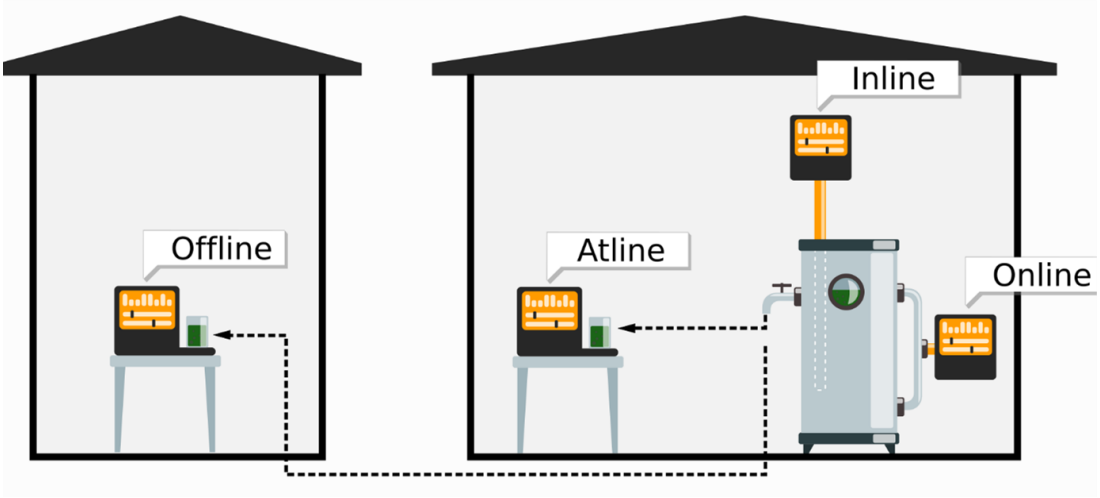


Figure 4 : Various modes of process monitoring

PAT Tools for Real Time Batch Release :

There are various PAT tools available in the market for each unit operation. The user needs to identify what to monitor in the process based on the critical attribute of the in-process material or the critical process attribute which can impact the final product quality, based on a risk assessment. For example, a polymer content (instead of API) in the blend may be monitored in case of modified release formulation.

Table 1 : PAT Tools for various unit operations

Sr. No.	Stage	Critical Parameter	Available PAT Tools
1	API manufacturing	Identification of molecule and estimation of concentration	Real time Raman process spectrometer
		Crystallization end point – particle size	Focussed beam reflectance measurement (FRBRM), Laser diffraction method
2	Powder blending	Water content	NIR tool
		Blend uniformity	
3	Fluid bed process (fluid bed granulation and pellet coating)	Water content	Microwave moisture analyser, NIR moisture analyser tools
		Residual solvents	Process mass spectrometer (e.g., Promaxion)
		Particle growth rate/end point	Malvern's Parsum/Eyecon

Procedure for Implementation :

1. Forming a PAT team: a group of experts should be formed with representatives from development, manufacturing, quality control, quality assurance, and regulatory affairs. A data analyst/statistician should be present in the team as well. It is recommended to have a facilitator to see the implementation from an overall perspective. The facilitator may also be the contact person with FDA or other authorities.

2. Reviewing the process to identify the risk on CQA :

- The process flow chart should be reviewed with current control points.
- The CQA should be correlated with process control points.
- The historical data should be reviewed to identify the sources of variability.
- Out of Specification (OOS) or Out of Trend (OOT) data, and Corrective and Preventive Action (CAPA) information should be reviewed.
- Specifications should be evaluated with a risk-based approach.
- An attempt should be made to correlate the yield difference with process parameters and with output quality inconsistency.
- Multivariate data analysis tools or statistical process control techniques should be used to find correlations and possible problem areas.
- The in-process quality attribute or parameter should be identified.
- Possible PAT applications for monitoring the identified in-process quality attribute or parameter should be investigated.
- Possible suggestions may be found by a literature search and by contacting vendors for the choice of real time monitoring tools.
- There should be an analysis of the accuracy or sensitivity, pre-requisites for installation, price and operational complexities and errors, if any. For example, a direct/impeller torque sensor installed near the impeller in rapid mixer granulator is more sensitive and reproducible than an indirect torque calculation from motor power consumption. However, it needs around 30 cm space to install.

- The impact of installation, if any, on the product, should be analyzed. For instance, does it impact the existing process? Or is the probe coming into contact with the product?

- If the sensor is coming into contact with the product, it is important to ensure that it complies with the MOC (material of construction) requirements (recommended stainless steel grade), GMP norms, cleaning procedure in place (with the support of vendor) following site quality SOPs, if any.

- A model should be developed using analytical support and statistical applications in order to predict a process end point or define a process signature.

- If the measurement replaces an existing QC analysis, then a comparative dataset is also required for regulatory filing, which is not required in case the PAT is used for process understanding.

- A qualification protocol needs to be prepared and, if required, it may be communicated with the regulatory agency for any queries.

- A model validation report and comparative data from multiple batches (20-30 batches) with existing QC method and PAT employing statistical analysis tool should be prepared. This may be used to justify the real-time batch release.

Validation of PAT:

- Multivariate statistical process control can be feasible and valuable in order to realize the full benefit of real time measurements. Quality decisions should be based on process understanding and the prediction and control of relevant process/product attributes. This is one way to be consistent with relevant CGMP requirements, such as control procedures that validate the performance of the manufacturing process (21 CFR 211.110(a)).

- Risk-based approaches are suggested for validating PAT software systems. The recommendations provided by other FDA guidance documents, such as “General Principles of Software Validation,” should be considered. Other useful information can be obtained from consensus standards, such as “ASTM.”

- The predictive ability of the established correlation functions and multifactorial relationships is considered a key indicator of process understanding in such cases.

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Regulatory Filing for Real Time Batch Release :

- PAT can be implemented under the facility's own quality system. CGMP inspections may be done by the PAT Team or PAT certified investigator. The data collected for the purpose of improving process understanding, would be considered research data and would not normally be relevant for regulatory inspections.

- A supplement (e.g. CBE, CBE-30 or PAS) can be submitted to the regulatory agency prior to implementation, and, if necessary, an inspection may be performed by a PAT Team or PAT certified Investigator.

- A comparability protocol may be submitted to the agency outlining PAT research, method development, validation and implementation strategies.

- The combined PAT data and other test data gathered during the manufacturing process can serve as the basis for real time batch release (e.g., in process stage blend uniformity or compressed tablet content uniformity) and would demonstrate that each batch conforms to established regulatory quality attributes.

In practice, a series 10 to 30 commercial batches are used in NIR-PAT validation for blend uniformity and tablet content uniformity in order to establish a correlation with approved QC analytical data and build a confidence on the PAT based batch release. The ability to identity occurrence of non-compliance needs to be established by negative experiments.

US FDA (PAT guideline, 2004) insists that *"an approval should be obtained prior to implementing real time release. Process understanding, control strategies, plus on-, in-, or at-line measurement of critical attributes that relate to product quality provides a scientific risk-based approach to justify how real time quality assurance is at least equivalent to, or better than, laboratory-based testing on collected samples. Real time release as defined in this guidance meets the requirements of testing and release for distribution (21 CFR 211.165)".*

"Data from production batches can serve to validate the process and reflect the total system design concept, essentially supporting validation with each manufacturing batch" as per USFDA (PAT guideline, 2004).

Implementation Challenges and Resolutions :

"A Risk-Based Approach" and "Innovation and Continuous Improvement in the Pharmaceutical Industry" highlight the support of FDA for continuous improvement in pharmaceutical manufacturing. However, there is some reluctance in implementing PAT tools in industries due to :

- Lack of expertise/experience in selection of tools, implementation and interpretation.
- Need for model development, validation, supplementary/variation filing and approval for real time batch release.
- Burden of investment (cost, time, manpower and other resources) amid ongoing cost reduction programs.
- Hesitation to change a validated and approved process that may require regulatory approval again.
- One could debate that "It's just a recommendation, not a regulatory demand. It is neither good to jeopardize an existing approved product nor to introduce it in the ongoing developments due to time limits."
- US FDA (PAT guideline 2004) has indicated in its guideline that PAT data is "research data", which is not audited by the agency as long as it is used for improved process understanding. It is reviewed only when it is proposed as an alternate to QC method.

Other possible resolutions :

- Strategic initiative: if PAT is being implemented as a pet project at the manager or director level, there is a significant risk of failure. It involves a significant investment of time, resources, and expertise leveraged across sites (preferably a dedicated PAT team). It should only be undertaken with the sponsorship of top management.
- Quantified justification: the business case should be developed for an entire program over five years. Costs analysis must include additional personnel, training, instrumentation, software, support agreements, and computing resources. The benefits should include (i) increased quality, (ii) faster product release, (iii) reduced cycle time, (iv) labor cost and (v) improved energy savings. The credit for improved quality may be financially reflected as reduced batch failures, or reduced wastage or increased revenues. Improved quality could also result in better yield. Faster product release or real time release may allow material to flow through the process faster saving time and money. In many cases, materials are over-processed due to clock-based end point. The PAT-based end point can reduce the cycle time and hence save time and energy cost. PAT can reduce the number of samples submitted to the QC lab and reduce labor costs.

- Generating a clear business case based on tangible information and realistic assumptions is a key part of getting the organizational commitment for a successful program. Process development (PD), quality, manufacturing, and regulatory areas must ultimately be convinced of the benefits.

- System architecture planning: implementing PAT is more than purchasing analytical instruments. It should be viewed as an overall system, including instruments, modelling software, data management, process control, and integration of the components. This must be considered while projecting the business case.

- Cross-organizational involvement: successful implementation of PAT is a team effort requiring the willing participation of (i) process development, (ii) analytical development, (iii) manufacturing, (iv) quality, and (v) regulatory departments. The PD team would develop all new processes to utilize available PAT technologies. PD and AD are responsible for chemometric model development. The role of manufacturing is to deploy and support the PAT systems within production. The department must have the expertise to maintain the equipment and systems, and it is responsible for implementation of process control strategies through PAT. The quality department is ultimately responsible for the release of the product; therefore, it is necessary for quality team to be aligned with CQA - PAT correlation model proposal. The regulatory department submits documentation to regulatory authorities to get the process approved. If the PAT method is being introduced in to a process that is currently producing an approved product, the regulatory department will submit a variation in the approved process. This could include providing evidence that the new PAT is equivalent or better than the method it is replacing.

- The additional workload and skill sets cannot be viewed as just another part-time job heaped upon already overloaded people. This will cause failure of the program. It does make sense to rely on contractors with expertise to start the program. However, it is not possible to outsource the entire program.

- Program plan: The program plan should include a phased approach toward implementing the architecture, ensuring the right skills are in place, and a roll-out plan of how and when PAT will be deployed in production. It is possible the program plan could establish that PAT will only be included for new products to reduce the regulatory burden of approving changes to processes in production. Or, it may be started in a high-volume product that will deliver lots of benefit. Obtaining overall organizational commitment and applying good planning and resources are the keys to success.

References :

1. Heinze CL & Hansen JR (2005); Implementing PAT step by step as a process optimizing tool. *Pharm. Eng*., 25, pp.1-5.

2. Methfessel J & Roy JR (2006); A practical approach to PAT implementation, *Pharm Tech Eur*, 18, pp.13-25.

3. USFDA, Office of Regulatory Affairs (Sep 2004) : *Guidance for Industry PAT – A frame work for innovative pharmaceutical development, manufacturing and quality assurance.*

4. ICH guideline Q8-R2 (2009) : *Pharmaceutical Development*

5. USFDA, Office of Regulatory Affairs (Sep 2004) : *Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach.*

6. Hussain AS (2005), *Innovation and continuous improvement in pharmaceutical manufacturing*, in M Levin (ed.), Pharmaceutical process scale-up, 2nd edn, CRC Press, New York.

7. Lustri J, 'How to Implement PAT in Pharmaceutical Manufacturing'. *International Society of Automation*. Viewed on 15 May 2024. https://blog.isa.org/how-to-implement-process-analytical-technology-in-pharmaceutical-manufacturing.

2 Nir Spectroscopy for Blend Uniformity Monitoring

Introduction :

- The main purpose of this document is to serve as a guide for using near infrared (NIR) spectroscopy for blend analysis.
- This guide is not intended to be exhaustive; it is to provide a framework for users in their NIR spectroscopy journey and help achieve a successful method development.
- Blending is an integral step for the production of any solid dosage form product. Because of the erroneous sampling and time consuming offline chemical analysis, there was a need for an alternative method.
- A non-invasive NIR method has been used extensively for inline and online blend monitoring in batch as well as continuous manufacturing processes, using an interface or a probe with optical cable, respectively. Online or inline approaches for blend uniformity (BU) measurement gives a far greater understanding of the blending process.
- This document outlines the requirements for applications in which NIR spectroscopy (NIRS) is used inline for qualitative and/or quantitative analysis for blending process.

Instrumentation :

- Critical parameters to be considered while selecting the NIR instrument are light source, light dispersion principle of the optical system (e.g., grating, FT-IR), the detector type (e.g., silicon, lead sulphide), the measurement method or mode (e.g., reflectance, transmission, transflectance) and the wavelength/wavenumber range used.
- The wide applications of NIR for blending has created a growing interest in smaller size, lower cost, highly robust, easy to operate instruments with ergonomic profile.
- Inline blend monitoring places specific demands on NIR instrumentation including wireless communication, battery operation, rapid data collection, appropriate hazards and cleaning rating and software-hardware validation and qualification.
- The instrument can be adaptable to lab, pilot, and production scale blenders to follow the development of the product.

- The wireless NIR instrument used for real time blending process monitoring in bin blenders (Octagonal/V-shape/IPC) have different technologies like diode array (Corona® from Zeiss and Lancir II® from CPS Bruker), linear-variable filter (MicroNIR™ from Viavi), acousto-optic tunable filter (Luminar from Brimrose), micro-electro-mechanical optical systems (SentroPAT BU from Sentronic), etc.

Spectra Acquisition :

- Using these NIR instruments, the blend sample measurement is highly simplified, and it is possible to record characteristic spectra in diffuse reflection mode without direct contact and through an interface in a dynamic mode.

- These instruments are mounted onto the lid of the bin blender. The lid has a sapphire window through which the NIR measurements are taken. The instrument contains an acceleration sensor, which determines the position of the blender. Thus, the spectrometer is triggered to acquire an NIR spectrum when the blender is upside down, which is the point when the sapphire window is covered with powder. Each rotation triggers an acquisition of NIR spectra.

- Spectra are sent wirelessly to a computer and imported into custom-made acquisition and analysis software. The spectra collection has a response time of less than a few seconds to allow real-time, inline, monitoring of the blend homogeneity.

- NIR spectra are acquired in real-time and using appropriate data pre-processing and chemometric analysis, blend 'homogeneity' plots are derived. NIR spectra collected in real-time for a blending process are shown in Figure 1.

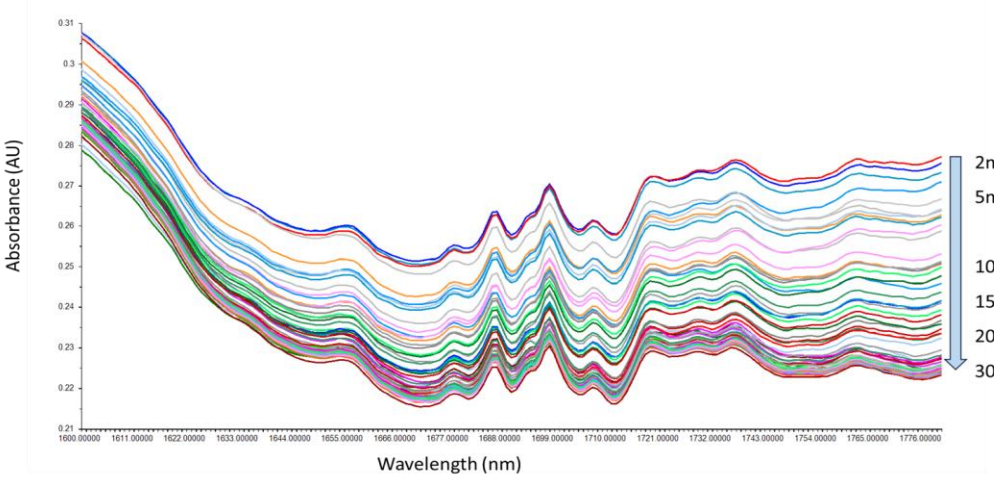


Figure 1 - Overlapping of NIR Spectra with the increase in the blending time

- With increase in blending time, the spectra begin to converge and overlay over each other.

- The spectra can be pre-processed and subjected to chemometric analysis to determine the homogeneity of the spectral data using qualitative or quantitative model development.

- Qualitative methods either rely on the fact that during blending spectral variance is reduced as components are mixed, or that blend spectra approach an 'ideal' reference spectrum.

- One of the earliest and most popular methods is to calculate the moving block standard deviation (MBSD), which monitors spectral variance in a block of spectral data progressing with time.

- Similar qualitative analytical methods that analyze qualitative change in the spectra without direct use of reference spectra are based on the chi-square analysis, bootstrap error-adjusted single-sample technique, mean square of difference, principal component (PC) score-plots or PC score distance analysis. Qualitative methods that compare blend spectra to a training set (supervised methods) include conformity index, dissimilarity, PLS discriminant analysis, SIMCA and PC-MBEST.

- The moving F-test method removes some of the challenges of both qualitative and quantitative methods mentioned before. It provides a probability-based approach with a more detailed statistical analysis and relates the non-uniformity risks to the regulatory BU criteria. The end-point criterion is defined statistically, not empirically and thus does not suffer from threshold ambiguities as with the MBSD. It also offers simpler calibration and better transferability to different blenders.

- Typically, rate-of-change models are used to monitor and detect the endpoint of blending. A predefined threshold is set, and the endpoint usually will coincide with the measured rate of change reaching a predefined threshold that indicates that the process is complete.

- These models can be based on a change in (1) the concentration of the active ingredient or other component, or (2) the spectral magnitude related to the component of interest.

- For blends in which a component of interest is present in a low concentration, the risk exists that the endpoint represents a uniformity of the major components. For these blends, the endpoint criteria should indicate a uniform distribution of the low-level component.

- If a rate-of-change model for blend uniformity is based on a quantitative model for either the active ingredient or another component, the rate-of change model and the quantitative model should separately be developed and validated to ensure an accurate and reliable endpoint detection.

- An effective sample for NIR measurements is important and calculated considering the diameter of the NIR beam, the beam's depth of penetration, and the density of the sample. For monitoring blend homogeneity, the effective sample size should be comparable to a unit dose of the finished drug product.

Qualitative Analysis Using Moving Block Standard Deviation (MBSD) Method :

- Moving block analysis is a common method in determining blend homogeneity. A typical way is to calculate MBSD over a given block size (number of rotations) and observe the flattening in the MBSD value during the blending.

- The data are arranged into a time by wavelength matrix. A new matrix is calculated over all wavelengths by determining the standard deviation (SD) of intensity values over a predefined time-window or block. Finally, a mean value is calculated from each of the resulting SD spectra over all wavelengths. The mean SD can be plotted as a function of time, and the blending endpoint is determined to be the time interval at which the mean SD profile reaches a minimum value.

- The moving block standard deviation approach reveals qualitative information about the homogeneity and stability of blending processes and may also be used as a measure of conformance between batches.

- The definition of a ''minimum SD value'' has not been described yet.

- The determination of the blending endpoint using MBSD analysis is shown in Fig 2.

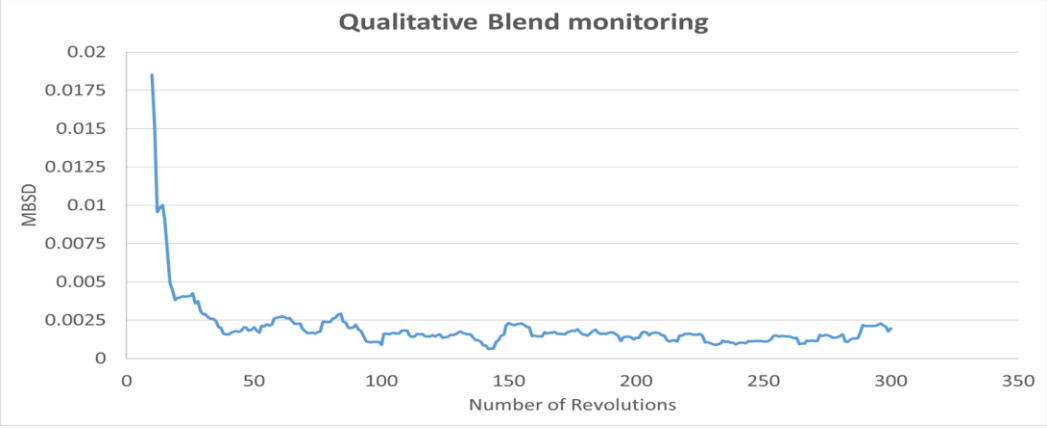


Figure 2 - Blending process monitoring using MBSD analysis

- MBSD has been shown to be a valid measure of homogeneity which focuses on a specific endpoint, supported by sound rationale and analytical evidence of the procedure's predictive ability. The link between endpoint and true blend uniformity is to be established during method validation.

- One advantage of this approach is that no sample quantification is required.

- It is however very challenging to set a reliable blending end-point criterion for such qualitative methods, as it may vary significantly with chemical composition or blending process parameters.

- On the other hand, quantitative methods can translate the NIR spectra to the actual concentration of the API and ingredients, which is valuable information for the regulatory filings.

Quantitative Analysis :

- Quantitative approaches constructing univariate or multivariate calibration models have been used to express blending processes in terms of concentration variation, which is in line with the standard criteria of current regulatory requirements and allowing production to proceed directly to the next manufacturing step.

- However, the quantitative methods require extensive calibration and remain poorly transferable.

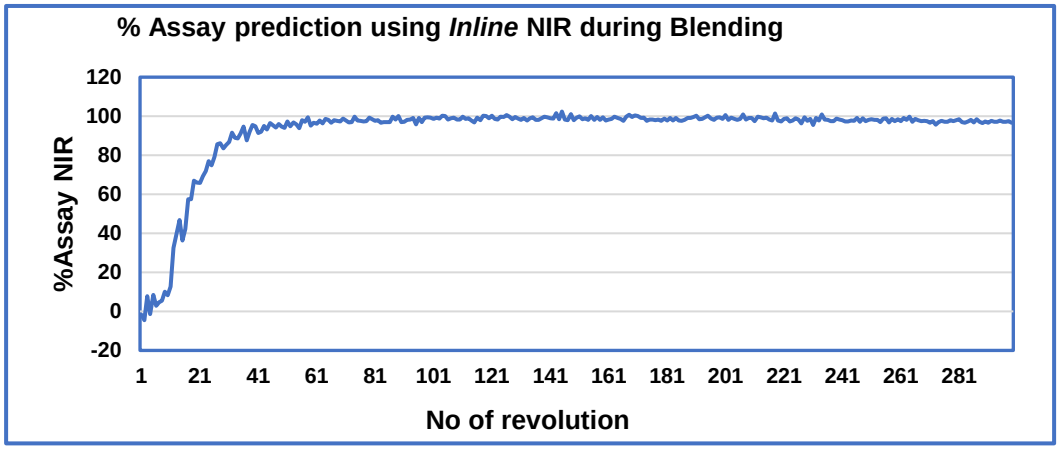


Figure 3 - Blending process monitoring using quantitative method

For the development of new NIR method, the steps given below are followed.

Feasibility :

The feasibility of using NIRS should be considered to demonstrate that it is suitable for the intended purpose. Such a feasibility study may include (but not limited to), the determination of a suitable NIR response, investigations into specificity, matrix interference and the effects of sample preparation. The NIR spectra of different components of the blend are shown in Figure 4.

