INNOVATION. QUALITY. GLOBAL REACH.

# 9th ADVANCED GMP WORKSHOP 2024

## IPA Best Practices Documents: PAT in Oral Solids and APIs

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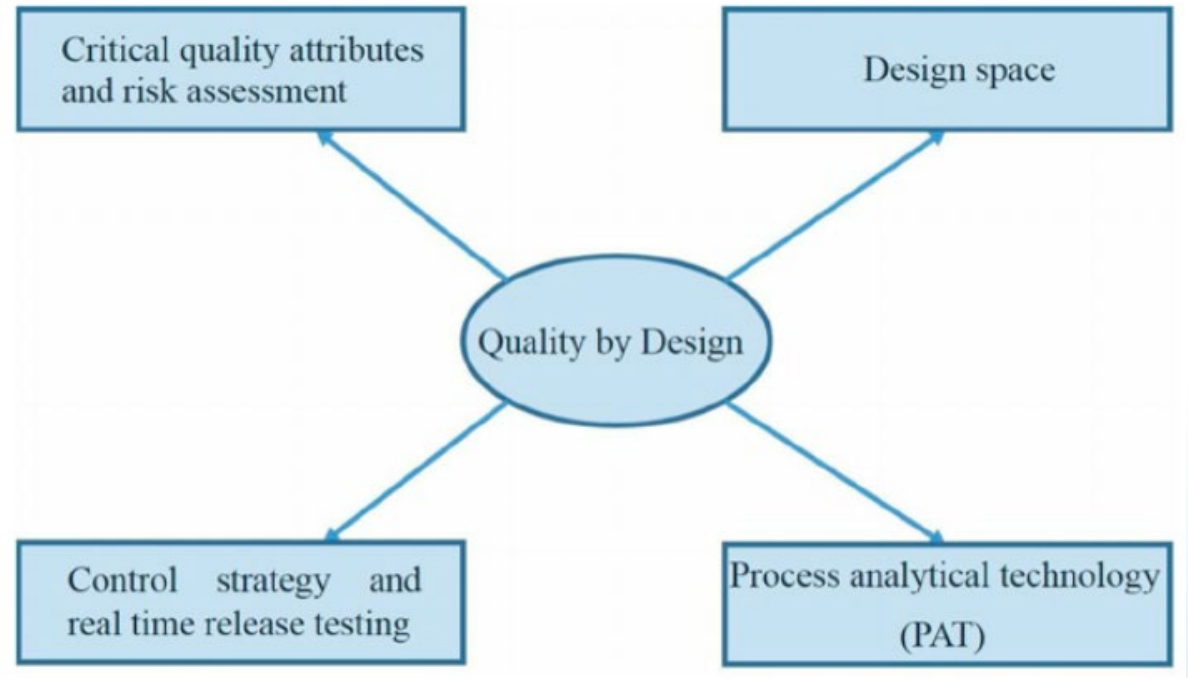
# Introduction

**PAT is Part of QBD:**




PAT is still a recommendation, not yet a regulatory demand.

PAT is an investment for product quality & process economy

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*" - ICH Q8 (R2)

*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 – USFDA (2004)".* Thus, PAT is part of QbD.