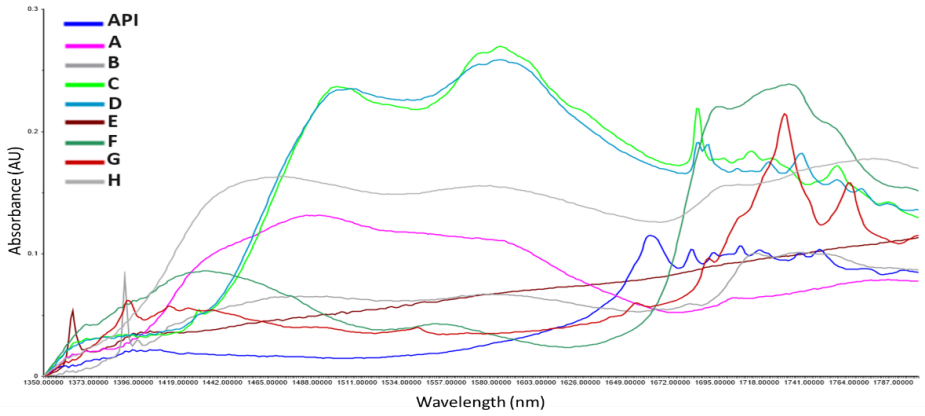


Figure 4 - NIR spectra of blend components

Risk Assessment :

- Each known potential variable that may affect the spectral response should be considered.
- Variability of relevant critical process parameters and critical material attributes should also be considered for checking the suitability of calibration or validation batches.

- These may include the environment in which measurement takes place, cleanliness of the sample interface, sample temperature, sample flow, concentration of the analyte of interest, particle size distribution, material suppliers, residual moisture and solvent content, qualitative and/or quantitative variations in the matrix (e.g., excipient grade, formulation).

- Those risks that may adversely affect the performance of the NIRS procedure in delivering valid results, which may then lead to an incorrect assessment of quality and/or "false positives," should be considered. It is of considerable value to identify high risk elements that require control and risk mitigation.

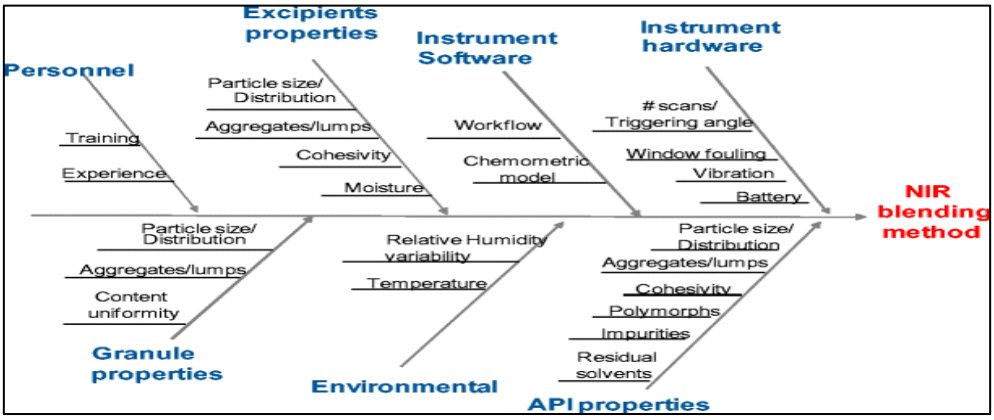


Figure 5 - Risk assessment for NIR BU method

Sample Preparation :

- An essential part of developing an NIR model is the construction of a calibration set.

- To create a robust model, calibration samples must include an appropriate concentration range for the component to be analyzed, must address potential sources of variability (variation in processes, the analyzer, the physical characteristics of the materials, the water content, or the temperature), and must cover the expected variations in process parameters (e.g., in-design space parameters) that have the potential to influence the spectral response.

- Samples for calibration and validation set should be representative of the commercial production process, and the expected variability within the scope of the NIR procedure.

- If the samples obtained from the process do not provide a sufficient range of variability, additional samples can be prepared under laboratory conditions.

- Samples included in the model should be representative of the samples that will be measured/predicted. Each set of calibration and validation samples should be representative of the intended scope of the NIRS procedure and include samples covering the full range of potential variation in the sample population.

- To capture the expected material variability, calibration samples of qualified materials from multiple vendors or from different manufacturing lots should be used.

- The NIR model is valid only for the variability or the range used in the the model.

- The NIR procedure should be able to reject samples that are outside of its defined scope, such as out of specification product, placebo, samples containing different quantitative composition of proposed excipients, and samples containing different active substance and excipients.

- The recommended approach is with a design of experiment (DoE) in which each individual ingredient is varied independently of one another. This creates a robust design space in the center of which the targeted product should sit.

- A robust model is insensitive to minor changes in production variables.

- For quantitative NIR models, concentrations of the analyte of interest should span a range that is wider than the acceptable specification limit to ensure that the model can characterize nonconforming materials. The target for BU is 100% of the label claim of the analyte of interest, and the acceptance criteria for each location mean is within 90.0% - 110.0% of target, and all individuals are within 75.0% and 125.0% of target claim. The calibration samples must cover this range and for PLS regression at least five different levels can be used.

- Validation samples should be independent from the calibration samples.

- Samples should include good as well as bad samples and from the production batches also, considering expected variation from material and process with respect to time.

- Validation samples should span the calibration space and test the model.

- Inclusion of spectra from multiple instruments of the same type can facilitate future extensions of the calibration to a new instrument or to a new site.

- Instrument characteristics may introduce a significant source of variability. This variability can be lowered by activating standardization options. The design of calibration sets to support this standardization can facilitate future extension of the calibration model to new instruments or to new sites.

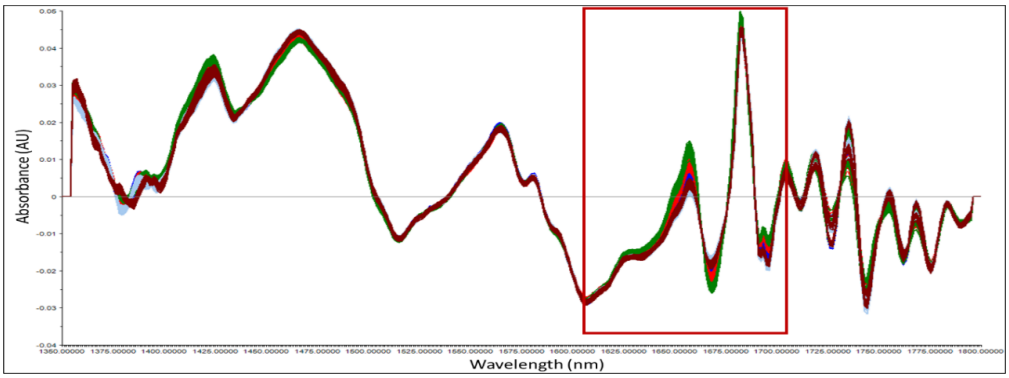


Figure 6 - NIR spectra of the calibration samples showing a gradient response

Model Building :

- Following acquisition of spectral and reference analytical data for the calibration set of samples, the chemometric calibration model should be developed using a specified software package.

- Since NIR spectra are the cumulative effect of physical and chemical information of the sample presentation, raw NIR spectra are often treated mathematically prior to development of the calibration model to reduce their variability and to enhance spectral effects related to chemical composition.

- Such treatments include normalization and derivation, which are performed to minimize unwanted sources of variation from the data prior to calibration and to enhance spectral differences of the analyte of interest.

- The model can be presented in different ways depending on the algorithm used (principal component analysis, partial least square, and principal component regression).

- There are several approaches to selecting the spectral region(s) to be included in the model. Spectral selection may be the whole spectrum or a smaller region(s) of interest. Saturated regions should always be excluded from the model building process.

- The appropriate number of factors or latent variables should be chosen to avoid underfitting or overfitting the model.

- Model building is repetitive and iterative.

- There are tools within chemometric software packages to speed up the model optimization process.

- The optimization of a model is dependent on the selection of the samples included in the model, the choice of pre-treatments and the choice of calibration algorithm.

- Model statistics are a part of this decision-making process. The best practice is to interpret the model output with good scientific judgement and not to rely solely on the computational output.

- It is difficult to select the best possible model out of many available, since models can always be tweaked and changed. If given a certain set of parameters/calibration samples have not produced adequate results, improvements may be possible. Possible changes that could be made by adding more samples into the calibration (samples of known variation) or removing few samples from the calibration if scientifically justified to demonstrate that they do not represent production quality material. The aim is to achieve a robust and reliable model that adequately meets the testing requirements.

- The proposed calibration model should be characterized by graphical plots of reference values against NIRS predicted values of both the calibration and validation sets of samples, to give a visual overview of linearity, bias, slope, and outliers for both sample sets. It is expected that a good correlation coefficient is obtained (close to 1), with slope, bias and intercept not statistically different from 1, 0 and 0 respectively. For internal (cross) validation methods of optimization, the standard error of cross validation (SECV) should be reported. For the validation set, the SEP should be reported.

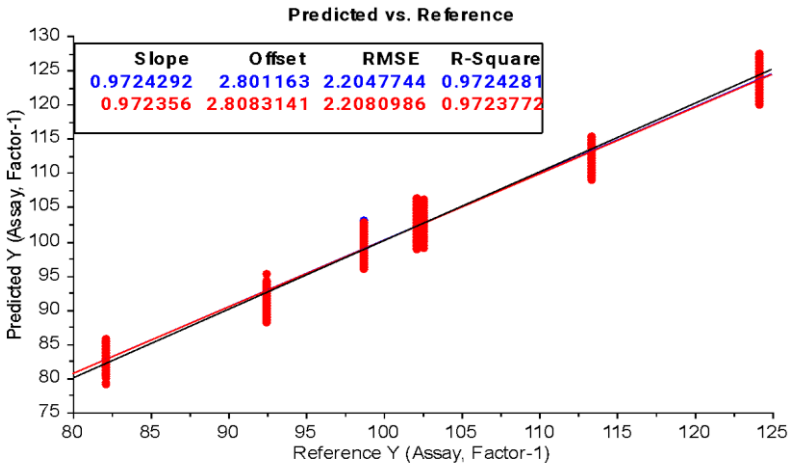


Figure 7 - Quantitative PLS model

Model Validation :

To validate rate-of-change procedures (e.g., blending or mixing), manufacturers should demonstrate both the adequacy of the NIR endpoint criteria and the specificity of the NIR procedure for components of interest.

- First, the adequacy of the endpoint criteria should be confirmed with an appropriate reference methodology (e.g., a traditional blend uniformity analysis).
- Second, specificity can be demonstrated by showing that the wavelength region used for the NIR procedure included major bands of the components of interest.
- Validation of the model using independent samples allows the user to complete the model development and test it against the validation criteria.
- It is always possible after analyzing validation samples to revisit the calibration process either with physical samples, measurements, or model re-building of existing data.
- While generating the validation data for the NIR method, it is necessary to quantify the accuracy, linearity, and precision for both the reference method and the NIR method to make a meaningful comparison as per regulatory guidance.
- Accuracy should be established across the specified range of the NIR procedure, which would normally be done by comparison of results with the validated reference method.
- Bias should not be statistically different from zero. By appropriately randomizing real-world variables, such as instrument, operator, and day for both methods the success criteria for the equivalent method can be demonstrated by comparison.
- Repeatability and intermediate precision should be determined, covering the specified range.
- Evidence to demonstrate the robustness of an NIRS procedure should cover chemical and physical sample variables, the conditions employed for sampling and sample preparation, as well as variations in procedure parameters.

Implementation :

- Before an NIRS model is applied, each sample spectrum should be subject to a statistical spectral quality test to determine whether the characteristics of the sample fall within the range of variation for which the model was calibrated and validated.

- In practice, such tests (e.g., Hotelling's T2 or distance to model plots) show whether the spectra for the sample fall within a pre-defined range of variation or if the sample is an outlier.

Method Life Cycle : Model Maintenance throughout the product life cycle

- NIRS procedure life cycle management should ensure critical appraisal and revalidation of the NIRS procedure on a regular basis, and enable continuous improvement and appropriate change control, when necessary, during its life cycle.

- Changes with respect to the product life cycle (e.g., changes in manufacturing processes, composition, site of manufacture, etc.) would normally also require that the NIR procedure is updated after the initial regulatory application. Because of planned changes (managed by internal quality procedures through an implemented change control policy) and unplanned changes, spectroscopic methods may evolve over time.

Challenges to Overcome to Realize the Full Potential of NIR Technology :

- Not working well for lower concentration of analyte of interest.

- Application of chemometrics.

- Model updating and validation at different scales.

- Model transfer on different instruments.

References :

1. USFDA, Guidance for Industry, 2004, PAT-A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance, October 2004.

2. USFDA, Guidance for Industry, 2021, Development and Submission of Near Infrared Analytical Procedures, August 2021.

3. El-Hagrasy, A, D'Amico, F & Drennen, J 2006, 'A Process Analytical Technology approach to near-infrared process control of pharmaceutical powder blending. Part I: D-optimal design for characterization of powder mixing and preliminary spectral data evaluation', *J. Pharm. Sci.* vol. 95, pp. 392-406.

4. El-Hagrasy, A, Delgado-Lopez, M & Drennen, J 2006, 'A Process Analytical Technology approach to near-infrared process control of pharmaceutical powder blending: Part II: Qualitative near-infrared models for prediction of blend homogeneity', *J. Pharm. Sci.* vol. 95, pp. 407-421.

5. EL-Hagrasy, A & Drennen, J 2006, 'A Process Analytical Technology Approach to Near-Infrared Process Control of Pharmaceutical Powder Blending. Part III: Quantitative Near-Infrared Calibration for Prediction of Blend Homogeneity and Characterization of Powder Mixing Kinetics', *J. Pharm. Sci.* vol. 95, pp. 422–434.

6. Biagi, D, Nencioni, P, Valleri, M, Calamassi, N & Mura, P 2021, 'Development of a Near Infrared Spectroscopy method for the in-line quantitative bilastine drug determination during pharmaceutical powders blending', *J. Pharm. Biomed.* Anal. vol. 204, p. 114277.

7. Momose, W, Imai, K, Yokota, S, Yonemochi, E & Terada, K 2011, 'Process analytical technology applied for end-point detection of pharmaceutical blending by combining two calibration-free methods: Simultaneously monitoring specific near-infrared peak intensity and moving block standard deviation', *Powder Technol.* vol. 210, pp. 122–131.

8. Bakri, B, Weimer, M, Hauck, G & Reich, G 2015, 'Assessment of powder blend uniformity: Comparison of real-time NIR blend monitoring with stratified sampling in combination with HPLC and at-line NIR Chemical Imaging', Eur. *J. Pharm. Biopharm.* vol. 97, pp. 78–89.

9. Puchert, T, Holzhauer, C, Menezes, J, Lochmann, D & Reich G 2011, 'A new PAT/QbD approach for the determination of blend homogeneity: Combination of on-line NIRS analysis with PC Scores Distance Analysis (PC-SDA)', Eur. *J. Pharm. Biopharm.* vol. 78, pp. 173–182.

10. Sulub, Y, Wabuyele, B, Gargiulo, P, Pazdan, J, Cheney, J, Berry, J, Gupta, A, Shah, R, Wu, H & Khan, M 2009, 'Real-time on-line blend uniformity monitoring using near-infrared reflectance spectrometry: A noninvasive off-line calibration approach', *J. Pharm. Biomed.* Anal. vol.49, pp. 48–54.

3 Pat Tools for High-shear Granulation

Granulation is a key unit operation in most of the tablet formulations during which powder particles agglomerate to give denser and nearly spherical grains. The objective of this process is to improve the flow property or/and compressibility of the powder blend. In wet granulation, the granules are formed by adding a granulating liquid (solvent or binder solution) on to a powder bed mixed continuously by an impeller in a rapid mixer granulator (RMG) or by air in a fluid bed granulator.

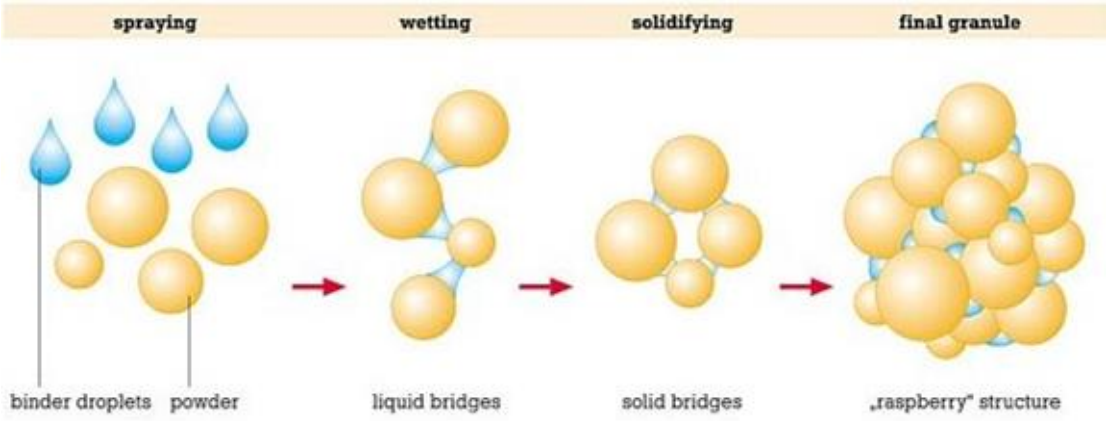


Figure 1 - Stages of Wet Granulation

The extent of granulation influences the density, porosity, and size of the granules, thus impacting the flow property and finished product CQA such as dissolution. This indicates a need for monitoring the process to obtain a quantitative end point so as to maintain consistent quality between batches. In absence of a PAT tool, the measurement is purely subjective (hand squeeze method) which is neither reproducible- nor acceptable in a GMP environment.

Figure 2 - RMG Bowl and Traditional End Point Test (Hand Squeeze Test)

A difference in wet mass consistency or granule size, density and porosity may lead to poor flow or poor compressibility of blend, or failure in finished product dissolution, resulting in a costly batch rejection.

Regulatory Expectation :

The quantity of granulating fluid and kneading time vary depending on the CMAs of input raw materials (e.g., particle size and moisture content) although they all meet raw material specifications. Thus, a common process time for all batches may lead to batch failures. As the US FDA (PAT guideline 2004) states, “currently, most pharmaceutical processes are based on time-defined end points. However, in some cases, these time-defined end points do not consider the effects of physical differences in raw materials. Processing difficulties can arise that result in the failure of a product to meet specifications, even if certain raw materials conform to established pharmacopeial specifications.” This indicates why some industries avoid investing in PAT tools by fixing the process time. Sometimes, this leads to batch rejections.

Selection of PAT Tool :

Thorough process understanding and risk assessment are needed before choosing any process monitoring tool. Granule size and density represented by wet mass consistency are critical in RMG granulation due to the high shear force of mixing, whereas, particle size and particle growth rate are critical to monitor in fluid bed granulation. Parameters monitored through PAT (impeller torque, drag force, acoustic emission, NIR spectrum, thermal conductivity, particle size, etc.) represent wet mass consistency, density/porosity and particle size of the granules, impacting flow property of the blend and drug release from the finished product.

Table 1 : PAT Tools for RMG Granulation:

Sr. No.	Stage	Critical Parameter	Available PAT Tools
1	Power consumption or ammeter readings	Motor power consumption	Relatively less sensitive method, because motor power is influenced by multiple factors such as age, wear and tear, etc.
2	Indirect torque (calculated based on motor ammeter reading)	Load on motor due to impeller load	Relatively less sensitive method since the torque is calculated from motor power consumption. It is difficult to discriminate for every small fluid addition or kneading.
3	Focused Beam Reflectance Measurement (FBRM) sensor	Particle size of the granules through laser light beam	End point based on particle size distribution. It is suitable if dissolution is sensitive to particle size (not much impacted by density/porosity or wet mass consistency).
4	Drag Force Flow (DFF sensor	Drag force of granules on the sensor probe, influenced by particle size, density, and wet mass consistency of the blend	End point is based on the wet mass consistency and particle size/density. Thus, it is more sensitive and precise.
5	Impeller torque sensor (direct torque)	Rotational force required to rotate the impeller, influenced by the wet mass consistency	It directly reflects the load on the impeller. Thus, it is more sensitive, accurate and precise
6	Near Infra-Red (NIR) sensor	Shift in baseline NIR spectra happens based on density and particle size of granule. Water band gives information on free water/bound water with excipients available for granulation	End point is based on base line spectral shift overlapped with reference batch.

The power consumption (ammeter reading) is a relatively less sensitive method since it measures the entire load on the motor (in some, also cases gear box). Therefore, a small additional fluid or kneading may go unnoticed. Wear and tear of motor and power fluctuations may cause variations. Since the "calculated torque" value also involves motor power consumption (ammeter reading), this also leads to poor sensitivity and issues related to the age of the motor. FBRM sensor is discussed under fluid bed granulation in another chapter.

Drag Force Flow Sensor and Operating Principle:

DFF sensor is an in-line PAT tool to monitor the flow force of the powder in a RMG. The tool is manufactured by Lenterra Inc, New Jersey.

The sensor consists of a probe with a hollow cylindrical pin connected to an optical interrogator through a probe support and an optical cable. The data from the interrogator is processed by computer software for real-time monitoring. Since the probe pin positioned inside the powder is dragged by moving powder particles in the RMG, the force experienced by the sensor is called drag force. Minute deflections of the pin are detected by an array of optical strain gauges in the inner surface of the pin. A plot of time vs force during RMG granulation indicates the rate of increase in wet mass consistency and particle growth in real time.

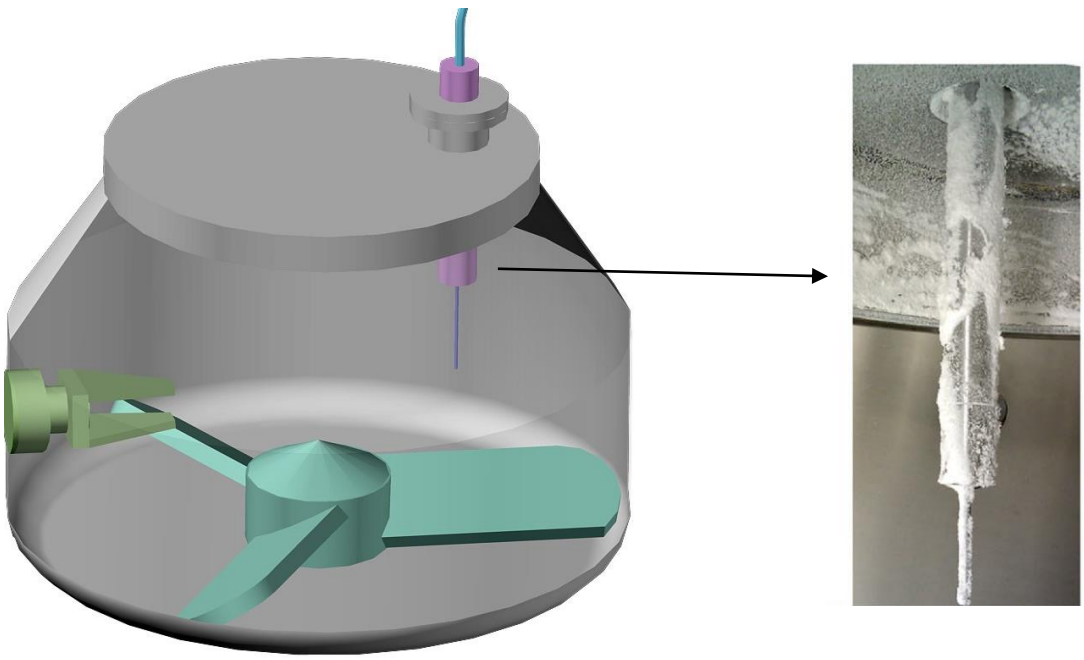


Figure 3 - Drag Flow Force (DFF) Sensor installed in RMG

Prerequisite:

1. Since the sensor comes in contact with the product, the material of construction used in the adaptor/holder and the sensor should be similar to that of the RMG bowl/lid or stainless steel MOC acceptable as per GMP, 21 CFR compliance.

2. An Audit trail should be available in the software for batches already executed

3. A port is required in the RMG-lid to accommodate the sensor. Alternatively, the lid may be modified to have a port, in consultation with the PAT tool vendor.

4. Depending on the manufacturing scale, the sensor with required sensitivity should be selected.

Installation:

1. The probe is installed through the RMG lid using a flange adaptor (perpendicular to powder flow) or through any port in the side wall (horizontal to powder flow).

2. In the vertical mounting method, the sensor may be mounted through a port in the lid at approx. 3/4th of the mixer blade length from the axis of the blade rotation. The tip of the sensor should be positioned at 2.5 cm above the blade at 90o angle of blade rotation.

3. The probe is connected to the interrogator which is connected to a computer installed with the LENFLOW measurement software.

Product Selection :

Product with sensitivity to rate and amount of fluid addition or kneading in granulation process is suitable (e.g., BCS class II drugs or modified release formulations). A few R&D experiments are suggested before trying in commercial products.

In model building exercise, the manufacturer needs to define the right end point in the model building experiments (approx. 10-15 batches) on the basis of the particle size distribution or finished product testing. Therefore, it is preferred to select a product showing a difference in particle size distribution due to change in granulation parameters such as fluid quantity and fluid addition rate and kneading time.

Data Interpretation :

Force Pulse Magnitude (FPM) is the difference between the greatest and smallest values of force measured in a given time period. By analyzing the raw force (F) signal, Lenterra's processing software calculates and provides FPM value vs time profile.

Another output from the sensor is Powder Consistency Factor (PCF) vs time profile. PCF indicates the particle size uniformity in the wet mass. If the material contains large agglomerates hitting the probe intermittently, the reflected PCF is low.

FPM vs time profile needs to be reproduced in every batch to get consistent granule quality. FPM increases with increase in wet mass consistency as shown in the figures 4 and 5. When binder concentration increases from 1 to 5%, the kneading step (after 180 seconds) improves wet mass consistency as reflected in the FPM profile. When kneading is continued further, the wet mass consistency decreases due to excess water on the surface producing a slurry, demanding more binder.

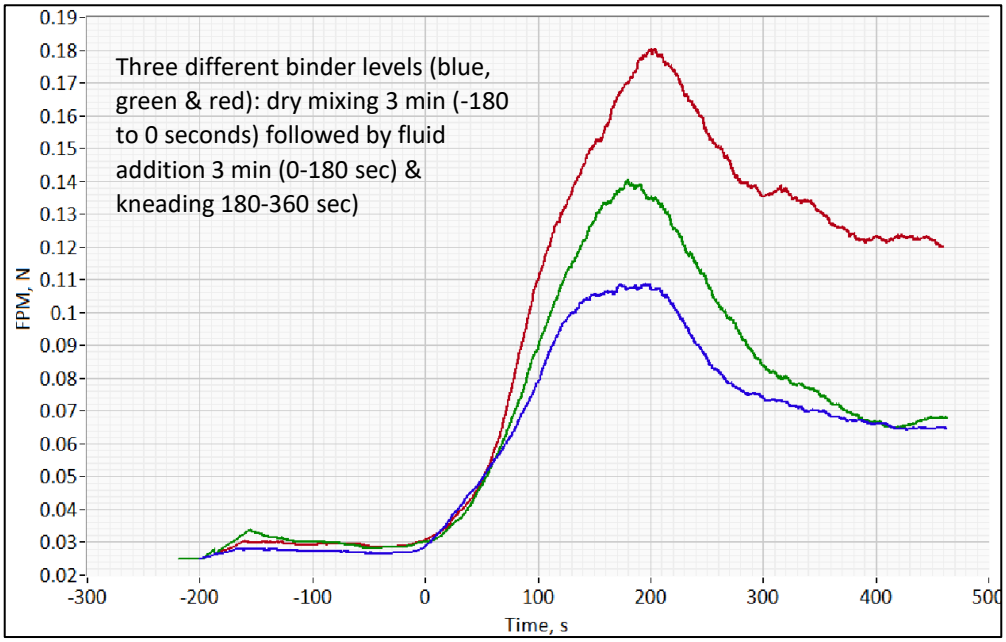


Figure 4 - Drag Flow Force (DFF) Sensor installed in RMG

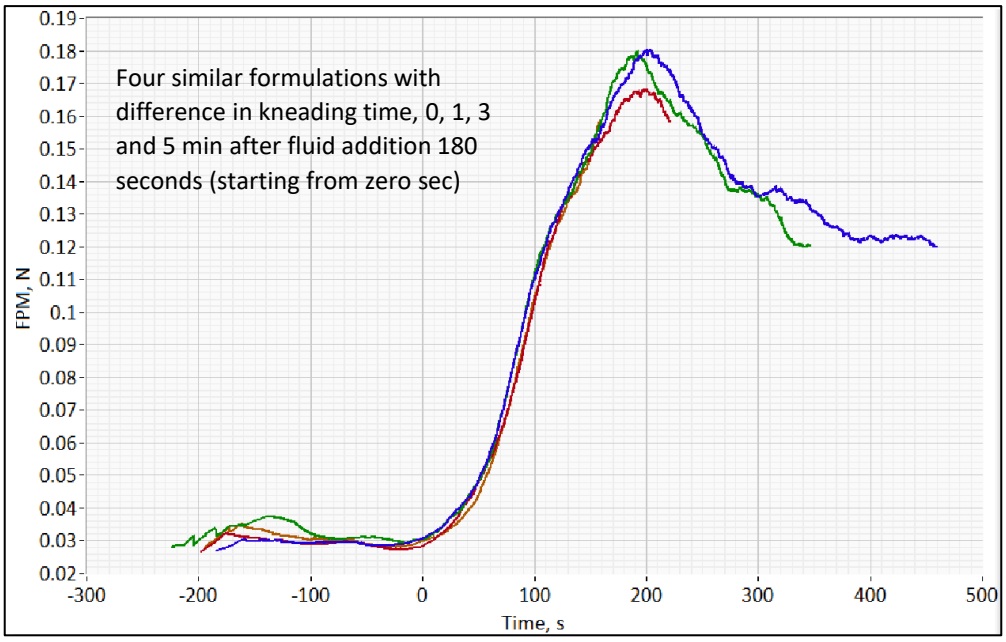


Figure 5 - FPM Vs time profile for a case study reported with different kneading time

The DFF sensor also provides the PCF profile. This is called the PCF signature of the granulation process. The process signature should match across the batches or match the reference batches to get consistent granule properties. In a typical process, initially the PCF is high indicating uniformity of dry powder particles. It decreases due to wider particle size distribution during fluid addition, and reaches a minimum before the chopper starts to break the lumps to provide a uniform distribution of particles later.

Given below is the mean FPM and PCF profile of a granulation process reflecting dry mixing (-2 to 0 min), water addition (0 to 2 min), wetting till 3.5 min, kneading with chopper on (breaking of lumps till 4.5 min) while kneading, secondary densification of the granules to give a gradual raise in MFPM (mean FPM) due to continued kneading (till 6 min), followed by a final phase in which a predominant chopper action (6 to 26 min) was observed, resulting in reduced drag force (Fig 6).

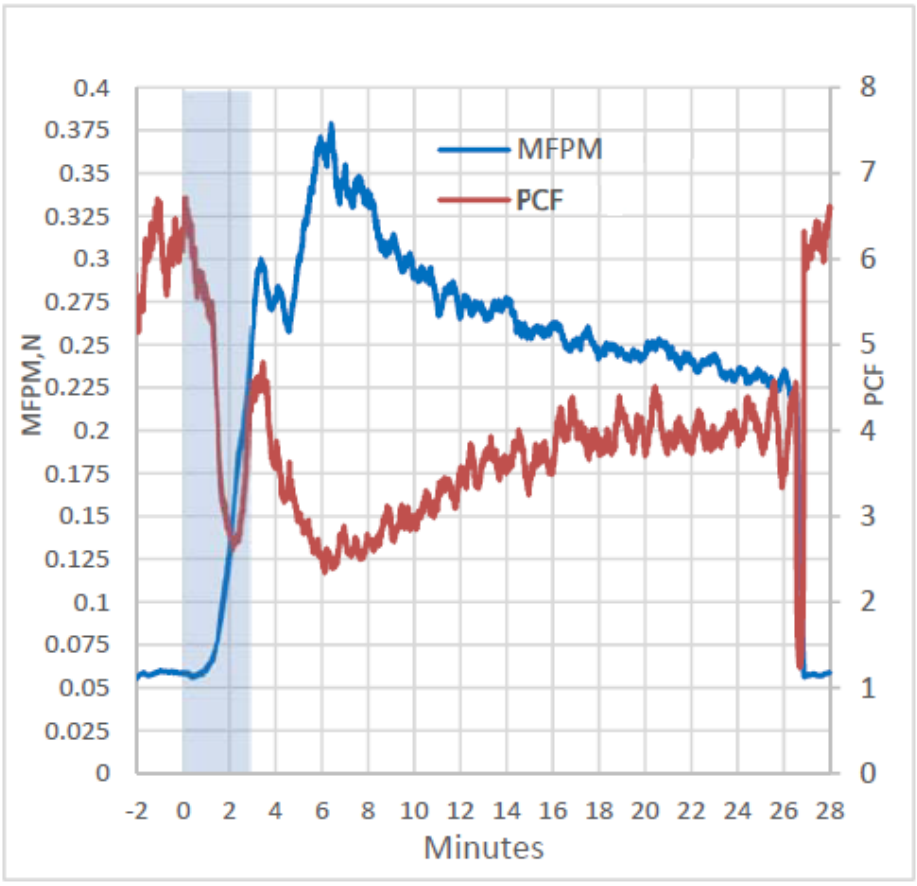


Figure 6 - FPM & PCF vs time profile for a reported case study

Impeller Torque Sensor and Operating Principle :

A twisting force required to rotate an axis is called 'torque'. In a granulation process, there is a twisting force in the axis of mixer blade (impeller) that keeps the axis in rotation against the resistance provided by the wet mass cohesive force that increases gradually during the process. In line time vs torque profile indicates various stages in granulation and the end point as well.
This is a well-known method of quantifying and reproducing the end point of granulation. Since the sensor is installed in the impeller axis and it measures the load on impeller directly, it is also called impeller torque, direct torque, or absolute torque. This is a more sensitive and reliable method compared to the indirect torque method which measures the power consumption of a motor to indirectly calculate the impeller torque. Torque energy loss due to age of the motor and gear box (wear and tear, etc.) is avoided in this method.

Prerequisites :

1. The sensor needs around 0.3 meter space along the impeller axis for the sensor of 1000 Nm rating, and the dimension varies according to the brand and measuring range

2. Brushless and contactless signal transfer, and complete absence of electrical component in rotation.

3. Site quality assurance team may assess the risk to rule out the possibility of impact on the existing process/product.

4. Audit trail should be available in the software for batches already executed, and it should be non-editable, password protected, and a backup should be available

Installation :

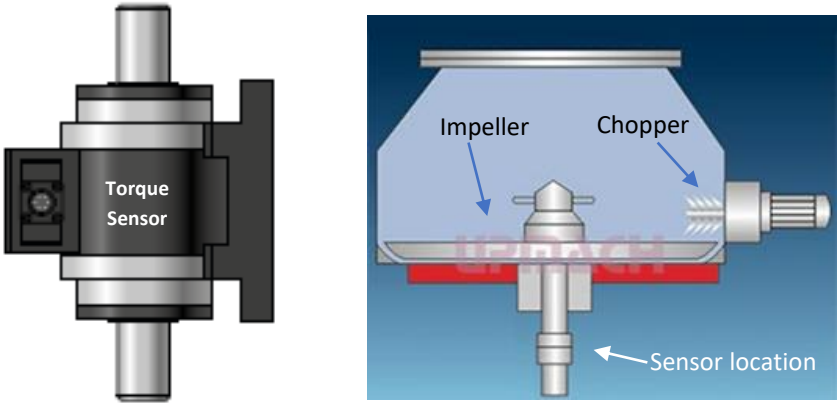


Figure 7 - Torque sensor and location in RMG for installation of torque sensor

5. Suitable sensor should be selected based on the RMG bowel volume with the support of the vendor and the operation manual (referring the torque-rating of the sensor model). A torque range of 1 to 100 Newton meter (Nm) may be recorded in 10 to 75L RMG machines, whereas 50 to 1000 Nm range is expected in 250 to 600L RMG with a typical powder blend.

6. The torque sensor should be mounted in the impeller shaft via couplings.

7. The assembly and installation must comply with the machine safety standards (ISO 12100 or similar applicable standards).

8. The sensor should be connected with an electronic signal processor to digitalize the signal. The processor gives digital display of the torque value. The processor is connected to a computer software for in-line monitoring Time vs Torque data, and retrieving historical data.

9. Specification / example: Magtrol TS100 Series model connects the sensor directly with a computer through USB port without a need of a signal processor. Depending on the model in this series, it can measure 1 to 500 Nm, whereas TM 314 model measures up to 1000 Nm torque and it needs a signal processor unit before connecting to a computer.

Data Interpretation :

An illustrative torque graph is given below for an ideal granulation process. The liquid is added in the first 30 sec, leading to a rise in torque, indicating agglomeration of the particles. Once all powder particles are moving, the torque starts dropping. Another increase is seen when particle growth starts, leading to a steady state when growth and breakage are in equilibrium.

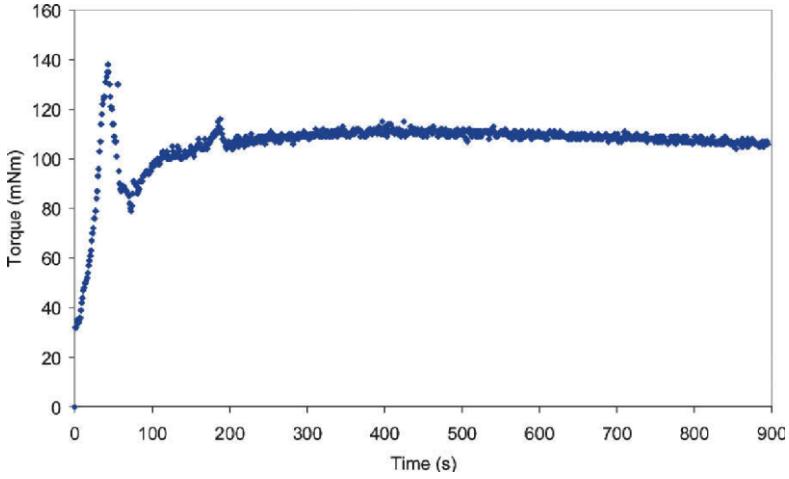


Figure 8 - Torque vs Time profile for an ideal granulation process

The torque profile for a typical production batch and a variation batch are given below :

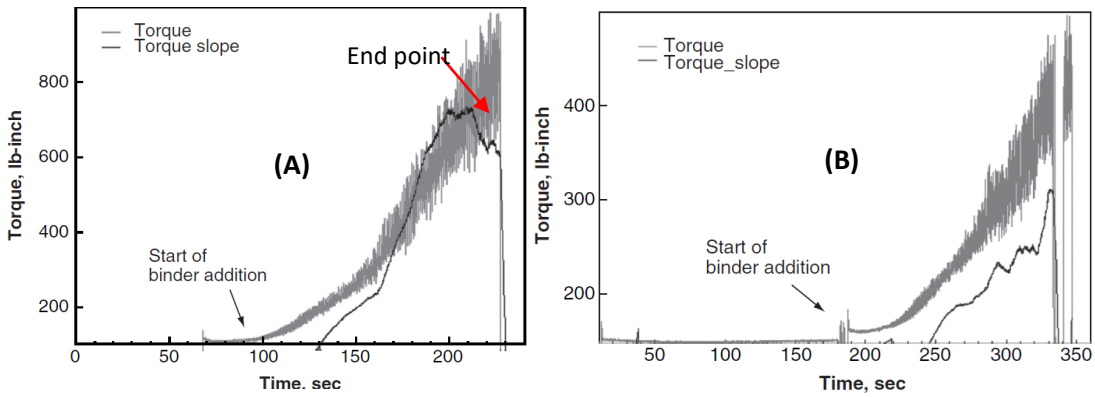


Fig.9 : (A) The torque profile for a typical production batch executed by an experienced operator and (B) that of other batch executed by an inexperienced operator (source: Levin M, Encyclopedia of Pharmaceutical Sciences and Technology, 4th Edn., Vol V, p 3854-3871)

As seen in the figures, the torque value ascends with time due to densification of powder after the fluid addition is started. A typical batch granulation is stopped in the downslope of the derivative curve in the graph on the left. Whereas on the right, an inexperienced operator stopped it a little earlier in the other batch and opened the lid to check the wet mass consistency, then continued kneading for another 10 seconds. Thus, the peak of the derivative did not reach the end point and the torque profile is different. Thus, a batch-to-batch variation is identified in the torque signature profile. It may impact the final product quality depending on the type of API / formulation.

There is a case study in 250L RMG installed with impeller torque sensor showing the advantage of torque reading over amperage reading. As seen in the table below, there is a clear difference in torque value in various stages of granulations (dry mixing, binder addition-1, kneading-1, followed by binder addition-2, kneading-2). However, there is no such significant differences in power consumption (amperage) for various stages of granulation. This is because the impeller torque directly measures the load on impeller (specific to the blend change). On the other hand, the amperage is the measure of power consumption indicating the load on motor, and is not sensitive to fine differences). Therefore, any torque value indirectly calculated from the motor load is also not so sensitive as impeller torque (or direct torque). The impeller torque values are reproducible between batches indicating the consistent output quality between batches.

Table 2 : Impeller torque reading showing consistency between two batches (case study)

Granulation Stages	Time duration (min)	Batch I			Batch II
		Amp	Torque (Nm)	Torque/ Amp ratio	Amp
Dry mixing	5	14.62	63.74	4.36	14.37
Water 1.5 L	5	15.11	118.19	7.82	14.86
Kneading-1	2	15.36	152.14	9.91	15.42
Additional Water 1.5 L	1	15.67	175.09	11.17	15.68
Kneading-2	2	15.64	187.06	11.96	15.43

Advantage and Disadvantage :

The sensor is not in contact with the product. However, it is not portable to another machine.

Challenges and Probable Solution :

For the purpose of installation, the sensor needs 0.2 to 0.4 meter space along the impeller shaft below the working platform, just above the gear box of the motor. Most of the old RMGs do not have enough space for the installation. However, space and installation can be customized while procuring new RMGs.
The supplier of the sensor may also try to customize the sensor size to some extent to install it in the available space. Alternatively, the user may create more space by replacing the entire set of motor and gear box with a variable speed motor (without a need of gear box). Space may also be increased by lifting the platform (working bench) and extending the impeller shaft. The choices are based on the risk assessment on the commercial product running in the said machine.

NIR Sensor for RMG Granulation :

NIR PAT is widely used in multiple unit operations of pharma manufacturing such as blending, granulation, tablet compression, pellet coating for monitoring one or another in process critical attributes. Its scope in RMG granulation is discussed below :

Principle of Measurement :

The molecular mechanism related to binding water distribution in the powder particles is considered critical in high shear wet granulation while using NIR tool to monitor the granulation process. When the NIR radiation penetrates deeper into the granules with the increasing particle size, back reflected light decreases and an apparent increase is observed in the absorbance. Thus, the baseline changes occur with the progress of granulation due to increased path length.

Installation and Operation :

An NIR spectrometer is attached to the discharge port of the RMG as in figure 10. The spectra are continuously acquired during the granulation process in a range (example 1100 to 2150 nm) in order to cover the O-H bond stretching of water. A predefined number of scans (approx. 30 scans) are set in the system to give each spectrum. Compressed air purging is recommended to avoid probe-fouling/adherence of the powder or wet mass to the glass window through which the NIR light passes to the product. Alternatively, a diffuse fiber optic probe may be inserted through one of the ports in the RMG lid.

Principal component analysis (PCA) and partial least square regression (PLSR) were used to evaluate the NIR spectra acquired during the HSWG process for the qualitative and quantitative analyses of the formulation. Spectra may be pretreated to negate the effect of physical properties of the granule (e.g., particle size) using methods such as standard normal variance (SNV) in chemometrics.

Interpretation of the Result :

An upward shift in the blend-NIR spectra baseline demonstrates that the particle size increased with the progress of the high shear wet granulation process. This baseline change accounts for the light scattering of the NIR spectra, as elucidated by the Kubelka–Munk scattering theory. Further in a water-based granulation, the NIR also shows a remarkable change in the absorption peaks at around 1450 and 1900 nm indicating amount of water in the wet mass. A quantitative chemometric model is required to quantify water. Alternatively, a signature overlap may be done to monitor consistency between batches in absence of a chemometric model.

Figure 10 - Torque vs Time profile for an ideal granulation process

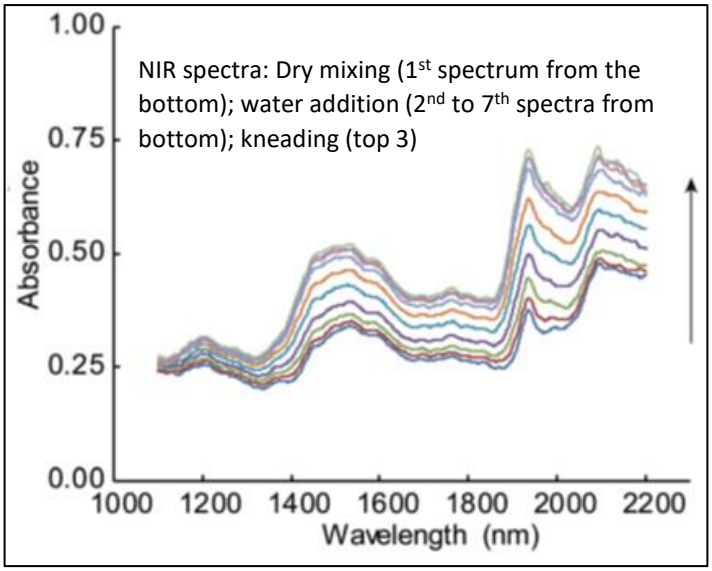


Figure 11 - Typical NIR spectra showing baseline shift quantifying the end point

A study indicated that the powder blend with soluble component (lactose) in the formulation (F-1), the baseline shift was low compared to the formulation containing starch (F-2), and formulation with mixture of lactose and starch (F-3) when water was added (10ml/minute) for 50 minutes followed by kneading for 10 minutes. The baseline maxima happened in lactose formulation in shorter time (12 minute) and less fluid compared to starch formulation (21 minute). Further water addition beyond this point probably causes formation of a slurry with decreasing wet mass consistency as reflected in decline of the baseline (60 minutes). Since lactose gets partially dissolved in water, it shows densification and baseline maxima earlier. However, the intensity of baseline shift is low compared to starch formulation. The delay in baseline-maxima in starch formulation is due to initial water absorption and swelling. The extent of baseline shift is higher due to availability of more free water in the surface of swollen starch particles for inter particulate aggregation. This reflects in relatively more intense water peak (5200 and 5400 cm-1) in this formulation when baseline maxima was attained (21 minutes). Thus, the fluid quantity and mixing time may also be dependent on the particle size and inherent moisture of the raw materials.

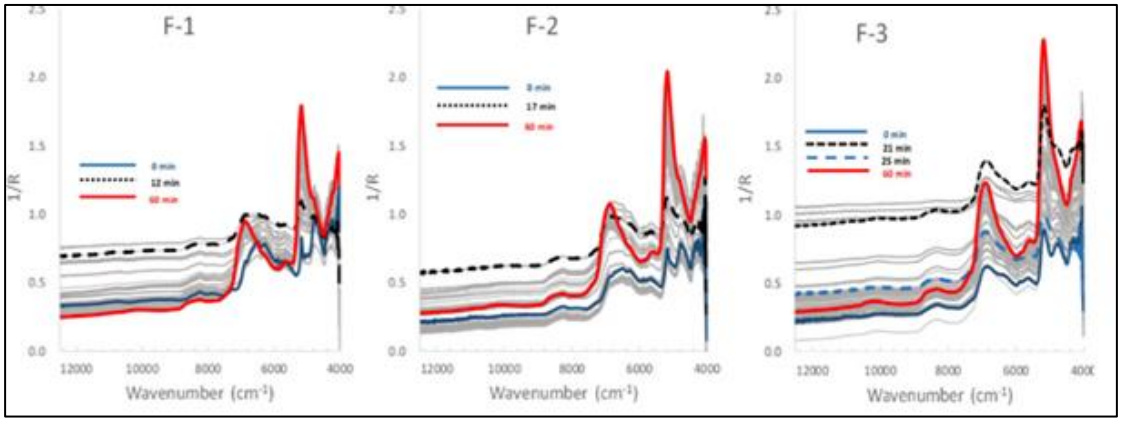


Figure 12 - NIR spectral changes for wet granulation of lactose containing formulation (F-1), starch formulation (F-2) and formulation with mixture of lactose and starch (F-3)

NIR based monitoring of wet granulation reveals molecular interaction of water with different raw materials in the blend thus creating a physico-chemical signature for the specific formulation apart from quantifying the end point. Thus the process-signature is one of the recommendations for consistent quality between batches.

Product Selection: This is especially suitable for aqueous granulation.