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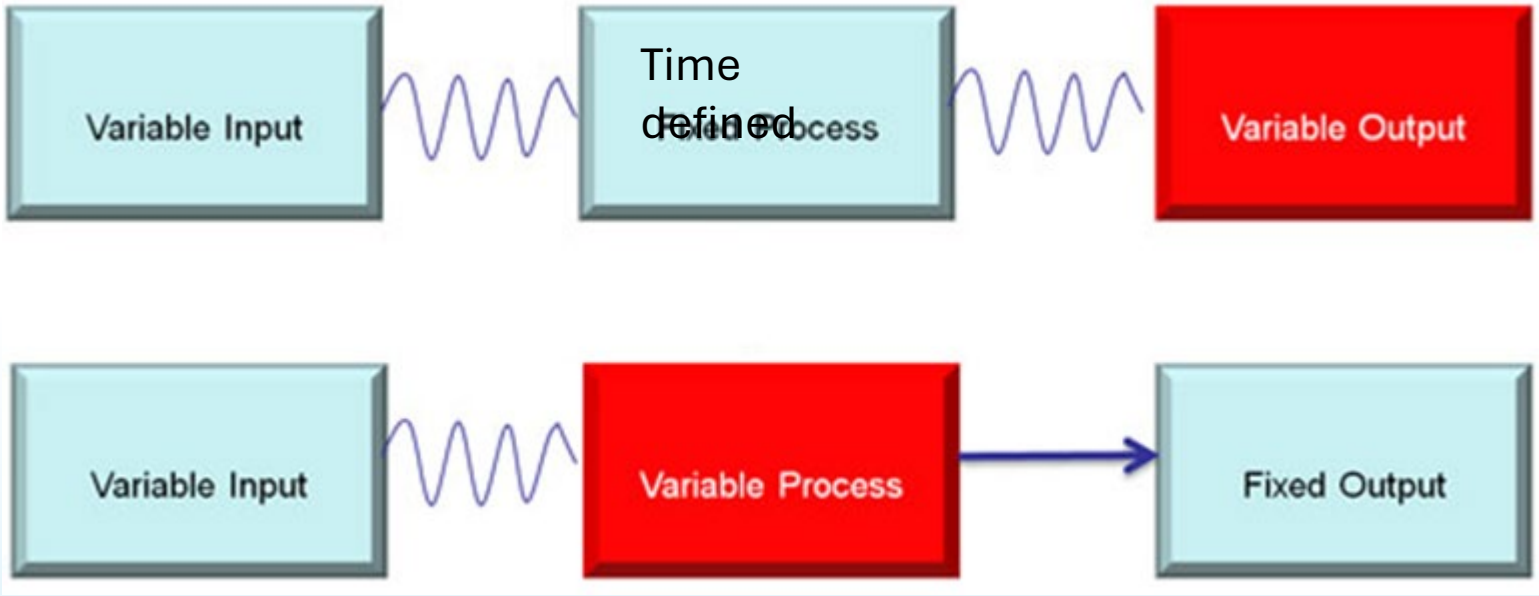
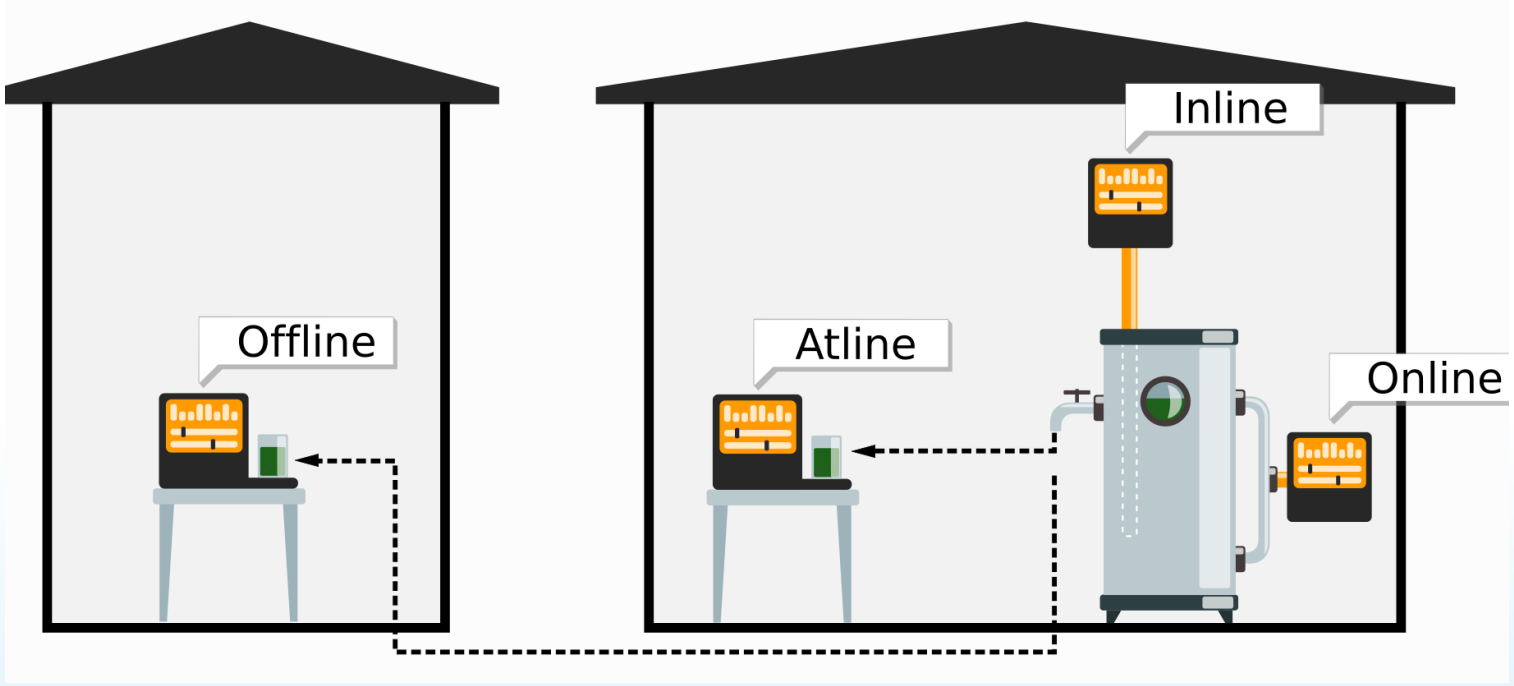
**Role of PAT:**