Advantage and Disadvantages :

Both contact and non-contact probes are available. Therefore, it is not necessary for the sensor to be in contact with the product. It is also portable to another machine easily. However, probe fouling is reported although it can be managed by automatic wiper/air purging system. Chemometric model building/validation is a cumbersome process.

Business case evaluation for Granulation PAT Tool :

An organization may decide to use a PAT tool proactively in new and commercial products or basis the regulatory queries in other products. Frequency of batch failures due to moisture and particle size variability in raw materials may be considered and a product list may be prepared. A quantitative assessment of procurement and operation cost compared with benefit of saving a batch and time in 1- 3 year period may help to make decision.

References :

1. USFDA, Office of Regulatory Affairs (Sep 2004): Guidance for Industry PAT – A frame work for innovative pharmaceutical development, manufacturing and quality assurance.

2. Ajit SN, Sherif B, Valery AS & Dilbir SB (2015). Realtime measurement of granule densification in high shear wet granulation and application to scale up of a placebo and a brivanib alaninate formulation, J Pharm Sci., 104, pp.1019 - 1034.

3. White paper publications in the manufacturer's website for Drag Flow Force sensor. Lenterra. Viewed on 15-05-2024: https://lenterra.com/white-papers/

4. Michael L (2013), Wet granulation: End-point determination and scale-up in Encyclopedia of pharmaceutical science and technology: Vol.5, Taylor & Francis, USA.

5. Zhibing Z, Seville JPK, ingram A & Henderik F (2005), The relationship between granule size, granule stickiness, and torque in the high shear granulation process, Pharm Res., 22, pp.270-275.

6. Shikata F, Kimura S, Hattori Y & Otsuka M (2017), Real time monitoring of granule properties during high shear wet granulation by near infrared spectroscopy by chemometric approach, RCS Adv., 7, pp.38307-38317.

7. Ryo O, Yusuke H, Tetsuo S, Tomoaki S & Makoto O (2020). Elucidation of the molecular mechanism of the wet granulation for pharmaceutical standard formulations in a high-speed shear mixer using near-infrared spectroscopy. Pharmaceuticals, 13, p.226

4 NIR SPECTROSCOPY FOR TABLET COMPRESSION

Introduction :

This guideline offers a comprehensive outline for the development and validation of spectroscopic methods used in quantifying drug products. In this section, we delve into the utilization of at-line NIR spectrometry to create analytical models for assessing the content uniformity of a given drug product. Commonly employed HPLC methods for quantitative analysis are not only destructive but also generate chemical waste, necessitate several hours for result reporting, and demand significant manpower1. On the other hand, techniques such as NIRS and FTIR offer nondestructive capabilities, facilitating real-time release (RTR) of products. They are cost-effective and require less resources compared to traditional methods2.

Core technology of spectrometry consists of four parts :

1. The optics system comprises essential components such as the light source, beam splitting system, detectors, and various accessories necessary for sample analysis.

2. The mechanical system includes prime movers, transmission components, and executive systems crucial for operational functions.

3. The electronic system encompasses circuits for power supply to the light source and detectors, as well as circuits for signal amplification.

4. The computer system is indispensable for recording and storing data in compliance with CFR-21 regulations, and for the control of NIR devices.

Procedure for spectrometric method development :

The spectrometric method development procedure generally encompasses the following steps :

- Instrumentation Elements: Choose appropriate instrumentation, such as a spectrophotometer, along with either a reflectance or transmission probe, and specialized spectral analysis software, depending on the application requirements.

- Acquisition Parameters: Define the acquisition parameters necessary for optimal data collection, including integration time, scan speed, and resolution.

- Sample Presentation Interface: Develop a suitable sample presentation interface to ensure consistent and accurate measurements, considering factors like sample size, shape, and positioning.

- Sampling Scheme: Establish a sampling scheme tailored to the specific process applications, considering factors like sampling frequency, location, and representative sampling.

- Spectral Datasets: Gather spectral datasets comprising measurements from representative samples, ensuring a diverse and comprehensive dataset.

- Spectral Pretreatments: Implement spectral pretreatments to enhance data quality and address issues such as baseline drift, noise, and spectral interferences.

- Wavelength Ranges: Determine the appropriate wavelength ranges for analysis based on the spectral characteristics of the samples and the targeted analytes.

- Chemometric Model: Develop a chemometric model using techniques such as principal component analysis (PCA) or partial least squares regression (PLSR) to extract relevant information from the spectral data and establish quantitative or qualitative relationships between the spectra and analyte concentrations or properties.

Instrument selection :

The selection of the NIR instrument configuration is paramount due to its significant impact on the lifecycle of the analytical method. Changes in the instrument during its lifecycle may necessitate the re-development of the NIR model and/or re-validation, which can be time-consuming and costly.

Organizations should try to implement the same model of the instrument, whenever feasible, across various sites. This approach facilitates the maintenance of the method's lifecycle and streamlines analytical technology transfer between sites.

Once a model has been developed and validated, transcribing data from one vendor's instrument to another vendor's instrument becomes nearly impossible. Therefore, consistency in instrument configuration is essential to ensure the reliability and continuity of analytical processes.

A number of benchtop models are available commercially; some examples are listed below for reference3:

Table 1 : Bench top spectrometers of different companies

Company/Vendor	Name of Model	Type	Wavelength range
Foss	XDS Rapid Content Analyzer™	Dispersive grating	400-2500nm
Bruker	MPA	FT	12800-3600cm^{-1}
Buchi	N-500 FT-NIR	FT	800-2500nm
ThermoFisher	Antaris™ II	FT	833-2630nm
Perten	DA 7250 NIR analyzer	Diode array detector	950-1650nm
PerkinElmer	Frontier NIR Reflectance System	FT	700-2500nm
ABB	MB3600	FT	11,000-3,900cm^{-1} (909-2564)
ASD	LabSpec 4 Bench Benchtop	Silicon array detector	350-2500nm
Unity Scientific	2600 XT-R	Predispersive scanning monochromator	680-2600nm

Measurement for NIRS implementation :

- Off-line: the samples are analyzed away from the process area, typically in QC lab. For example, samples collected from production line are sent to laboratory for analysis using NIRS.
- At-line: the samples are isolated and tested in close proximity to the process stream. For example, tablets can be analyzed using a spectrometer located near the tablet compression area.
- In-line: the spectrometer analyzer is set up near the process area and is interfaced directly on the sample giving spectral measurements. No sampling required, and measurements are obtained directly from the process4.

Considering the at-line mode of measurement for this guideline, the following factors are critical to focus :

- Measurement
- Spectral acquisition time
- Sampling
- Sample preparation

Spectrometric model development

A. Drug product selection and feasibility assessment for NIR content uniformity

The selection of drug product for NIR analysis are based on multiple factors such as formulation complexity, regulatory requirements, feasibility of implementation within the manufacturing process, resource availability, return on investment, etc. A thorough feasibility evaluation has to be conducted to determine the suitability of the selected drug product for NIR content uniformity analysis. This involves scanning individual raw materials to identify unique wavelength ranges or distinguishable peaks for each excipient. A significant spectral difference observed between placebo and drug product is a likely candidate for model building5. This ensures that the developed NIR model can effectively distinguish between different components and provide accurate content uniformity assessment.

For example, Fig-1 shows the Montelukast API spectra and placebo exhibiting significant difference at 9300 cm-1 to 8500 cm-1 & at 7200 cm-1 to 5500 cm-1 wavelength ranges. These distinctive regions can be considered as important wavelengths crucial for further development of the spectrometric model.

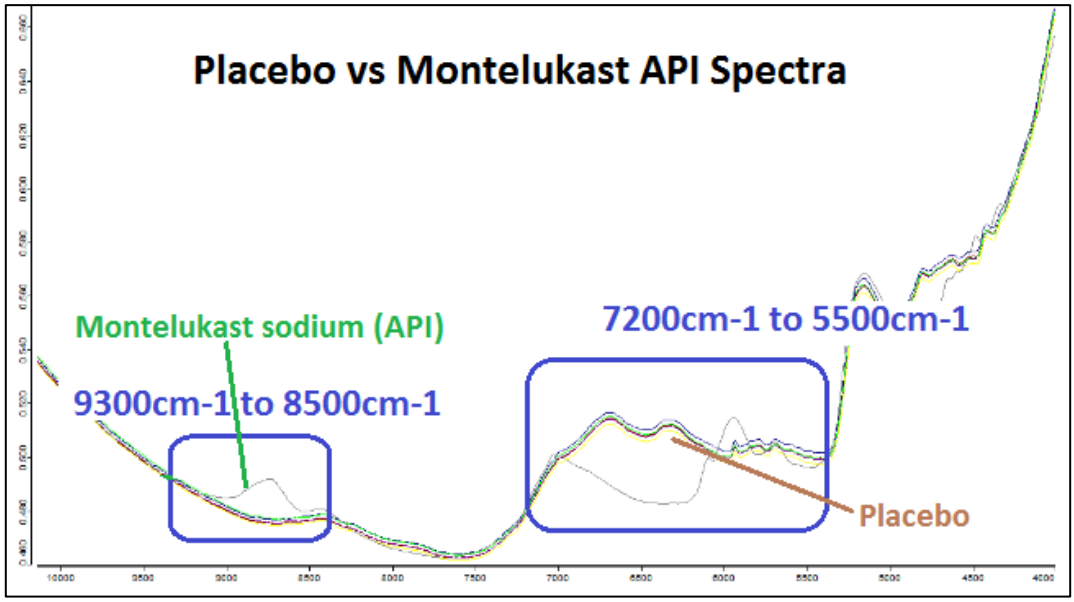


Figure 1 - Placebo tablets spectra comparison vs active drug substance spectra (Montelukast)

Sample preparation :

For at-line studies, sample preparation for calibration analysis typically involves minimal alteration to the physical form or characteristics of the sample. Specifically, this means refraining from grinding tablets or modifying their original state6. Once the sample is prepared, the subsequent step involves constructing a spectrometric model through the creation of a calibration set. This set serves as the foundation for developing the calibration model used for subsequent analysis.

B. Calibration sample preparation for calibration of model

Development of the calibration model :

For the development of an at-line Content Uniformity (CU) model, it is essential to have a traditionally validated reference analytical method, such as HPLC, RRLC, or UV method. This reference method data is used to train the spectrometric instrument software, to establish correlations between the concentration of the drug substance in the formulation and the corresponding spectral changes.

The reference method details should also be a part of regulatory filing, while submitting the NIR CU method for approval. This reference method, typically an HPLC-based method, serves as an alternate method of analysis, validating the accuracy and reliability of the model.

US FDA guidance suggests that: “An essential part of developing an NIR model is the construction of a calibration set. The spectra that comprise the calibration set are acquired from the calibration samples. To create a robust model, applicants should build a calibration set with samples that;

a. Include an appropriate concentration range for the component to be analyzed;

b. Address potential sources of variability (e.g., a variation in the processes, the analyzer, the physical characteristics of the materials, the water content, or the temperature); and

c. Cover the expected variations in process parameters (e.g., in-design space parameters) that have a potential to influence the spectral response.” 4

Appropriate concentration range of analyte :

It is suggested that the selection of the calibration sample range is based on prior knowledge of the variation in the drug product. However, it is strongly recommended to choose samples within the range of 100 ± 25% w/w of the drug substance label claim in the dosage form (such as tablets or capsules). Opting for a wider range in calibration samples enhances the robustness of the model. Typically, these calibration samples are prepared at the laboratory scale.

Potential sources of variability :

It is suggested to include all possible variations that may arise from process-driven variables, critical material driven variables and other factors. When implementing NIRS method for new products in product development, incorporating calibration samples that encompasses potential variability is relatively straightforward. However, for legacy products, the implementation of NIRS necessitates substantial effort to generate calibration samples that adequately represent the variability in process and material attributes. This could involve separate trials or batches to generate calibration samples that accurately capture the variability inherent to manufacturing process and material characteristics.

It is necessary to consider all potential parameters that can influence spectral response and capable of impacting the test results. Parameters such as water content or LOD range, hardness, compression machine run time, and others can be considered relevant. To ensure model robustness, it's advisable to encompass an acceptable range for each parameter. This comprehensive approach aids in capturing the full spectrum of potential variations encountered during the manufacturing process.

B. Construction of calibration set

For calibration sample preparation, it's crucial to account for any potential heterogeneity arising from the sample presentation. By incorporating these potential sources of heterogeneity into the calibration set, the model can better account for real-world variability encountered in sample presentation, leading to more accurate and robust calibration results.

The US FDA suggests that “Calibration samples should mimic as closely as possible the samples that are expected to be representative of the commercial process”4.

When preparing calibration samples, it's essential to consider all real-world variables such as weight variation, hardness, thickness, height, and others that mimic commercial manufacturing conditions. These variables should be within ranges that accurately reflect the variability encountered during production. The analyte range, which refers to the concentration range of the target analyte, is pivotal in determining the optimal combination of concentrations for calibration and subsequent observations. It's crucial to ensure that the calibration samples cover this analyte range adequately to facilitate accurate calibration. Furthermore, all samples prepared at the laboratory level for calibration should be in sufficient quantities to enable the calibration process to proceed smoothly4, 7.

Critical points to consider : 4

i. Maintaining Homogeneity: ensure homogeneity during sample preparation to stay within an accurate and precise calibration range. Any variations in the sample can potentially impact calibration results, maintaining consistency throughout the preparation process is necessary.

ii. Consistency in Tablet Attributes: during lab scale manufacturing, each attribute of the tablet, including morphology and physical form, should closely resemble those of commercial batches. This ensures that the calibration samples accurately represent the characteristics of the products encountered during actual manufacturing processes.

iii. Variation in Sample Concentrations: For each desired process variable sample, samples should be prepared with different concentrations. This variation allows for a comprehensive assessment of the calibration model's performance across the entire concentration range.

iv. Assessment of Material Variation: Calibration samples should be prepared by changing suppliers or manufacturing lots to assess the impact of material variation. This helps capture the predicted material variabilities encountered during the manufacturing process.

v. Consideration of Environmental Variables: Samples may be prepared while considering environmental variables such as temperature and humidity. Additionally, spectral acquisition or scanning can be adjusted to accommodate these variables, ensuring robust calibration under varying environmental conditions.

vi. Minimization of Differences in Physical Characteristics: Any differences in physical characteristics between commercial samples and lab samples should be minimized. Spectral preprocessing techniques can be employed to reduce the impact of these differences on the observed spectra, ensuring accurate and reliable calibration results.

Analysis method selection :

The sample presentation to NIR instrument can significantly impact the spectral quality. Few options for the presentation using a typical NIR are as below4, 8.

- Diverse reflectance - In this method, the spectral scan will cover a smaller area from the top and reflect back. Consequently, there is a reduced likelihood of unwanted substance interaction, resulting in decreased noise levels9.

- Transmission measurements - In this approach, scanning involves capturing spectra from the entire tablet, from top to bottom. While this comprehensive coverage increases the likelihood of encountering noisy spectral lines, it proves advantageous during calibration as it encompasses a broader range of variations10.

- Single and multiple sample holders – Different types of sample holders are utilized to secure tablets in a fixed position for analysis, such as tablet wheels or trays. When using a single sample holder, it's important to ensure there is no extra space around the tablet, as it can lead to unwanted particle interactions, resulting in unnecessary spectral responses. Additionally, if employing a multiple sample holder, it's crucial to maintain consistency in the number of samples placed within the holder. Changes in the material or supplier of the sample holder may impact spectra, necessitating calibration with standards and comparison of results against predefined acceptance specifications for both old and new sample holders11.

- Different probe window

- Variety of individual fibers in a fiber cable

The firm should determine the appropriate option from the aforementioned methods for model preparation, which should then be consistently utilized for both life cycle management and routine analysis. Any alteration in tablet presentation, particularly with embossing or stamping, can notably affect NIR predictions. To mitigate, it's essential to maintain consistency in sampling, ensuring the sample is presented to the instrument in the same way each time or by factoring this variation into the method itself 8.

Example of experimental design :

Under typical circumstances, the expected variation in content uniformity is within 100 ± 25%. However, this variation can vary between different products. Alongside content uniformity, hardness is another known variable. Considering the product's defined hardness value and varying concentrations of different samples, the firm should incorporate the hardness range of samples into the model calibration set. An example provided here includes proposed hardness limits for product lifecycle based on QbD-based product development.

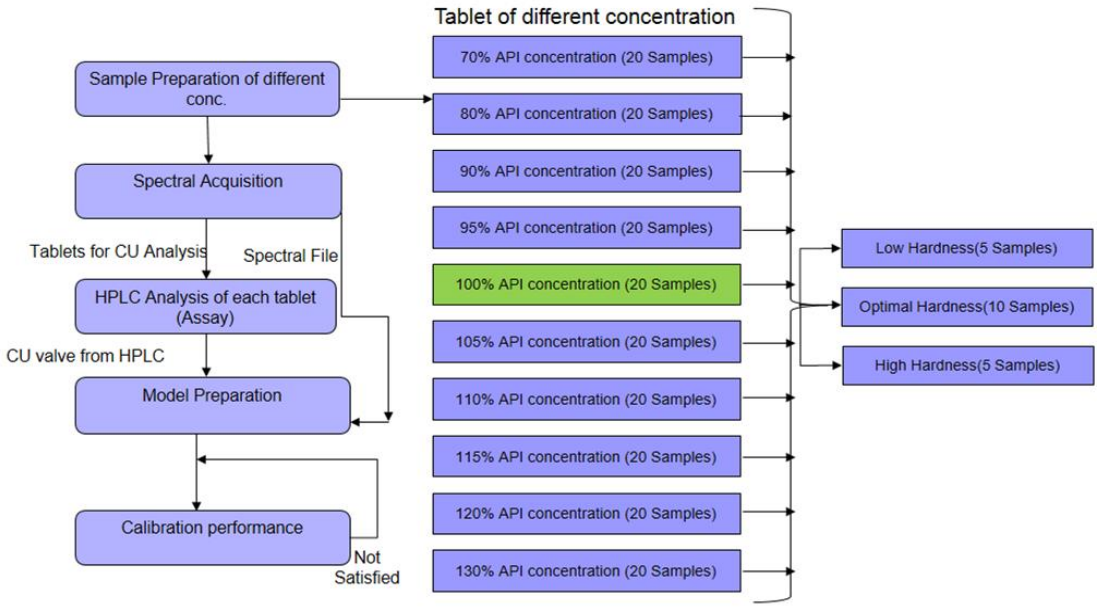


Figure 2 - Experimental Design and sample selections

During the selection of the calibration set, tablets should be collected to cover the entire compression process run for optimal hardness. Each tablet should have a unique identification number corresponding to its location in the compression run. Individual samples should be scanned first in the NIR instrument, followed by analysis of the same sample using an alternate/reference method such as HPLC.

To encompass all potential variations, each single tablet sample should be scanned on both sides twice, and the average spectra should be used for model preparation. This approach aids in incorporating variability from environmental conditions and instrument fluctuations during the model calibration process itself. If necessary, preprocessing should be applied during the model calibration phase where applicable.

These steps can be conducted at a small or lab scale to create the calibration set. After achieving successful calibration performance with lab scale data, the model can be extended to commercial scale batches to incorporate variations encountered at commercial scale. Refer example decision making process for model building and release for use as following:

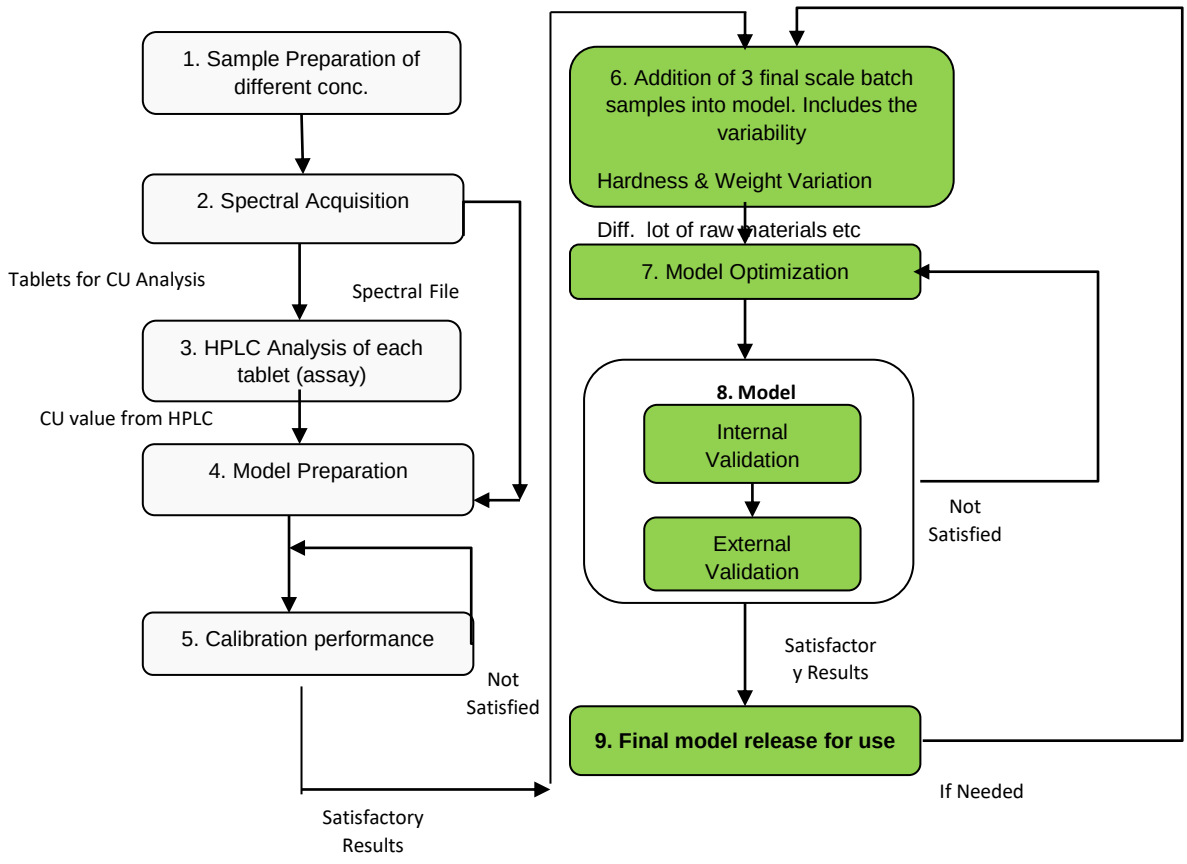


Figure 3 - Experimental design for model development

Pre-processing in a NIR analytical model for content uniformity of a drug product is a crucial step that involves transforming and enhancing raw spectral data to enhance the quality and reliability of the model. This process is essential for removing unwanted variations and noise in the data, ensuring that the resulting spectral information accurately reflects the precise chemical composition of the samples3, 5.

Before pre-processing can commence, spectra are collected from the drug product samples using a NIR spectrometer. These spectra usually span a wide spectral range, capturing molecular vibrations and overtones within the instrument's scanning capability for the required wavelength range3. The three commonly used pre-processing techniques are baseline reduction, scattering reduction and noise reduction.

Pre-processing sequence may influence the model outcome. Thus, the followings are critical :

- The order in which pre-processing techniques are applied can influence the results. For example, it is common to perform baseline correction and smoothing before applying more advanced techniques like MSC or SNV. The sequence should be carefully considered so as to avoid introducing unintended artefacts3.

- The ideal sequence is baseline reduction --> scattering reduction --> noise reduction.

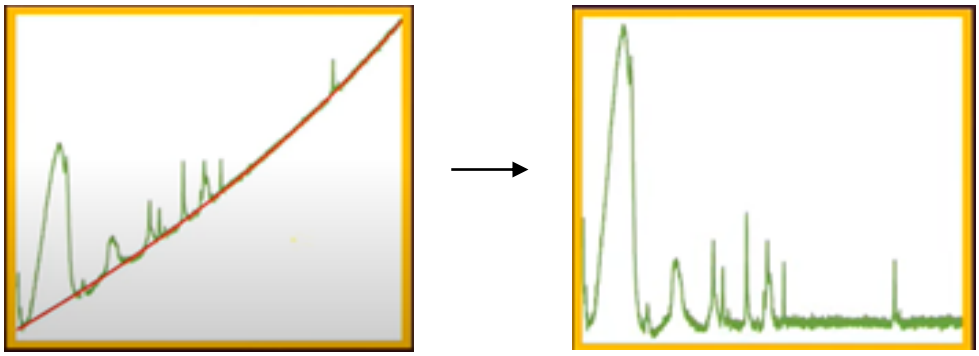
- Change in sequence can result in variation in results.

- The firm should carefully select pre-processing technique, as inaccurate selection of pre-processing may lead to loss of critical information and reduced model accuracy.

- The firm should apply minimum possible pre-processing techniques during model development, in order to gather maximum possible variation in the model, so as to make an accurate predictable model.

1. Baseline artefacts and correction technique :

Baseline correction is a technique used to remove baseline offsets present in NIR spectra due to various factors such as instrumental and environmental influences, impurities, and properties of the analyte. By eliminating these offsets, the spectral data is centered, ensuring that only the desired spectra are retained for further analysis4. This process helps to obtain precise results by nullifying the effects of offsets. During model development, it is advisable to avoid baseline reduction as it may lead to loss or alteration of data, considering that each spectrum may have a different polynomial5.

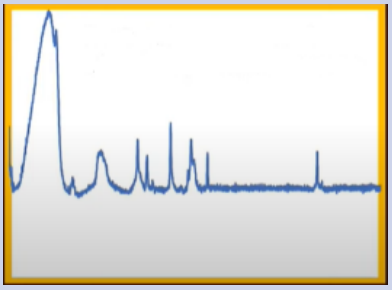
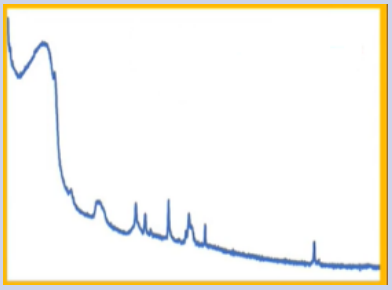


Before Pre-processing

After Pre-processing

Figure 4 - Example of pictorial spectra before and after pre-processing3

Table 2 : Causes of baseline offsets

Examples of Baseline Offsets	Pictorial Representation	Cause Of Offsets
Vertical offset baseline		Observed mainly due to instruments effects or luminescence.
Slope offset		Observed mainly due to instruments.
Curved slope offset		Observed usually due to fluorescence from impurities or the analyte properties. When fluorescence impacts, it may result in to smaller peaks instead of tall sharper peaks.

Following are the commonly used baseline correction methods :

- De-trending (polynomial fitting): It involves subtracting a polynomial of a specific order that adjusts to the spectra12.

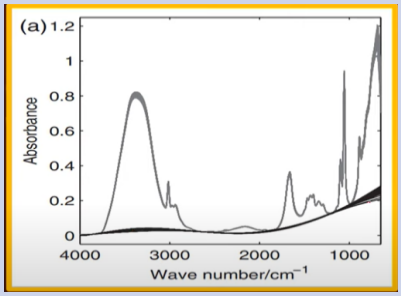
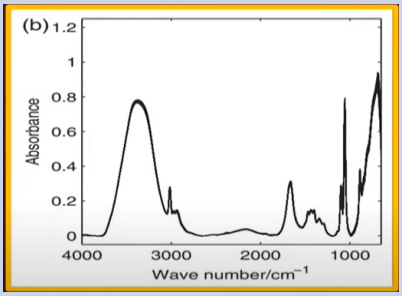
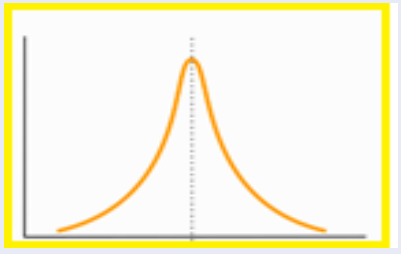
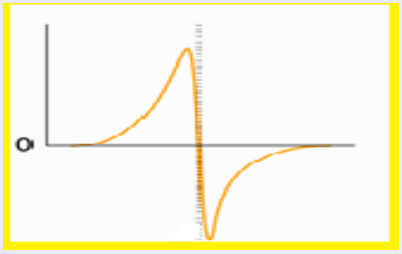
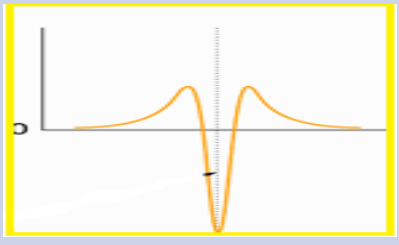
- Asymmetric least squares smoothing (AsLS): This requires subtracting a smooth line with an asymmetric weight for deviations12.

- First order derivative (SG-1 or Savitzky- Golay filter): It is utilized to eliminate the vertical baseline, resulting in peaks on both sides of the baseline3, 12.

- Second-order derivative (SG-2 or Savitzky-Golay Filter): It is used to eliminate both vertical and slope baselines, resulting in a peak on the lower side of the baseline; also used as noise reduction method3.

- First order and second order derivatives: This adjust polynomials within a specific range to reduce noise and separate pre-vibration mode peaks; also used as noise reduction method.

Table 3 : Pictorial comparison of spectra in baseline correction

Pictorial representation of spectra before baseline correction	Method applied	Pictorial representation of spectra after baseline correction
	Detrending & Asymmetric least squares smoothing (AsLS) method	
	1st order derivative method	
	2nd order derivative method	

2. Baseline artefacts and correction technique :

Scattering in artefacts is observed when samples of the same concentration exhibit changes in spectral intensity. This can arise from sample heterogeneity, sample detection error and instrumental effects.

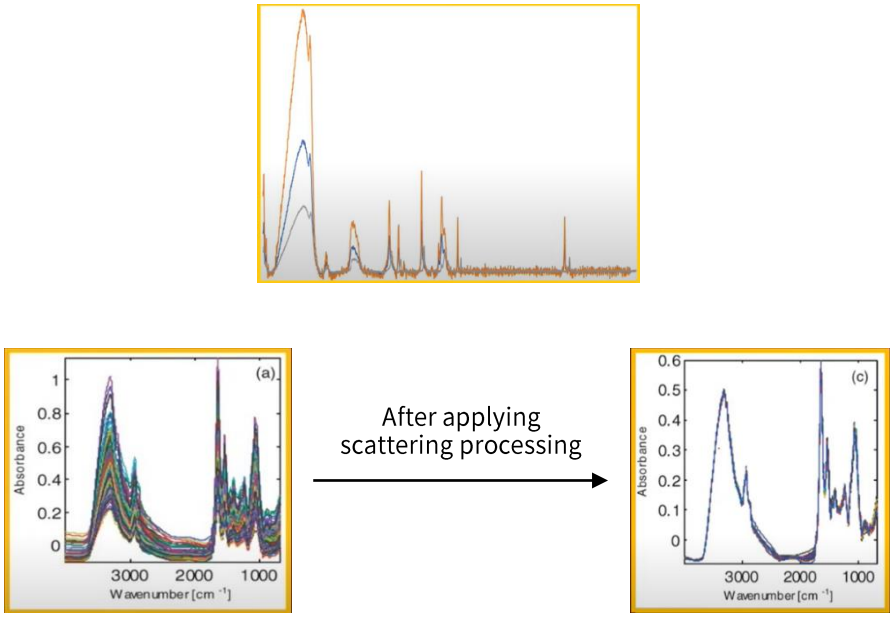


Figure 5 - Pictorial presentation of scattering of spectra having same concentration

Following are the commonly used scattering reduction methods :

- Standard Normal Variate (SNV) Transformation: In solid samples, NIR reflected light is frequently influenced by irregular particle shapes. Smaller particles may induce larger baseline offsets, and variations in path length can alter spectral peaks. The SNV transformation standardizes spectra to zero mean and unit variance, aiding in reducing spectral variability stemming from scattering and other factors3.

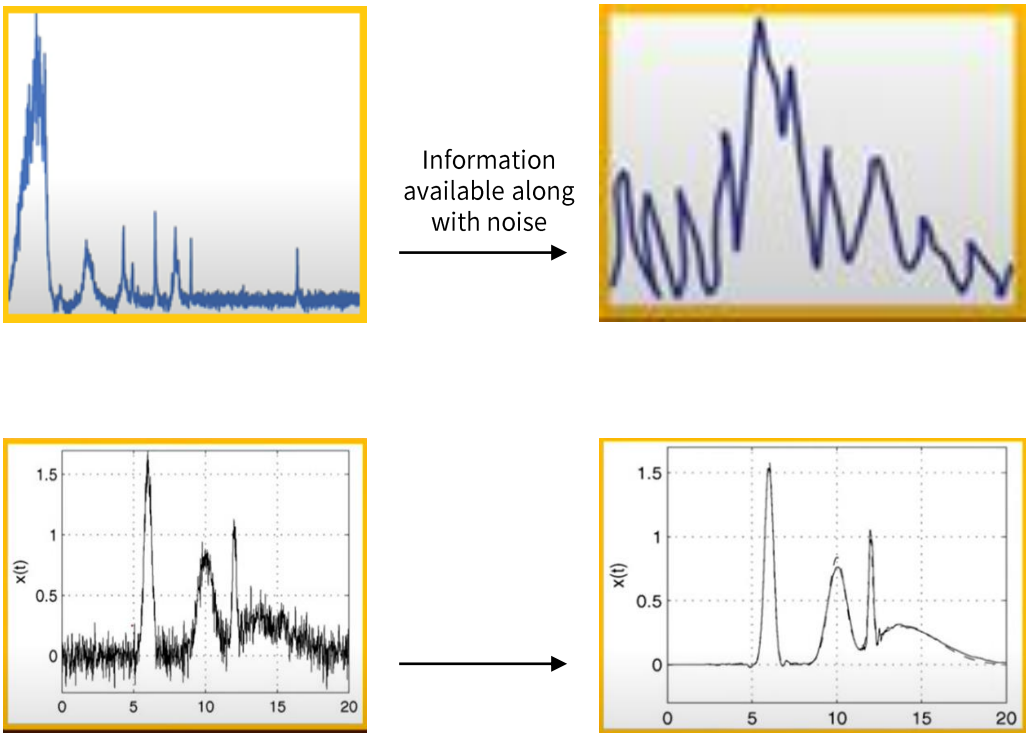
- Robust Normal Variation (RNV): Robust Normal Variate (RNV) transformation is an adaptation of the Standard Normal Variate (SNV) transformation method. While SNV normalizes spectra by subtracting the mean and dividing by the standard deviation at each wavelength, RNV subtracts the median and dividing by the standard deviation. RNV is more resilient to data distortions caused by outliers or non-normal distributions, resulting in enhanced performance, particularly in spectroscopic analysis of complex samples where variability or noise may be prevalent.

- Multiplicative Scatter Correction (MSC): MSC corrects light scattering effects which can distort the spectra. It involves dividing each spectrum by a reference spectrum that represents an ideal, scatter-free response3.

- General Normalization: Apart from above three methods, other general normalization methods can be applied by area normalization and maxima; these reduce scattering by identifying a constant aspect between samples and allow all samples to have their impact3.

3. Noise reduction methods :

Noise is spectral variation that are fast, random, and not displayed in the same form every time if multiple scans are taken for the same sample with the same measuring conditions. This is mainly dependent on the instruments and techniques used for measurement of the sample.
Noise reduction during model development can tamper with the data and may lead to loss of important information; hence noise reduction techniques can be applied carefully to get more precise and predictable results.



Pictorial spectra before noise reduction

Pictorial spectra after noise reduction

Figure 6 - Noise in spectra

The commonly used noise reduction approaches are as below :

- Noise reduction is possible with the first and second derivative methods discussed earlier in the section on baseline reduction processing. This is preferred method during model development.

- Moving average smoothing algorithm is alternative method for noise reduction. However, it is less effective for retaining original spectral shape. Hence this method is not recommended for use during model development but can be used for routine day to day analysis. This is calculated by substituting each point in the signal with the average of 'm' adjacent points.

- The best way to deal with noise is to scan the sample multiple times during model development, and by averaging the spectra; this helps to retain the original spectra and remove noise, as noise is typically not reproducible in each spectra3.

Calibration model :

There should be a defined approach for the construction of a calibration model. If needed, a mathematical pre-treatment or pre-processing should be done, which is cited as one of the important steps in chemometric analysis of the spectral data. Once the pre-processing steps are complete, the resulting data is used to develop the calibration model for content uniformity analysis.

The major algorithms for calibration are Multiple Linear Regression (MLR), Principal Component Regression (PCR), Partial Least Squares Regression (PLSR), among others. Since NIR spectroscopy relies on multiple signals, the calibration model should be developed by the multivariate methods14.

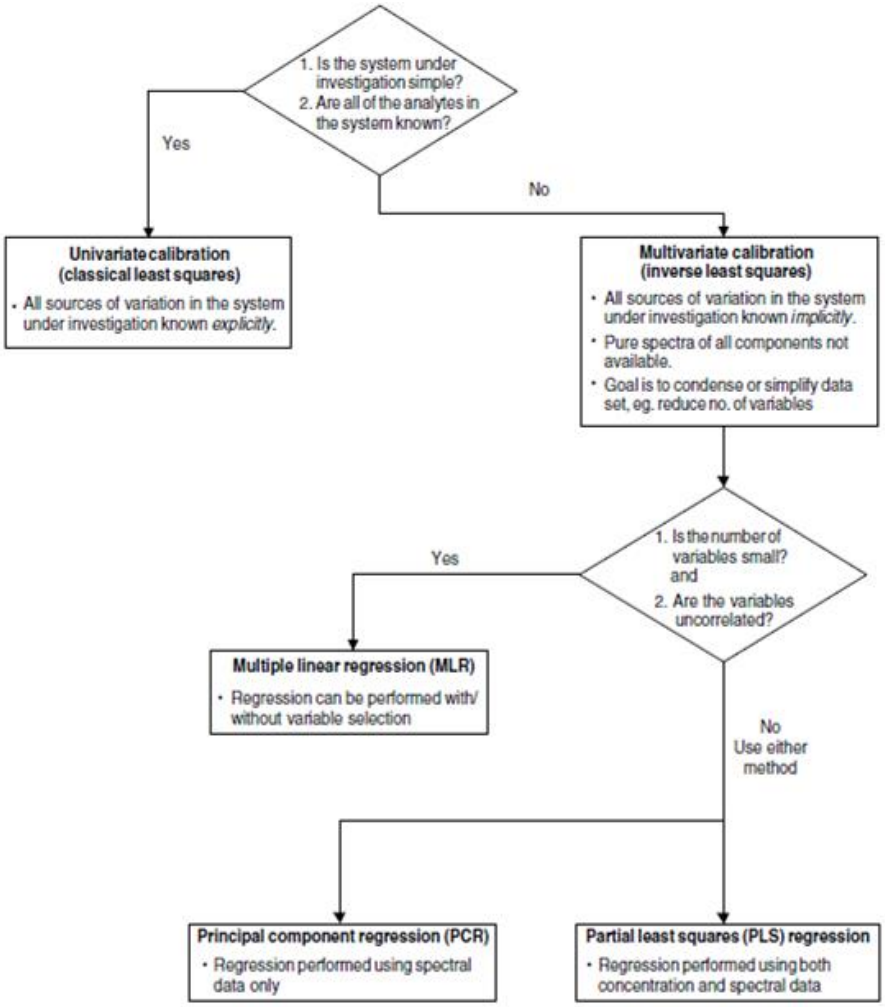


Figure 7 - Decision tree reflecting the construction of the quantitative model14

Model validation :

Various internal validation or cross-validation techniques can be used to evaluate the performance of the model and to ensure that the pre-processing steps have effectively improved the quality of the spectral data4.

The US FDA guidance described internal validation as below :

"Two common approaches for internally validating quantitative calibration models include

1. *Cross-validation using the calibration set*
2. *Validation using an internal validation set.*

1. Cross-validation using the calibration set :

The cross-validation process involves the following steps :

a. *Removing one or more spectra from the calibration set*

b. *Creating a model based on the remaining spectra*

c. *Applying that model to the spectra that have been removed*

d. *Calculating the differences between the known reference values and the values predicted by the model (i.e. the residuals)*

These steps should be sequentially applied to the entire calibration set and the resulting residuals can be used to calculate the root mean square error of cross-validation. 4

2. Validation using an internal validation set :

Validation using an internal validation set involves applying one or more models that were obtained from the calibration set to the internal validation set. The resulting residuals can be used to calculate the standard error of prediction (SEP).

The root mean square error of cross-validation or SEP can be used as one criterion for model optimization. The optimum model for the analytical procedure usually exhibits an acceptable error but minimizes the sensitivity of the error to small variations in either sample characteristics or model parameters.

At the end of the optimization process, the standard error of calibration (SEC) should ensure that the measurement is performed with the accuracy necessary for the intended purpose of the analytical procedure, such that the accuracy of the NIR method is comparable to that of the reference method." 4

External validation of NIR analytical procedures

US FDA suggests external validation as under :

"Internal validation of the chemometric model is not considered a substitute for external validation.
The samples used by applicants for external validation should :

1. *Span a suitable range of operating conditions (including the range expected during commercial production);*

2. *Be independent from the calibration and internal validation samples used during the development of the NIR models;*

3. *Be of a sufficiently large number to provide statistically meaningful results; and*

4. *Either be produced at the intended commercial scale or represent the commercial process. Also, results should be acquired either (1) from the NIR and reference analytical procedures using the same sample when feasible, or (2) by using representative samples and providing a justification for those samples."4*

The accuracy and precision of the NIR method should be comparable to those of the reference method. Consideration should be given to Root Mean Square Error of Calibration (RMSEC) and Root Mean Square Error of Prediction (RMSEP), residuals and calibration variable factor selection, etc. The regression coefficient (R2) for the NIR method can be calculated but does not have the same relevance or importance as it does for traditional univariate methods, and reliance should not be placed upon it. 15

*"**Accuracy**. The accuracy of the NIR procedure should be determined by comparing the results from the NIR analytical procedure using external validation samples with the results from a suitable reference analytical procedure.*
The SEP can be calculated as a measure of accuracy relative to the external validation set. Significant differences between the SEC and SEP, as well as significant biases, could indicate either differences between the calibration samples and the validation samples or an inadequately optimized calibration model, both of which should be appropriately investigated and rectified. The independent validation set used to determine the accuracy of the NIR procedure should span a suitable range of sample concentrations." 4, 15

"Precision. The standard deviation of repeat measurements (i.e. repeatability) can be a useful measure of precision. Samples for repeatability measurements should cover the expected range of sample variation. Multiple measurements should be made of each sample. If possible, the sample should be repositioned in the sample holder or on the sample presentation module after each measurement. Intermediate precision, which involves different analysts or different days, should also be determined." 4, 15

*"**Specificity**. Specificity is conventionally considered to be verified if the main features of the loading plots correspond to the loadings plots of the NIR spectrum of the analyte of interest. The NIR spectrum should be pretreated in the same way as spectra used in the model. Another element of specificity is the ability of the method to reject outliers (e.g., samples with high leverages or high residuals)." 4, 15*

*"**Linearity**. To evaluate linearity, analytical results for the external validation samples obtained using the NIR analytical procedure should be compared to the results obtained using the reference analytical procedure. If the resulting values are plotted over a suitable range, a correlation coefficient close to 1 and, where applicable, a y-intercept close to 0 indicate an acceptable linearity." 4, 15*

*"**Range.** As recommended in ICH Q2 (R1), the appropriate range for validation studies should depend on the attribute being evaluated." 4*

*"**Detection and Quantitation limits**. If the NIR analytical procedure will be used near the limit of its detection capability, detection limit and quantitation limit should be determined by, for example, analyzing minor components or detecting the endpoint for drying." 4*

*"**Robustness**. Robustness can be addressed during the calibration model's development by including anticipated sources of variability (e.g., raw materials and operating and environmental conditions). Robustness can be confirmed during validation by using validation samples that include sources of variability that may occur during commercial production." 4, 7*

Outlier detection and removal

As the guidelines suggest *"Potential outliers in the calibration set (e.g., samples with high leverages or high residuals or atypical NIR spectra or reference results), which can often be identified either by visual inspection of the data or during internal validation, should be investigated. Most software programs contain outlier and model diagnostics during prediction. Data resulting from spectral acquisition or reference analysis errors should be considered confirmed outliers and therefore rejected. Any inclusion or exclusion of outliers should be justified".4*

Outlier relates to findings that are unusual or fall outside of the designated range as define below : 4

- A "reference outlier" is spectrum data outside the range but reference value inside it.
- A "spectral outlier" is a spectrum data outside the range but contains predicted result inside range of spectral values.

There can be many reasons for data outliers, such as :

- Specimens belonging to a different set than the rest.
- Instrument defects.
- Reference method errors.

Identifying and removing outliers or spectral data points that are significantly different from the majority can improve the reliability of the model.

The approach described for method validation for tablet NIR content uniformity can also applied for other quantitative tests with preapproved calibration sample sets, e.g., assay.

Life cycle management

Just like any analytical method, PAT models that are developed and used in production require maintenance. A risk assessment is recommended to trace down the sources of variation and reduce the unknown sources of variation. Multivariate models are not perpetual due to the dynamic nature of processes and equipment, impacting the chemical and physical properties of drug products. While monitoring these variations is advantageous for ensuring final product quality, ongoing process enhancements introduce variability, necessitating model maintenance. Evaluating new variations and validating parameters becomes essential due to the evolving samples. Models developed under challenges such as inadequate sample size during calibration, limited consideration of short-term variations, and data generated from continuously improving yet poorly defined manufacturing processes require periodic maintenance to accurately capture the variations inherent in evolving processes.

Life cycle management assures the consistency and validity of the model throughout the life cycle of the product, ensured by periodic review and updates. Maintenance is critical like any analytical method and it should follow a standardized work flow to monitor as part of life cycle management. Because each PAT tool is unique and complex compared to traditional methods, the reporting of changes must follow certain rules to determine the impact of changes and the risk associated with each change. The regulatory authority has detailed it for the NIR procedure in the guideline, covering different reporting mechanisms based on the potential impact, categorizing changes as major, moderate, minor, or minimal changes. For a periodic verification, it is necessary to do the parallel testing challenge, and the number of samples depends on the cadence of periodic review and frequency of model utilization for predictions to have significant advantage.

While it is easy to state that models need to be reviewed and updated, the actual process of determining when and how to initiate such reviews and updates poses a considerable challenge. The following instances can be considered for maintenance of chemometric models to ensure accuracy and reliability in usage. The triggers for such maintenance should also be covered and determined as part of risk assessment, along with the criticality of application. The objective of model maintenance is to preserve or improve model performance over time and changing conditions, minimizing both cost and effort.

- Periodic review – determine the routine maintenance at regular time intervals (e. g., annually, or quarterly), to ensure that the NIR model remains accurate and reliable over time. One additional consideration in determining the interval is how frequently the model will be employed for making predictions and the robustness of model performance.

- Change in API – whenever there is a change in API, due to cost improvement projects or alternate vendor, it is necessary to revisit the model.

- Change in raw materials – revalidation is necessary when there are changes in suppliers or sources of raw materials; it is necessary to understand the impact of physical parameters like particle size, water content etc., even if the chemical purity remains the same.

- Process change – any modification or improvements to the manufacturing processes can affect the final product. In such cases, the model should be revalidated to account for these alterations.

- Dynamic sample variations - as fresh samples are continuously gathered for analysis during ongoing production, it becomes crucial to evaluate the model's ongoing accuracy in reflecting the current state. Integrating this evolving variability into the model ensures its adaptability to changing conditions. For a comprehensive understanding, it is essential to determine whether these variations are due to bias or variance.

- Performance deviations – when the model predictions begin to show deviations or drifts from expected results, it is a clear signal for urgent maintenance. Predictions with high deviation may indicate that the model can no longer account for the variations from evolving samples. Monitoring these deviations using statistical process control with appropriate tests for randomness can help detect early events.

- Regulatory changes – any guideline or new requirement changes would trigger a review of the model to comply with the new standards. Revision of specification limits by regulatory authorities, forcing the firm to reassess and/or recalibrate the model to meet new requirements, can be one such scenario.

- Process optimization/continuous improvement – during process optimization or continuous improvement efforts (within design space), it is essential to ensure that the model remains effective. Revalidation or adjustments to the model may be necessary when such optimization and/or improvement can impact the spectral sensitivity.

- Technology/instrument update – any change in instrument accessory, software upgrade/revision that may affect the spectroscopic aspects will require a risk assessment to ensure compatibility and accuracy.

- Periodic revalidation - NIR models should be periodically verified to check for any deviations or changes in the performance. Regularly scheduled revalidation helps prevent issues from arising and ensures consistent, accurate results.