"*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*" – *USFDA (2004)*

*"A process end point is not a fixed time; rather it is the achievement of the desired material attribute"*

## Modes of Measurement




**Off-line:** Sample analysis away from the process stream (eg. 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 a side stream then bringing back to the main stream manufacturing. The sample may be returned to the main stream after analysis (measurement of cell density in an anaerobic fermentation process using flow through cell)

**In-line:** Analysis within the process stream, without removing sample (eg NIR tool attached to a blender for scanning powder)

**PAT in Different Stages:**

| Manufacturing Stage | Critical Parameter | Available PAT Tools |
|---|---|---|
| API manufacturing | Identification and concentration | Real time Raman process spectrometer |
| | Crystallization end point – particle size | FBRM, Laser diffraction method |
| Powder blending | Water content | NIR tool |
| | Blend uniformity | |
| Fluid bed process (Granulation & pellet coating) | Water content | Microwave moisture analyzer, NIR analyzer |
| | Residual solvents | Process mass spectrometer (e.g., Promaxion) |
| | Particle growth rate/end point | Malvern's Parsum /Eyecon / Camsizer |
| | Droplet size | Malvern's spray tech droplet size analyser |
| Wet granulation | Wet mass consistency in RMG | Impeller torque sensor, ammeter, Drag Flow Force (DFF) sensor |
| Sizing | Particle size distribution | Particle Image analyzer (Eyecon) / Parsum |
| Compression | Blend uniformity and content uniformity | Tab NIR (*online/atline*) |
| | Assay | Tab NIR (*online/atline*) |
| Tablet Coating | Film thickness/end point of coating | Terahertz pulse image analyser |

**Implementation Procedure:**

1. Forming a PAT team - development, manufacturing, QC, QA, regulatory affairs and statistician
2. Select a product basis the failure history and commercial volume, impact in the existing process / approval.
3. Correlate the process control with CQA, applying statistics
4. Identify a PAT basis the monitoring parameter, accuracy, pre-requisites, MOC, its direct contact with the product
5. Installation of PAT can be done under the facility's own quality system / SOPs.
6. A study protocol may be prepared and, if required, it may be communicated with the regulatory agency
7. Model development trials to predict the process end point and define the process signature
8. A model validation report and comparative data from multiple batches to replace an existing QC test
9. A supplement (e.g. CBE, CBE-30 or PAS) should be submitted to the regulatory agency prior to implementation

**Challenges in Implementation:**

1. Lack of expertise / experience in selection of tools, method development, validation and interpretation of results
2. Burden of investment (cost, time, manpower and other resources) and cost reduction programs.
3. Time limits in new developments (time shortage in complex products; no need of PAT for simple ones)
4. Hesitation to change an approved process as it may require an approval again with more data as of today's guideline (e.g. discriminatory dissolution, elementary risk assessment etc)
5. Risk in data generation from commercial batches due to site SOP, GMP, and regulatory audits.
6. PAT is a PET project or part time KRA at a manager level, with no resource and least priority

**Possible Solution:**

1. Quantified Business Case with cost and benefit analysis for instrument, man power, reduced batch failures & time
2. Sponsorship from the top management with resources across the departments
3. FDA does not audit PAT research data generated in the production facility. Hope the same from the other regulators also