- ❖ Diagnostic trending – as part of continued process verification, it is necessary to trend the diagnostics of the predictions with well-established acceptance criteria. Two significant measures are the distance from center of model or the measure of variation in each sample within the model, and the distance to the model i.e., magnitude of variation or the measure of variation remaining in each sample after projection through the model.

The outcome of the above review or assessment should be based on the risk associated and its criticality should trigger the need and level of maintenance. All these activities should be thoroughly documented for traceability.

Methods to Update the Model

There is no hard and fast rule on the methods to update the calibration model; however, simple approaches should be tried first before using complex methods. Given below is the list of approaches in order of complexity and how each can be addressed.

Table 3 : Model improvement techniques

Model Updating Methods	Description
Slope and bias adjustments	Simple post-processing method involving adjustments to the slope and bias of predictions. Effective under limited circumstances, such as fixed concentration changes in analytes or alterations in optical properties. Ineffective for correcting new variations in data.
Adding samples to existing calibration model	Expansion of the calibration set by adding samples exhibiting new variations. Suitable when a new analyte is introduced or a previously fixed analyte starts to vary. Multiple samples may be needed, and methods for up weighting new samples exist.
Instrument standardization/calibration transfer procedures	At times, there could be a need to transfer models between instrument of the same make or of a different make. Transfer learning in such scenarios requires to measure samples in both instruments and develop the estimates for the target instrument. This utilizes methods like Direct Standardization (DS), Piecewise Direct Standardization (PDS), Spectral Space Transformation (SST) variants, and more. Methods may reduce net analyte signal but preserve common features. Challenging in regulatory environment.
Complete recalibration	Considered a last resort, complete recalibration is performed when the original model lacks relevant information. Typically done when the model has essentially no useful data. Rarely recommended due to its drastic nature.

References :

1. Bidlingmeyer, B.A (1993). *Practical HPLC methodology and applications.* John Wiley & Sons.

2. Peeters, M., De Beer, T. and Kumar, A (2023). *Near-infrared Spectroscopy as Process Analytical Technology in Continuous Solid Dosage Form Manufacturing.* In Continuous Pharmaceutical Processing and Process Analytical Technology (pp. 311-337). CRC Press.

3. Sun, D (2018). Virtualization and real-time analysis of pharmaceutical and food products by near infrared spectroscopy.

4. Development and *Submission of Near Infrared Analytical Procedures, Guidance for Industry (2021).* U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER).

5. Broad, N., Graham, P., Hailey, P., Hardy, A., Holland, S., Hughes, S., Lee, D., Prebble, K., Salton, N. & Warren, P (2002). *Guidelines for the development and validation of near-infrared spectroscopic methods in the pharmaceutical industry.* Handbook of vibrational spectroscopy, 5, pp.3590-3610.

6. Smith, M.R., Jee, R.D., Moffat, A.C., Rees, D.R. & Broad, N.W (2003). Optimization of partial least squares regression calibration models in near-infrared spectroscopy: a novel algorithm for wavelength selection. *Analyst*, 128(11), pp.1312-1319.

7. European Medicines Agency (2012). *Guideline on the Use of Near Infrared Spectroscopy (NIRS) by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations.*

8. Kawano, S (2002). *Sampling and sample presentation. Near-Infrared Spectroscopy.* Siesler, HW, Ozaki, Y., Kawata, S. and Heise, HM WILEY-VCH Verlag GmbH D-69469 Weincheim, Germany.

9. Wetzel, D.L (1983). Near-infrared reflectance analysis. *Analytical chemistry*, 55(12), pp.1165A-1176A.

10. Sulub, Y., LoBrutto, R., Vivilecchia, R. & Wabuyele, B.W (2008). Content uniformity determination of pharmaceutical tablets using five near-infrared reflectance spectrometers: A process analytical technology (PAT) approach using robust multivariate calibration transfer algorithms. *Analytica chimica acta,* 611(2), pp.143-150.

11. Xiang, D., Konigsberger, M., Wabuyele, B., Hornung, K. and Cheney, J. (2009). Development of robust quantitative methods by near-infrared spectroscopy for rapid pharmaceutical determination of content uniformity in complex tablet matrix. Analyst, 134(7), pp.1405-1415.

12. Peng, J., Peng, S., Jiang, A., Wei, J., Li, C. and Tan, J. (2010). Asymmetric least squares for multiple spectra baseline correction. *Analytica* chimica acta, 683(1), pp.63-68.

13. He, X., Fu, X. and Rao, X., 2018. Model robustness improvement by absorption and reduced scattering spectra in short wave near infrared spectral region. *Biosystems engineering*, 176, pp.114-124.

14. Chalmers, J.M. & Griffiths, P.R., 2002. *Handbook of vibrational spectroscopy.*

15. Li, W., Luo, Y., Wang, X., Gong, X., Huang, W., Wang, G. and Qu, H (2022). Development and Validation of a Near-Infrared Spectroscopy Method for Multicomponent Quantification during the Second Alcohol Precipitation Process of Astragali radix. *Separations*, 9(10), p.310.

5 PROCESS ANALYTICAL TOOLS FOR FLUID BED PROCESSING

1. Introduction :

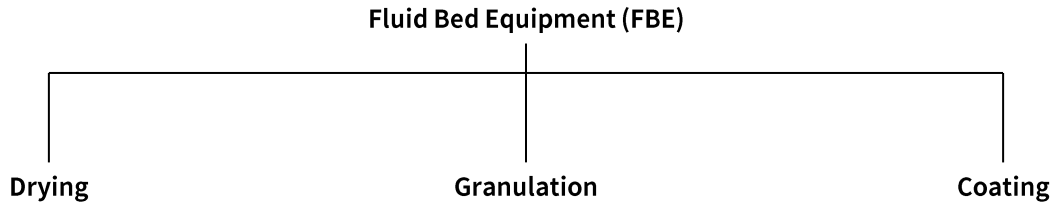
Fluid bed processing has become a common operation in pharmaceutical companies because of closed and controlled 'one pot' process capability of Fluid Bed Equipment (FBE) for granulation and drying unit operation. Wherever Rapid Mixer Granulator (RMG) is used for granulation operation, FBE serves the purpose for drying operation.

FBEs are also being increasingly used for coating operations for pellets or spheres where drug and polymers are loaded either separately or in combination to serve final formulation as control release, enteric coated or taste mask product.

Although the use of FBE has served as an efficient equipment for processes of the above-mentioned units by saving considerable turnaround time, end point determination remains a largely laboratory dependent operation. Hence waiting for in-process clearance may require sampling and analysis by carrying sample to either QC or in-process test area where getting results may takes a considerable amount of time. This results in holding the granules or blend inside the equipment for next stage until clearance is obtained.

Table 1 : Fluid Bed Process Parameters and Quality Attributes

Fluid Bed Processes Unit Operations	Typical Process Parameters	Quality Attributes
Granulation (top spray)	❖ Spray nozzle size ❖ Spray nozzle location ❖ Inlet temperature ❖ Product/exhaust temperature	❖ % Weight gain ❖ Moisture content ❖ Solvent content ❖ Particle Size Distribution (PSD) ❖ Rheology
Drying	❖ Air flow ❖ Inlet temperature ❖ Product temperature	❖ Loss On Drying (LOD) ❖ Moisture content ❖ Solvent content
Coating	❖ Spray rate ❖ Atomization pressure ❖ Air flow ❖ Gun nozzle size ❖ Inlet temperature ❖ Product temperature ❖ Column height ❖ Air distribution plate type	❖ % Weight gain ❖ Moisture content ❖ Solvent content ❖ PSD



- Rate of water loss
- Rate of solvent evaporation

- Rate of particle growth
- Particle size distribution

Fig.1 Parameters monitored in Fluid Bed Process by PAT

Process analytical tools offer multiple benefits in fluidized bed process related unit operations. Selection of tools depend on each unit operation, and this can be further classified as in-line, on-line or at-line PAT based upon its actual location.

Table 2 : Typical process analytical technique and tools available

Fluid Bed Processes Unit Operations	Typical Process Parameters	Quality Attributes
Particle size Distribution	Direct imaging particle size analyser (Eyecon) Focussed Bed Reflectance Measurement (FBRM) Laser diffraction PS analyser (Insitec system, Parsum)	Direct imaging particle size analyser (Eyecon) Focussed Bed Reflectance Measurement (FBRM) Laser diffraction PS analyser (Malvern)
Moisture content loss on drying solvent content	❖ Moisture analyser ❖ Near Infra-Red (NIR) ❖ Mass spectrometer (MS)	❖ LOD moisture analyser
Powder rheology (bulk, flow & shear properties)	--	FT4

These techniques are termed on- or in-line, where on-line methods automatically take samples to be analyzed without stopping the process, and includes an option to return the sampled material to the process stream, and in-line methods directly measure the process stream with no sample removal or diversion. On-line and in-line analyses permit continuous process control.

2. Process Analytical Tools for Particle Size Measurement :

Particle size is an important parameter to control during Fluidized Bed Processing (FBP) operations, granulation, drying, and coating. Various process conditions (temperature, air flow, atomization, etc.) affect the PSD, hence the resulting granules need to be characterized and controlled wherever required. Analysis of particles and characterization of their size and shape are of great importance not only during the design of the process, but also during scale up and commercial manufacturing through Process Performance Qualification (PPQ) and Continued Process Verification (CPV) depending on the product nature. During FB processing, due to heat and mass transfer, critical material attributes get modified thanks to densification, size enlargement, and due to undesirable size reduction. PSD of the granules, pellets, spheres that are used in the manufacture of capsules, tablets, and other modified dosage forms, influence the release of the drug and thereby have direct impact on the efficacy of the formulation. Various tools used during processing, based on the different techniques like laser diffraction, dynamic light scattering and direct imaging, are being employed by the industry as process analytical tools. These tools provide immediate, real-time data and are discussed here in terms of their fundamental principles, correlation with particle properties, instrument configuration, and the limitations of each method.

Particle size analyzer using direct imaging

Direct imaging particle size analyzer (e.g., Eyecon®) measures size and shape information of particles in the size range of 50 - 5500µm in real-time. It is a non-destructive, non-product contact analytical measurement tool which can be used as a bench-top laboratory instrument and in-line as a process analytical technology. The method of direct imaging allows images of samples to be captured which convey surface morphology and reports shape information. It is suitable for measurement of wet and dry powders and bulk solids. This measurement allows tracking of particle size growth and decrease in process time as it continuously captures and processes data in real-time.

In principle, it calculates particle size distributions based on the measurement of individual particles within a sample image. By utilizing intense pulses of light from an array of front facing LEDs, particles which are moving up to 10 m/s can be captured by the camera sensor without the presence of motion artefacts. The LEDs pulse at high intensity every 0.65 seconds illuminating the sample to be measured. The front facing direct illumination provides the ability to distinguish overlapping particles. The camera sensor is synchronized with the pulsing of the LEDs to capture the sample material while it is illuminated. These captured images are then processed by the software where the particle detection algorithm identifies and measures individual particles within the captured image. Measurement data which is recorded and calculated include the D10, D25, D50, D75, D90 as numeric and volumetric size with Mean and Median values all trended in real time with live histogram and S-curve results. Determination of the D-values is achieved by first fitting individual particles with an ellipse in order to determine the minimum and maximum diameter of the particle, i.e., Dmin and Dmax. The magnitude of the third dimension is predicted by the average of Dmin and Dmax to get Davrg. The 3D volume of the ellipse which surrounds any particle is calculated using an equation, in which the D-values are computed notionally by arranging all particles measured in order of ascending volume. The total volume is computed first. An iterative algorithm then adds the volumes starting with the smallest and working up to the largest. The D10, D25, D50, etc., are the particles which corresponded to reaching 10%, 25% and 50% of the cumulative volume respectively. All recorded data is analyzed in real-time to determine the overall process D-values based on the data captured throughout the whole recording session.

Correlation :

Particle dimensions that are identified by the software, are fitted with an ellipse that is constructed based on an applied edge detection algorithm. Applying an ellipse to a particle for the determination of the volume based on the maximum and minimum diameter and average of the min and max will result in a tighter, typically smaller volume fit than the cubed diameter of an equivalent circle fit to the same particle. This allows an instrument to more accurately calculate particle volume which will affect the subsequently calculated D-values.

The eccentricity or shape of each particle is calculated and is presented as an average eccentricity for the full recording session, as well as the relative standard deviation of the eccentricity. Eccentricity can aid in blend uniformity and homogeneity analysis. A key advantage of front facing direct illumination, compared to other direct imaging methods that use a backlight, is the ability to distinguish overlapping particles. Backlight imaging can silhouette multiple particles which are overlapping on the same axial plane as the light source, which results in the erroneous identification of a larger particle than is presented. When the instruments can correctly identify overlapping particles, the particles at the forefront of the grouped particles will be analyzed. Particles whose boundaries are obscured will not be included for particle sizing. This prevents the error due to overlapping particles.

In-line instrument

On-line/At-line

Fig.2 Particle size analyzer using direct imaging (e.g., Eyecon®)

Limitations :

Every particle analyzer has areas in which it is not suitable for obtaining highly accurate measurement results. Eyecon has the following limitations :

Limit of detection of particles ranges from 50 to 5500µm in size.

- Difficulty in obtaining accurate measurement results of dark particles without algorithm optimization by user. This is a trial-and-error process and can take some time to optimize.
- It uses direct illumination of sample for particle identification within the algorithm; therefore, transparent materials such as glass and some polymers cannot be accurately measured.
- Highly reflective particles are difficult to measure due to the reflected light.
- The focal length of the system is limited. which means samples must be adequately close in order to appear in focus and measurable by the system.
- The depth of field is small which means that material with a very wide sample range distribution will be difficult to measure at the extremes of the distribution curve.

Particle Size Report and Sample Images from the Analyzer :

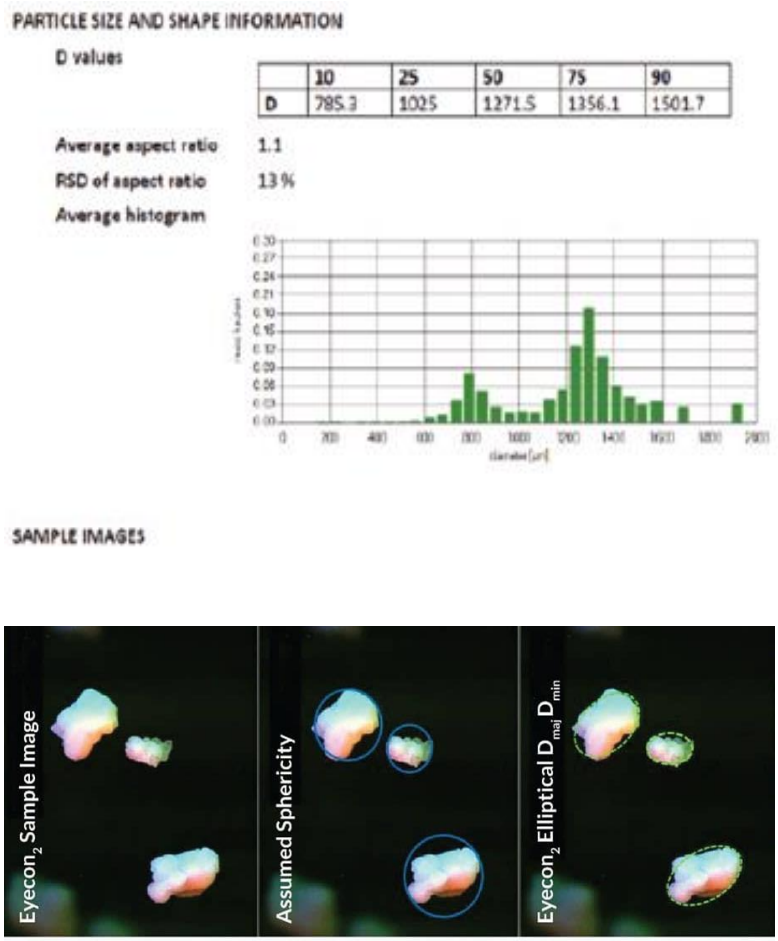


Fig.3 Sample report and images from the Particle size analyzer using direct imaging (Eyecon, Courtesy- Innopharma Technologies)

Laser Diffraction Particle Size Analyzer

Traditionally, laser diffraction-based analyzers are being used for analysis of particle size distribution at the end of the granulation or coating to determine the end point.

However, it can also be used for in-line, online and at-line measurements. When used in-line, it detects the image of the particles 'as is' in its true form, where it cannot differentiate agglomerates from individual particles. During at-line measurement, as the sample gets enough time and the agglomerates may get dispersed into individual particles while sampled through sampling port, thus giving narrower particle distribution compared to the bimodal distribution in inline mode.

The possible solution for the issue of agglomerates contributing error:

1. To establish correlation between the in-line and at-line measurements which need pilot-scale experiments.

2. Use of dispersion system during in-line measurement, if process not impacted.

3. On-line measurement where separate sample loop will provide air dispersion system.

4. To set a data acquisition range by excluding agglomerate.

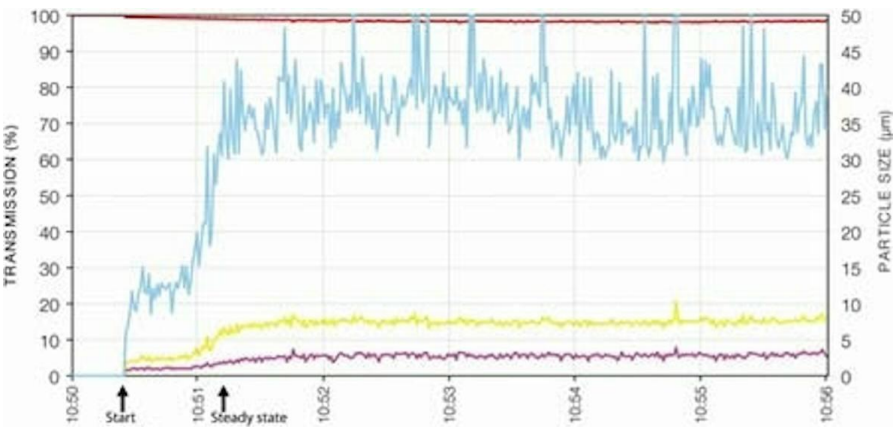


Fig.4 Laser diffraction PS analyzer data (e.g., Insitec)

Fig.5 Laser diffraction PS analyzer assembly (e.g., Insitec)

Features of such systems include :

- Suitable for the widest variety of process streams from dry powders to hot sticky slurries, sprays, and emulsions.
- Particle measurement can be performed in the size range 0.1 micron to 2.5 mm
- Useful to measure the spray droplet size between two scales of coating
- Both at-line and in-line measurement possible

Sample Measurement :

These systems use the technique of laser diffraction to rapidly measure particle size. Working with spray systems, complete particle size distributions are measured in less than a second, giving instantaneous monitoring. Even fine temporal fluctuations in spray patterns can be tracked effectively. It directly measures the spray or aerosol. Such materials may have very high particle concentrations and can present a challenge for many particle measurement systems. However, the multiple scattering algorithm ensures that the output is mathematically correct for the concentration-dependent effect of the source light interacting with the particles before reaching the detectors. Therefore, measurement is independent of sample concentration.

Data Presentation and Use :

Laser Diffraction Analytical systems can be integrated within the process plant. They can be operated as stand-alone units or from a centralized control room. Measurement results drive routine decision-making during development and in manufacture. Powerful software packages make integration and data interpretation straightforward.

Suitable softwares are available which integrate not only with the PS analyzer instrument but also with other instruments, simplifying multivariate control. e.g. Malvern Link II, RTSizer

System Specification :

Measurement type	Particle size
Measurement range	0.1 to 2500µm
Measurement principle	Laser diffraction
Optical models	Mie theory
Accuracy	±2% on Dv(50) reported using the verification reticle

General

Power	100/240V
Enclosure rating	IP65
Operating platforms	10 bar (g)
Software	RTSizer (for instrument control) Malvern Link II (for system automation and data link)
Maximum distance from instrument to PC	500m (up to 2 km using fiber optics)

Operating environment

Temperature	10°C – 70°C
Humidity	35% - 80% (non-condensing)

Focused Bed Reflectance Measurement (FBRM) :

FBRM can be used for in-line particle size measurement during fluid bed granulation /coating process. FBRM probe requires that particles flow in front of the probe window while a rotating laser beam is focused on particles. The probe detects backscattered light and records measured chord lengths. An at-line FBRM technique can be developed to monitor the granule growth during fluid-bed granulation.

The FBRM instrument is composed of three parts: a measurement probe (Fig. 6a), an electronic measurement unit, and a computer for data acquisition and analysis. The probe is typically immersed in a flowing suspension of particles. FBRM is easy to use and has minimal maintenance and calibration requirements. On the other hand, the major drawback of the technology is potential fouling of the probe window by the dispersed material. If material sticks to the probe window, the same particles tend to be counted multiple times. The newer Mettler Toledo FBRM® C35 probe and icFBRM software have addressed the fouling issue by including a scraper unit that keeps the probe window clean and software that corrects for multiple counting of any adhered particles. Briefly, the FBRM system uses a rotating laser optics design that can determine particle chord lengths by detecting reflected light from the particle. A laser beam is projected through a sapphire window (Fig. 6a), and when the focused rotating laser beam contacts the particle, light is reflected and propagated back through the probe sapphire window. The particle continues to reflect light until the rotating focused beam reaches the opposite edge of the particle. Particle size is measured in terms of a “chord length” (Fig. 6b), which is defined as the distance between the two edges of a particle. The software calculates the chord length by multiplying the optical rotating laser scan speed by the reflected signal time. The scan speed can be adjusted from 2 to 8 m/s to accommodate different sample particle size distributions, dispersion concentrations, and dispersion flow rates. Thousands of chord lengths are acquired per second and are organized in channels (size intervals). The chord length is expressed as a frequency distribution (Fig. 6c). The influence of particle shape, particle refractive index, dispersion media refractive index, focal length, suspension concentration, amount of fines, and particle size on chord length distributions have been investigated to relate chord length distributions to the “real or actual” particle size distributions. FBRM measurements can be used to qualitatively represent material particle size without converting it into the actual particle size or particle size distribution. For most applications, the relevant in-process and product attributes may be correlated directly with chord lengths and chord length distribution.