# NIR Spectroscopy for Blending and Compression

**Conventional Vs *Inline* monitoring**

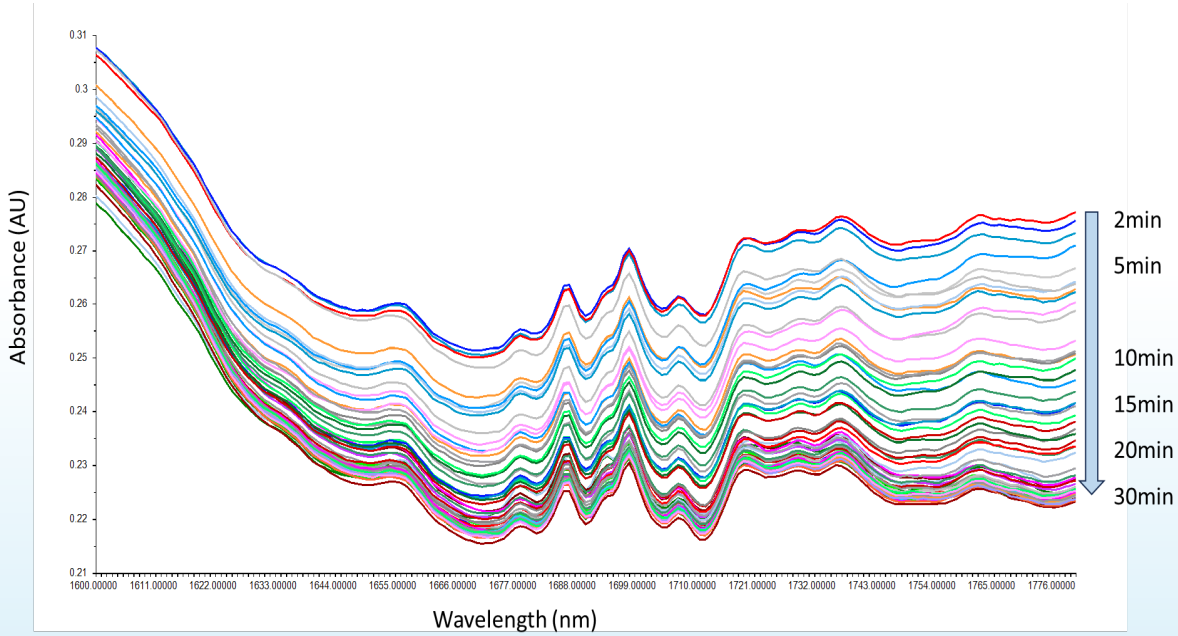
Conventional sampling

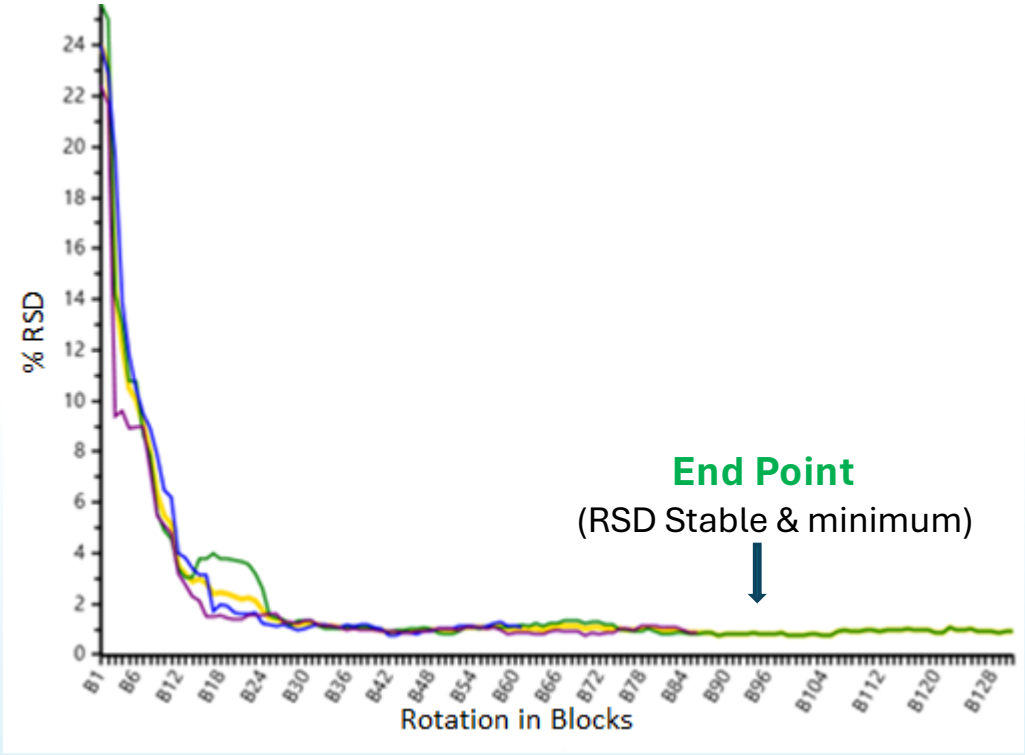
NIR for blender

NIR for Tablet Content Uniformity

- Sampling segregation due to density / PSD differences, costly QC analysis, resource and time in conventional sampling
- NIR PAT tool monitors BU and CU *inline / online*.
- Reduced QC analysis and real time batch release after regulatory approval