Components of FBRM Measurement: There are three components to discuss the FBRM measurements: FBRM probe, Chord length measurement, and Chord length frequency distribution

The diagrammatical representations are given below :

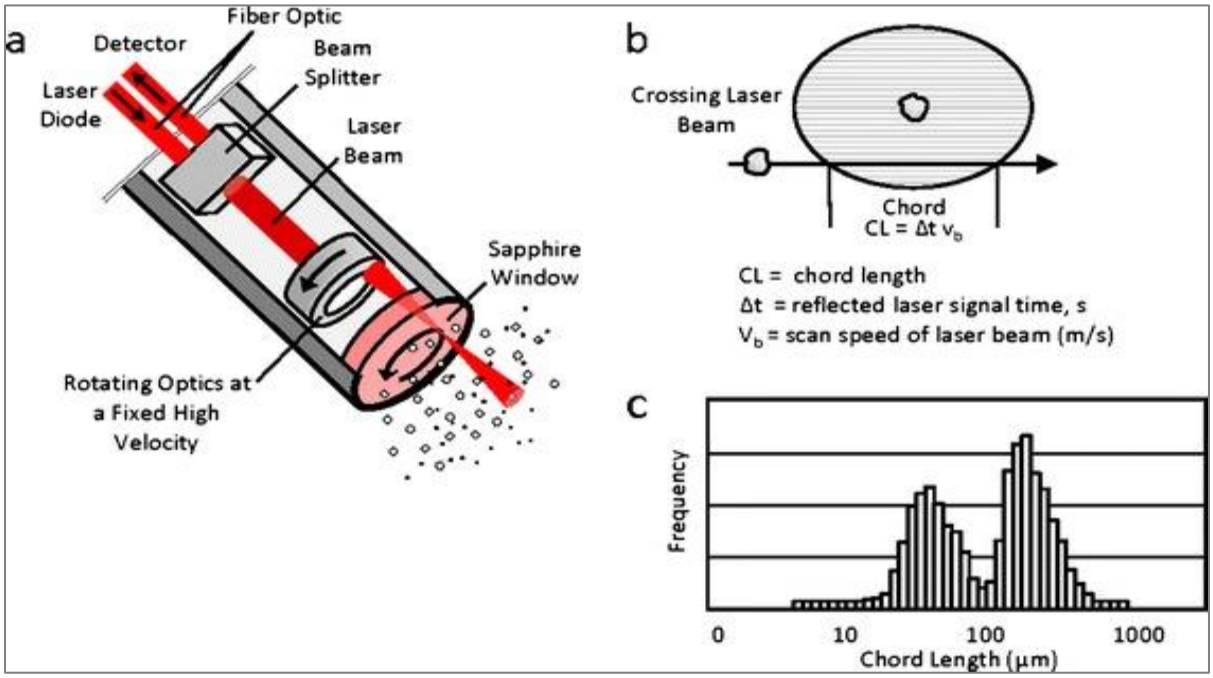


Fig.6 FBRM sapphire window, chord length, frequency distribution

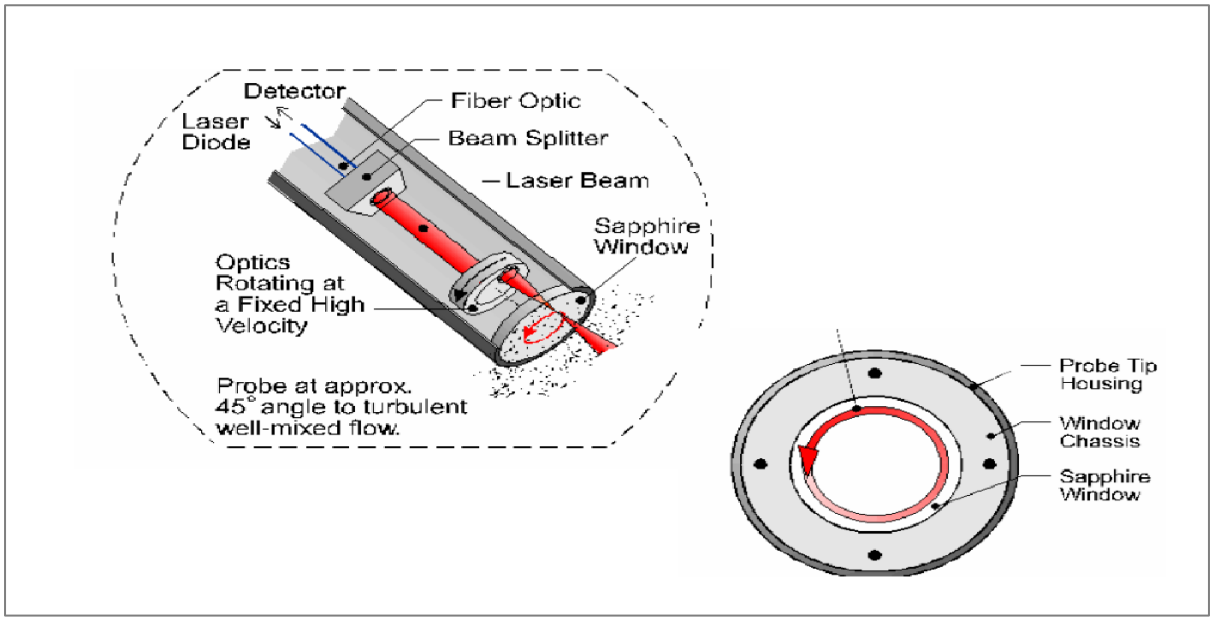
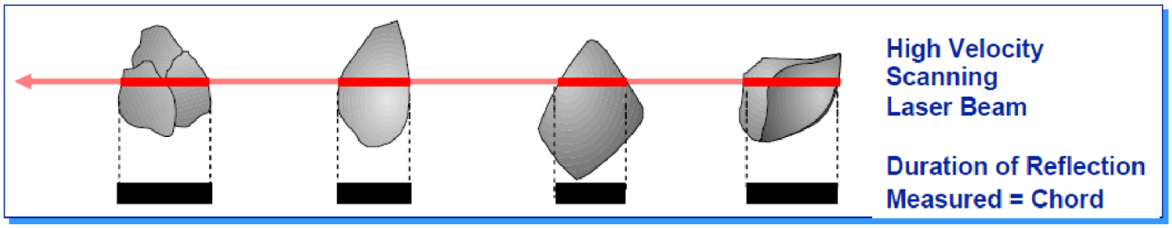


Fig.7 FBRM probe assembly



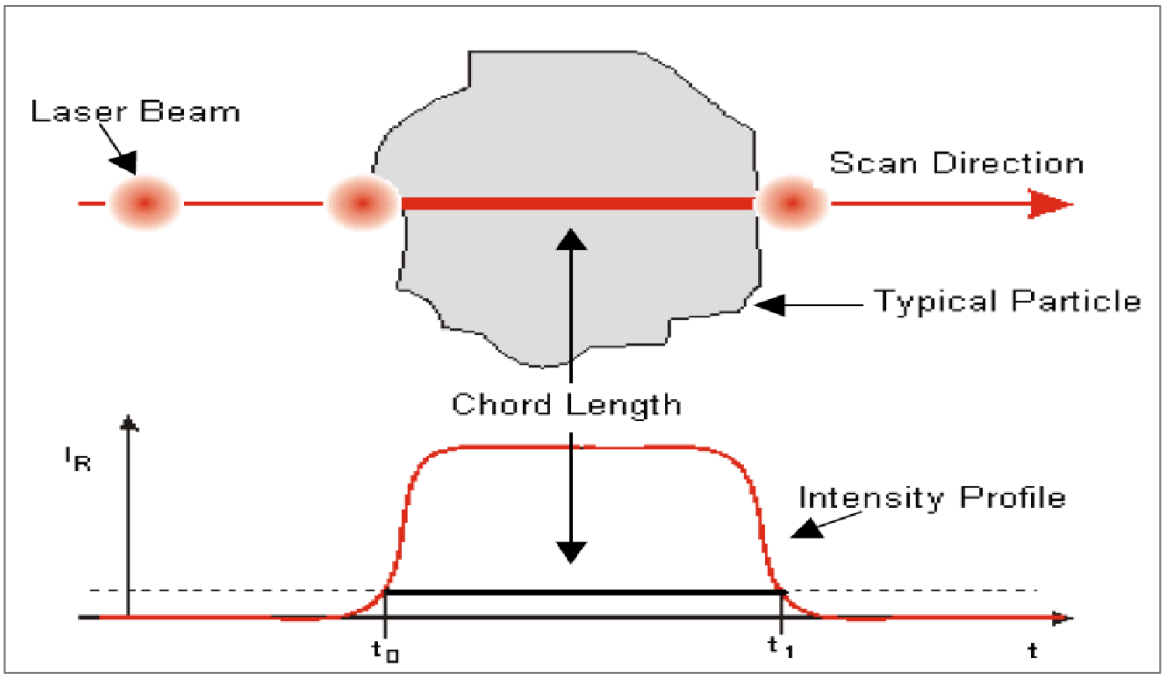


Fig.8 FBRM chord length concept

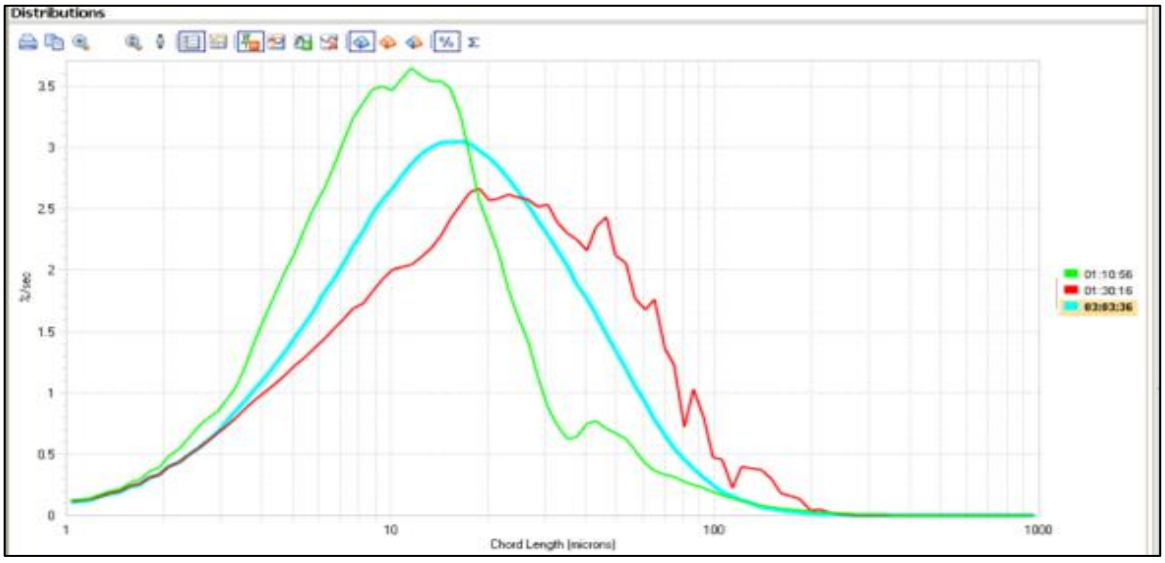


Fig.9 FBRM – chord length frequency distribution data

3. Moisture/Solvent Content Measurement and PA Tools Available :

Moisture and solvent content determination are critical as end point data of the drying operation as most of the solid dosage forms are typically granulated with either water or solvents.

Monitoring Moisture in the Drying Process using NIR Tool :

Moisture content can be determined with in-line near infrared spectrometer in fluid bed drying. Preparation of calibration is set by varying moisture concentration. PLS model needs to be developed by correlating NIR spectral absorbance of calibration samples with the reference values from laboratory.

Fig.10 NIR probe-FBE assembly

Regression Model Building :

Chemometric knowledge is required to build the regression model. Initial spectra are obtained as shown below.

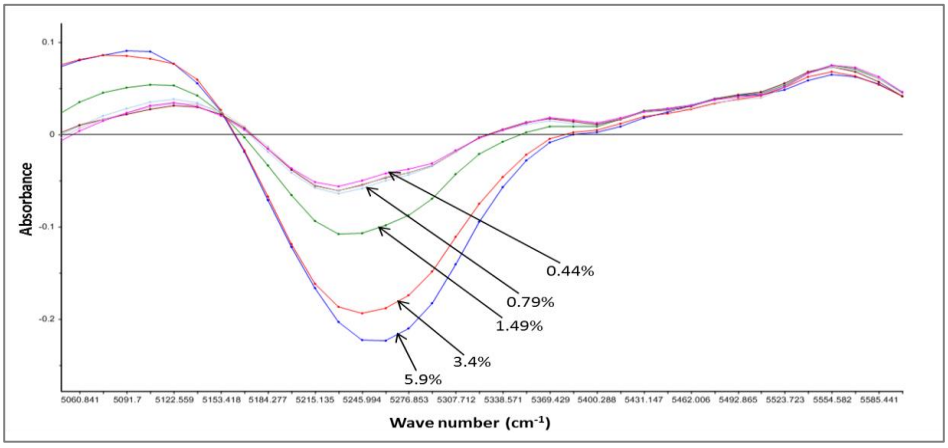


Fig.11 Typical NIR spectra (initial) for moisture content determination

Linearity Assessment for Different Moisture Samples :

Second derivative spectra show the linearity for different moisture samples.

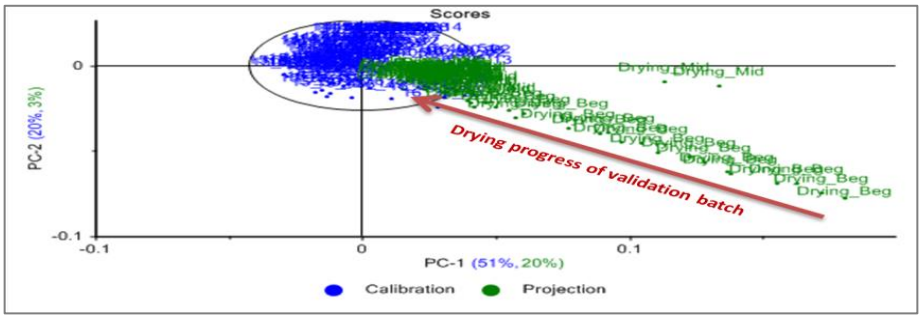


Fig.12 Typical NIR spectra (derived) for moisture content determination

End point can be seen in real time by projecting the validation batch spectrum on the PCA model developed with end point spectrum of calibration batches.

PLS model predicts the moisture content in real time.

NIR Predictions:

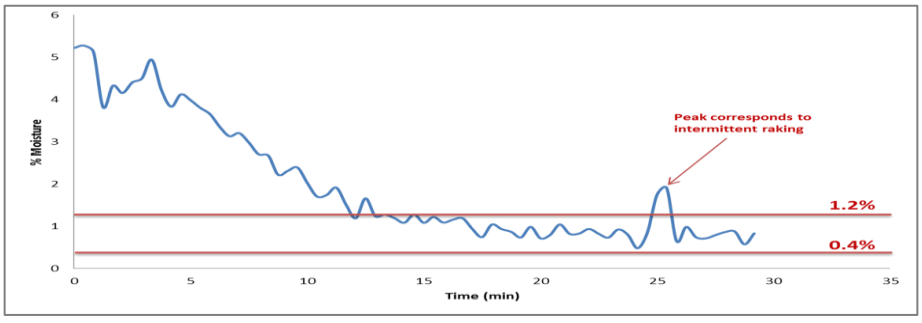


Fig.13 Typical NIR spectra (% moisture vs time) for moisture content determination

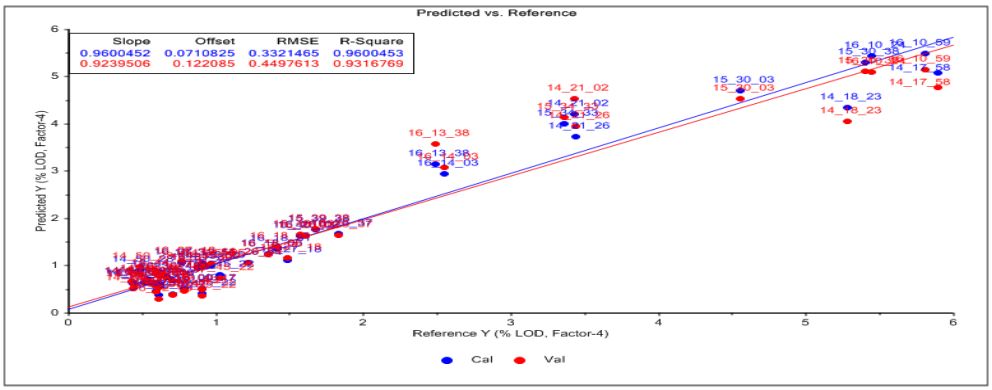


Fig.14 Typical NIR spectra (predicted vs reference) for moisture content determination

Residual Solvent monitoring using Mass Spectrometry (MS) :

Residual solvent is critical in the formulation. Overlapping the drying rate of reference batch in subsequent commercial batches ensures final product meeting the residual solvent test requirement. Gas chromatography in QC is a tedious and time-consuming test; hence real time data availability is not possible, resulting in batch loss once failure is declared. An in- line process mass spectrometer- comes in handy for the manufacturer in order to monitor the rate of solvent evaporation, and adjust the process parameter to build the quality in the product (QBD) during manufacturing.

MS is an extremely useful PAT tool for the qualitative analysis of drug, compound, and related substances. The mass spectrum is commonly employed to obtain the identity of two compounds, or to establish the structure of a new compound; this tool provide the accurate molecular weight or molecular formula to indicate the existence of a specific structural unit in a molecule. The main advantage of MS is its ability to measure several types of compounds with excellent discrimination over a very short analysis time. Moreover, it is used to quantitatively analyze known substances or identify unknown compounds in a sample and to reveal the structure and chemical properties of other molecules. To perform MS, a vacuum must be maintained, and the sample needs to be vaporized and ionized. Thus, the disadvantage of MS is that a sample cannot be analyzed if it cannot be decomposed and evaporated. The typical applications of MS include the real-time control of the drying process, particularly the monitoring of the trace amounts of organic solvents used in the production of intermediate and finished products.

Assembly and Main Components: The followings are the main components :

1. Ion source: to convert neutral gas molecules and atoms to positive ions.

2. Mass filter: to separate ions produced in the ion source based on m/z ratio.

3. Detection system: to measure the electric signal generated by ions.

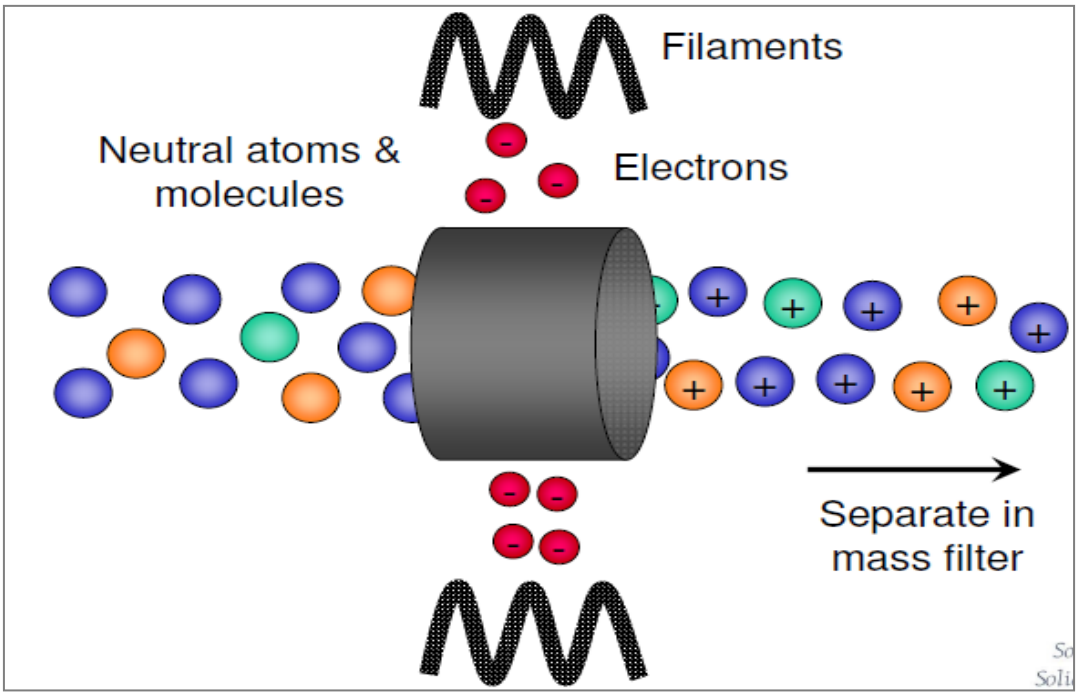
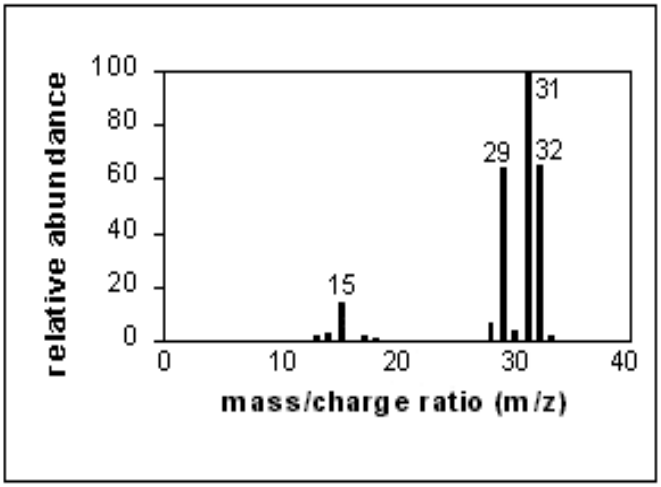


Fig.15 Mass spectrometer working principle

Fig.16 Mass spectrometer (ProMaxion)

***Discussion Based on Case Study*:** This tool is used to monitor the drying profile of organic solvent (e.g., methanol) and to detect the drying end point in real time.

- ❖ Fluid bed dryer exhaust gas was analyzed by mass spectrometer.
- ❖ Methanol solvent was sprayed on the mixture of lactose and MCC in fluid bed top spray granulator.



ions	m/z
$CH_3OH^{+\bullet}$	32
$H_2C{=}OH^{+}$	31
$HC{\equiv}O^{+}$	29
H_3C^{+}	15

Fig.17 Mass spectrometer spectra

Mass to charge ratio of 31 was used for the drying monitoring of methanol.

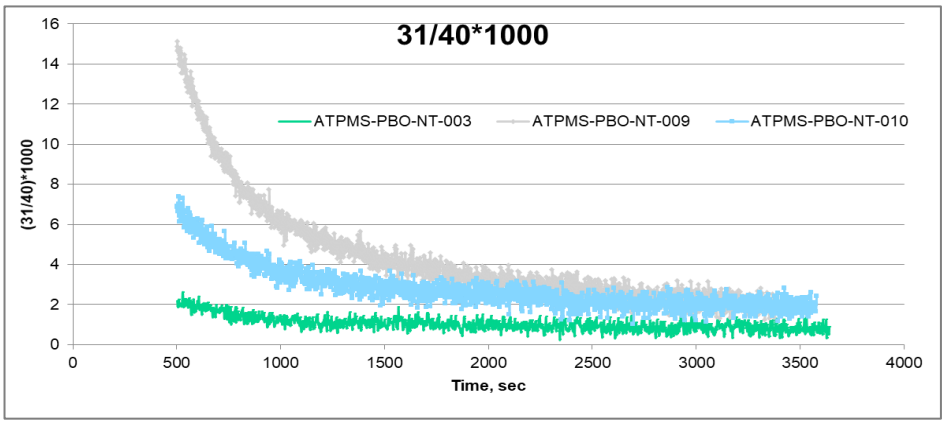


Fig.18 Mass spectrometer spectra vs time

- Drying end point reached after the (31/40)*1000 ratio value reaches below 3, which occurs after 2300 seconds of drying.

- There is no variation in the ion current after 2300 seconds at these particular process parameters, and this is confirmed by the methanol content by head space GC analysis.

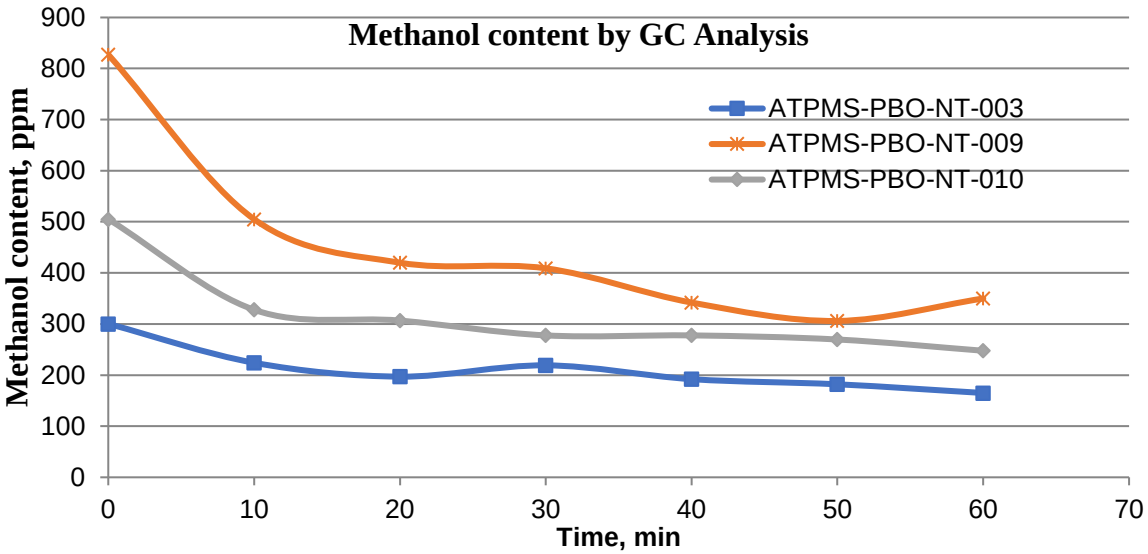


Fig.19 Methanol content by GC analysis

The validation batch shows that drying end point was reached after 40 minutes. The same was confirmed by methanol content analysis by GC.

Table 3 : Results of methanol content (ppm) vs time by GC analysis

Methanol Content, PPM	
Time, Min	**ATPMS-PBONT-011**
0	517
10	289
20	229
30	231
40	165
50	164

References :

1. Control Engineering Europe, In-line particle sizer proves its PAT credentials (2013). In-line particle sizer proves its PAT credentials (controlengeurope.com)

2. Jun Huang, Chimanlall Goolcharran, Julia Utz, Pedro Hernandez-Abad, Krishnendu Ghosh, Arwinder Nagi. J Pharm Innov (2010) 5:58–68. A PAT Approach to Enhance Process Understanding of Fluid Bed Granulation Using In-line Particle Size Characterization and Multivariate Analysis. Published online: 18 June 2010

3. Interphex 2010, 20 - 22 April, New York, US. Malvern exhibits proven PAT solutions for real-time particle sizing (manufacturingchemist.com, 2010). Viewed on 4th March 2024

4. Tim Freeman. The FT4 Powder Rheometer - Measuring Bulk, Flow and Shear Properties of Powders - Freeman Technology, Welland, Worcs, UK, info@freemantech.co.uk (2019). Viewed on 4th March 2024

5. Avila, C.R., Ferré, J., de Oliveira, R.R (2020). Process Monitoring of Moisture Content and Mass Transfer Rate in a Fluidised Bed with a Low Cost Inline MEMS NIR Sensor. Pharm Res 37, 84.

6. European Pharmaceutical Review (2013). Real-time monitoring of the moisture content in different type of dryers by NIR spectroscopy as a PAT tool.

7. Kim EJ, Kim JH, Kim MS, Jeong SH, Choi DH. Process Analytical Technology Tools for Monitoring Pharmaceutical Unit Operations: A Control Strategy for Continuous Process Verification. Pharmaceutics. 2021 Jun 21;13(6):919

8. Pro Maxion: Supplier Data Sheet. https://pdf.directindustry.com/pdf/ametek-process-instruments/promaxion-mass-process-spectrometer/14269-577550.html. Viewed on 4th March 2024

6 PROCESS ANALYTICAL TOOL FOR API MANUFACTURING

Introduction :

This guideline provides an overview of FBRM (Focused-Beam Reflectance Measurement) for crystallization end point/particle size simulation for quantitative analysis of drug substance.

Currently, the most commonly used method for determination of particle size is laser diffraction. E.g., laser diffraction done for products made using Malvern instruments. This is done by measuring the intensity of light scattered as a laser beam passes through a dispersed particulate sample. This analysis requires few hours for reporting of results and can be done only after crystallization comes to an end, which means real time analysis is not feasible.

The alternative - FBRM is a non-destructive, real-time analyzing tool, which ensures lesser human interventions and supports optimization of crystallization.

Laser Diffraction	FBRM
❖ Utilizes diffraction patterns of a laser beam passed through any object, ranging from nanometers to millimeters in size, to quickly measure geometrical dimensions of a particle. ❖ Uses Mie theory of light scattering to calculate particle size distribution, assuming a volume equivalent sphere model.	❖ Primarily used as a tool for development of crystallization processes and real time analysis. ❖ A probe-based instrument is inserted directly into processes to track changing particle size and count in real time at full process concentrations. ❖ Measures the chord length distribution, which in turn tracks how particle size and count change from the beginning until the end of a process.

The core technology comprises of the following four systems :

i. system: The key components of the optics system are the light source, beam splitting-system, detectors, and accessories for analysis of samples.

ii. Mechanical system: The mechanical system contains prime movers, transmission, and executive systems.

iii. Electronic system: The electronic system contains power light source supply circuits, detector source supply circuits, and signal amplification power supply circuits.

iv. Computer system: The computer system records and stores data based on the software used, and to control the FBRM device.

Procedure for FBRM Method Development :

FBRM analytical procedures typically combine the following steps:

- Instrumentation elements, e.g., an analyzer consisting of a cylindrical probe with a scanning laser beam, and software for analysis
- Acquisition parameters
- Performing design of experiments to generate data
- Data interpretation of FBRM results using conventional analysis
- Composition of raw datasets

Instrument Selection :

- Instrument configuration shall be defined based on end application e.g. crystallization end point, particle size simulation.
- Selection of FBRM instrument configuration tends to be one of the most important decisions for an organization as frequent changes in the instrument during the lifecycle may require redevelopment of FBRM model and repetition of validation procedure.
- Implementation of the same model of the instrument to the extent feasible enables longevity of the analytical method, which in turn requires lesser efforts in case of any changes to product composition, manufacturing equipment change, alternative vendor introduction, etc.
- Moreover, after development and validation of a model, transcription of data from one vendor's instrument to another vendor's instrument is nearly impossible.

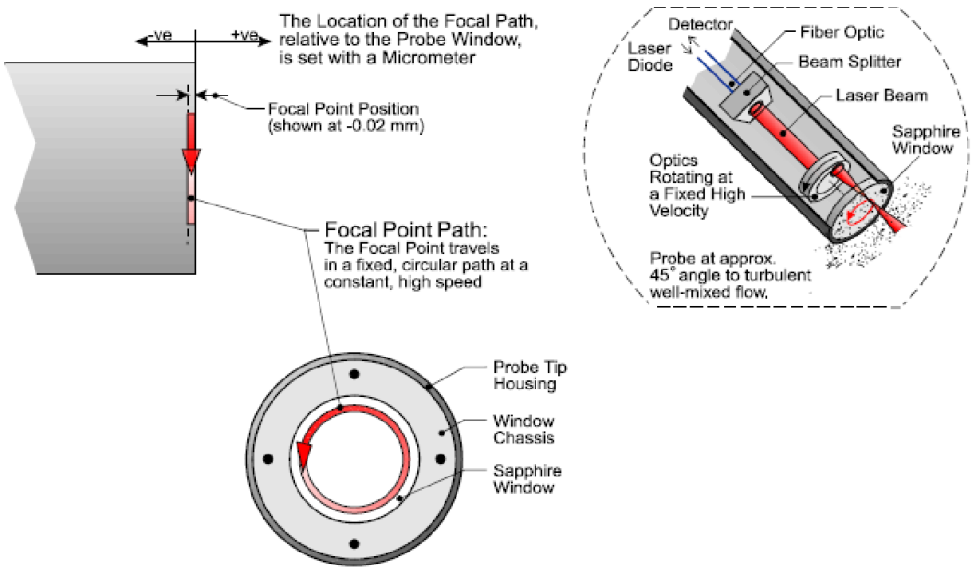
Measurement for FBRM Implementation :

- Off-line: Samples are analyzed far from the process area after isolation and drying of solid.
- At-line: Samples are isolated and tested in close proximity to the process stream.
- In-line/real time: The analyzer is brought into direct contact with the process stream at the designated location and orientation and is interfaced directly with the sample, giving the particle count and dimensions of particle population as readings.

Taking the in-line/real time mode of measurement into consideration for this guideline, the following factors are the areas of focus :

- Probe position and orientation
- Stabilizing analyzer
- On line data measurement with acquisition time
- Data interpretation

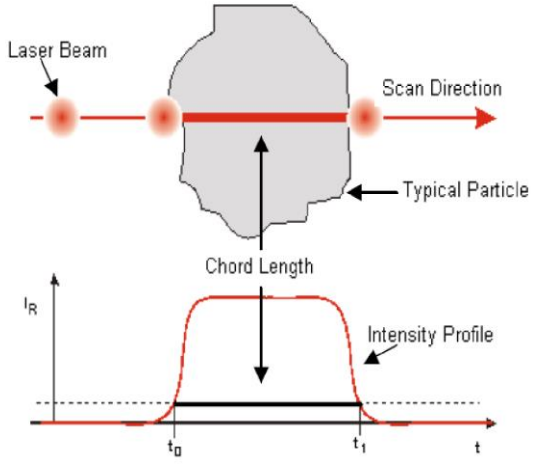
FBRM Measuring Zone & Location of Focal path :



Standard Focal Position :

- 0.02 mm inside the window is the standard focal position for excellent sensitivity, and this minimizes noise from the properties of the system that are not under inverstigation.

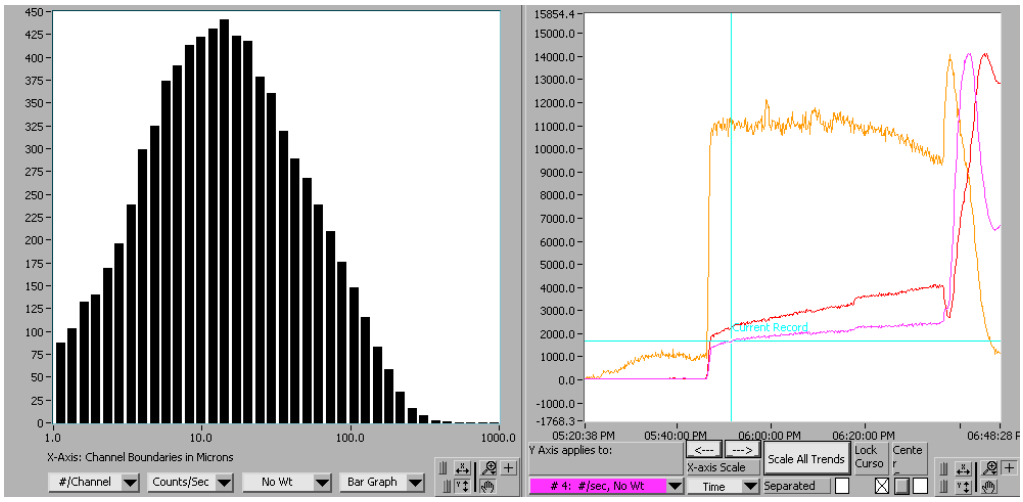
Schematic of Chord length :



- The focused beam will cross the particle or particle structure on a straight line between any two points on the edge of the particle structure.
- The distance between these two points is the chord length.
- Hundreds of thousands of chord lengths are typically measured and counted per second, producing a robust chord length distribution.
- Chord length is a function of particle shape, particle dimension, and particle concentration.

Output

Output in counts/second vs dimensions in micron graph



FBRM Model Development :

A. Selection of parameters :

- FBRM method development shall be done in such a way that the results are comparable with those of the conventional reference method.
- The methods shall be developed with different DOEs (Design Of Experiment) at lab scale with varying process parameters and instrument parameters to avoid batch-to-batch variation or batch reproducibility.
- Design of experiments shall be performed for development of method. Subsequently, method verification shall be performed at the development stage.

Sample Preparation :

- ❖ To initiate calibration, prepare the sample for calibration analysis. The sample is prepared without changing the process, physical and chemical compositions. The sample shall be prepared to exactly replicate the actual process stream composition.

- ❖ Once the sample is ready, a procedure shall be made for which the construction of a calibration set is required.

B. Sample Preparation for Calibration of the Model :

Development of Calibration Model :

- ❖ Development of an FBRM measurement model requires a traditional, validated reference analytical method. E.g., Laser Diffraction Malvern PSD (Particle Size Determination) analysis methods. The reference method helps correlate FBRM instrument software data (Chord length measurement) to Laser Diffraction Malvern PSD data.

- ❖ The details of relevant reference method used for the development of FBRM method, shall be provided to the regulatory agency.

To create a robust model, a calibration set shall be built with samples that

1. Include an appropriate concentration range for the component to be analyzed;

2. Address potential sources of variability (e.g., a variation in the processes, the analyzer, the physical characteristics of the materials, or the temperature); and

3. Cover the expected variations in process parameters (e.g., in-design space parameters) that have the potential to influence the reflectance response.

C. Construction of Calibration Set :

- Incorporation of potential heterogeneity from sample presentation into the calibration set shall be ensured during preparation of calibration sample.

- Calibration samples should mimic as closely as possible the samples that are expected to be representatives of the commercial process". (Ref: Development and Submission of Near Infrared Analytical Procedures Guidance for Industry, CDSR, August 2021 Pharmaceutical Quality/CMC).

- Calibration samples prepared in smaller scale, i.e., non-commercial by taking into consideration where the process variation can impact (concentration, temperature etc.) along with certain range, should be found similar to those of the commercial product. The analyst range plays a crucial role in predicting the optimum combination of concentrations for calibration and in further observations. All these samples at laboratory level (representatives for calibration) shall be prepared in ample amounts to proceed with the calibration.

The following points should be considered during preparation of calibration samples:

- Standard / reference sample selected for calibration should replicate the proposed main stream process, whether it is from laboratory process or commercial scale process.

- Homogeneity should be maintained during sample preparation so as to keep the sample within the accurate and precise calibration range. Variations should be avoided in the sample as they may affect the calibration results.

- Similarity of each of the attributes of the process, like solid concentration, PSD of solid or the sample to be prepared, should be ensured with the one manufactured at commercial location and a similar reflectance response should be obtained.

- For each desired process variable oriented sample, the sample shall be prepared with different concentrations.

- To assess the impact of material variation, the calibration sample should be prepared using multiple samples from manufacturing lots in order to capture the predicted material variabilities.

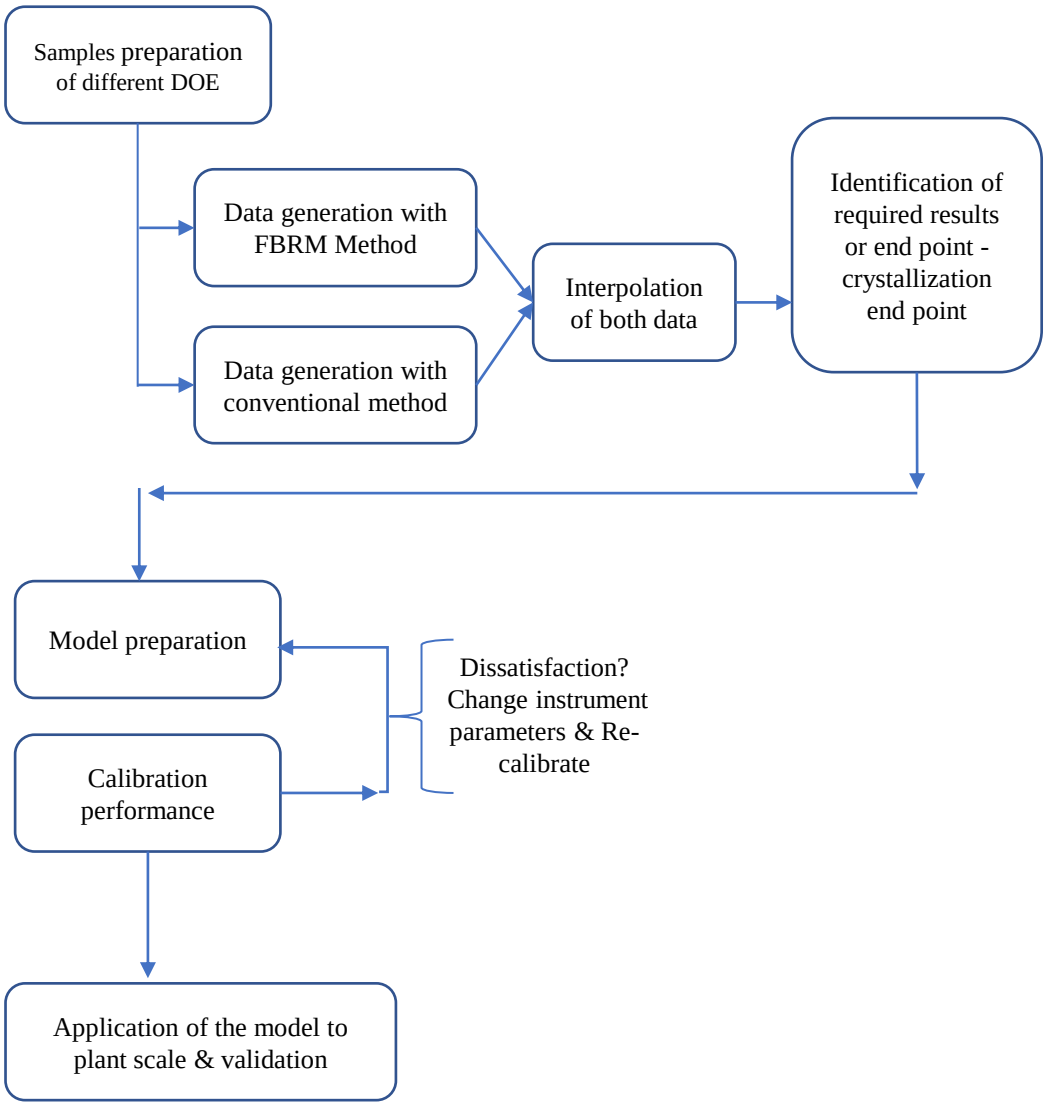
- The reflectance variations might get influenced by environmental conditions. Hence, the sample should be prepared by considering conditions like temperature or relative humidity where the batch is manufactured. This can be addressed by measurement of reflectance at different environmental conditions. The alternative method to counter this is may be to stay within the same environment at the time of sample acquisition and reflectance analysis.

- The difference in physical characteristics between the production samples and laboratory-prepared samples should be sufficiently minimized by reflectance preprocessing to reduce its impact on the observed results.

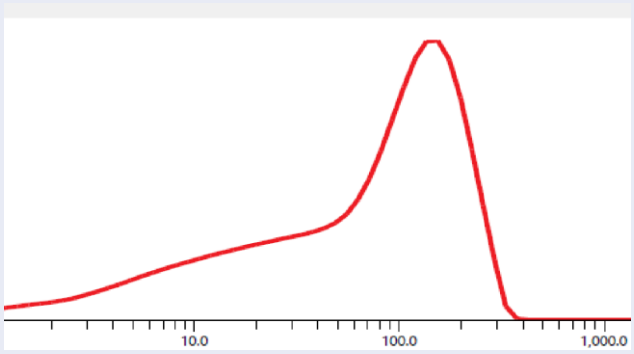
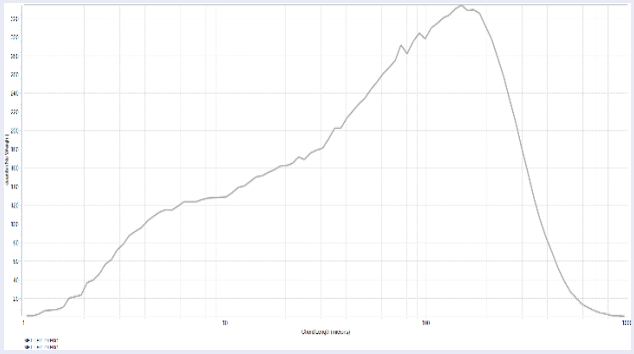
Experimental Design - FBRM :

The following example can be done at a small or laboratory scale for making a calibration set. After obtaining successful calibration performance of the model, it can be extended to commercial scale batches in order to include commercial scale variations in the model.

Refer example decision-making process for model building and release for use as below :

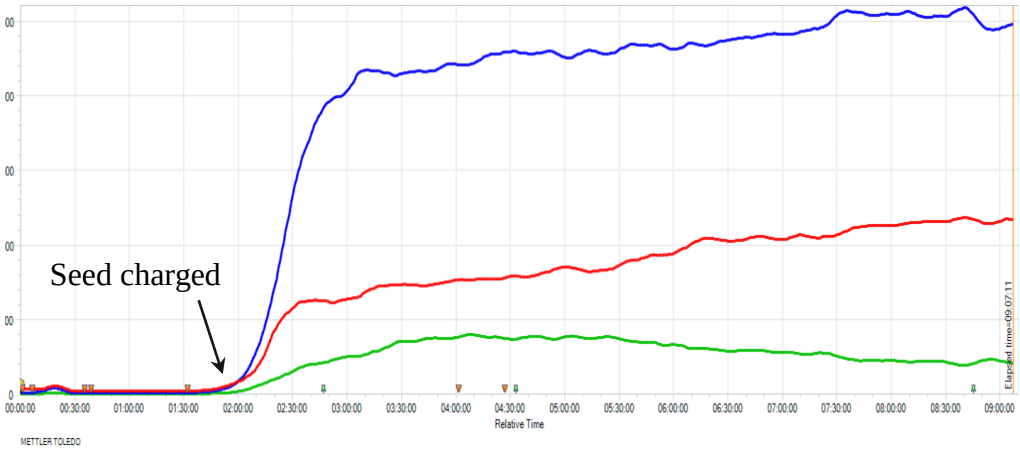


Typical Comparison of Particle Size – FBRM vs Conventional Method :

Laser diffraction	FBRM
Result: Dv (90): 210.669 µm	Result: Dv (90): 208.38 µm
	

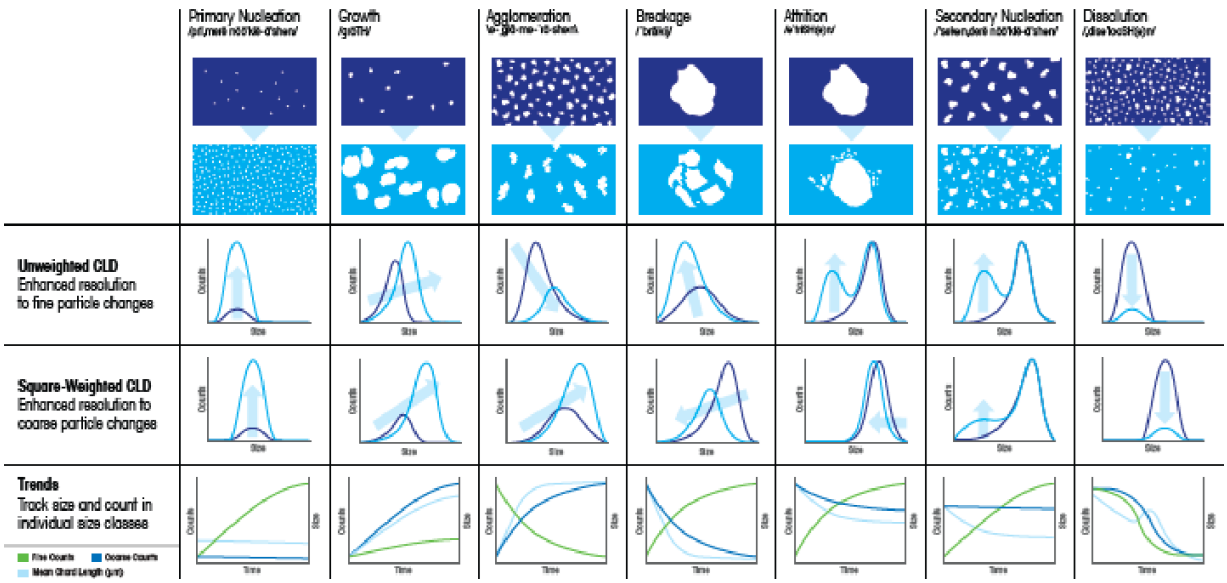
Application of FBRM for development of crystallization process :

- FBRM is a probe-based instrument that is inserted directly into the processes to track changing particle size and count in real time.
- The chord length distribution gives information about how the particle size and count change from the beginning to the end of a process. The chord length distributions and the particle trends can be used to understand and distinguish between various crystallization events like nucleation, growth, agglomeration, breakage, attrition, etc.
- As experimental conditions tend to vary, monitoring of the particles continuously helps in determination of the influence of process parameters on particle size and count, thereby allowing optimization of the process parameters.
- Typical FBRM trends and chord lengths comparison are shown in the chart below.



FBRM trends of particle counts with respect to time (< 10 µ, 10 – 50 µ and 50 – 150 µ)

Tracking of common particle measurement :



Challenges :

- Key challenges for implementing FBRM are :

    1. Fouling of FBRM probe due to sticky material at the time of crystallization.

    2. Change in crystal shape from previous trend may impact particle size result as FBRM measures Chord Length Distribution.

    3. Each model is product specific, thus a universal model cannot be developed.

- To overcome the said challenges, study of different variables and impact on the final outcome shall be studied and criticality shall be evaluated through risk assessment.

Lifecycle Management :

- During lifecycle management, risk assessment shall be done to record the sources of variation and reduce the impact of unknown sources of variation.

- Periodic maintenance is required to accurately capture the variations inherent in evolving processes.

- For a new product or any change in process parameters, risk assessment is a must.

- Periodic review shall be defined during life cycle management.

- Any change in instrument accessory, software upgrade and/or revision that may affect the spectroscopic aspects, require a risk assessment to be done in order to ensure compatibility and accuracy.

References :

1. Development and Submission of Near Infrared Analytical Procedures Guidance for Industry, CDSR, August 2021 Pharmaceutical Quality/CMC

2. Crystallization studies with Focused Beam Reflectance Measurement and Multimax by Mettler Toledo

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