## **Blending:** Interpretation of NIR Results




- Spectra superimpose over each other with increase in blending time. Variance / RSD decreases with increase in rotations
- Entire spectra or only one ingredient (e.g. polymer or API) or may be focused while monitoring the process
- Quantitative estimation is also possible by building a calibration model. It is not mandatory

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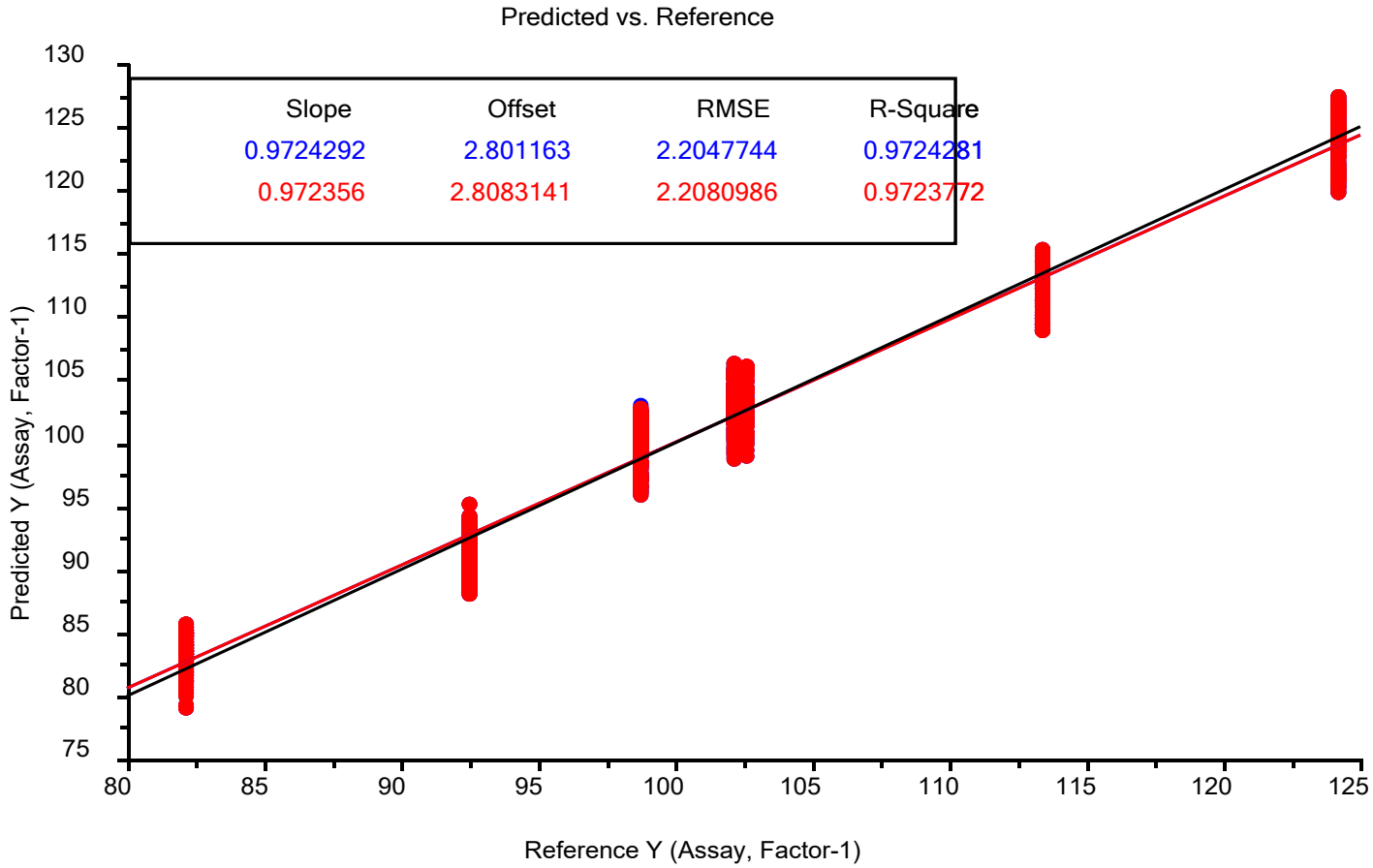
**Calibration Model:** HPLC Vs NIR Prediction

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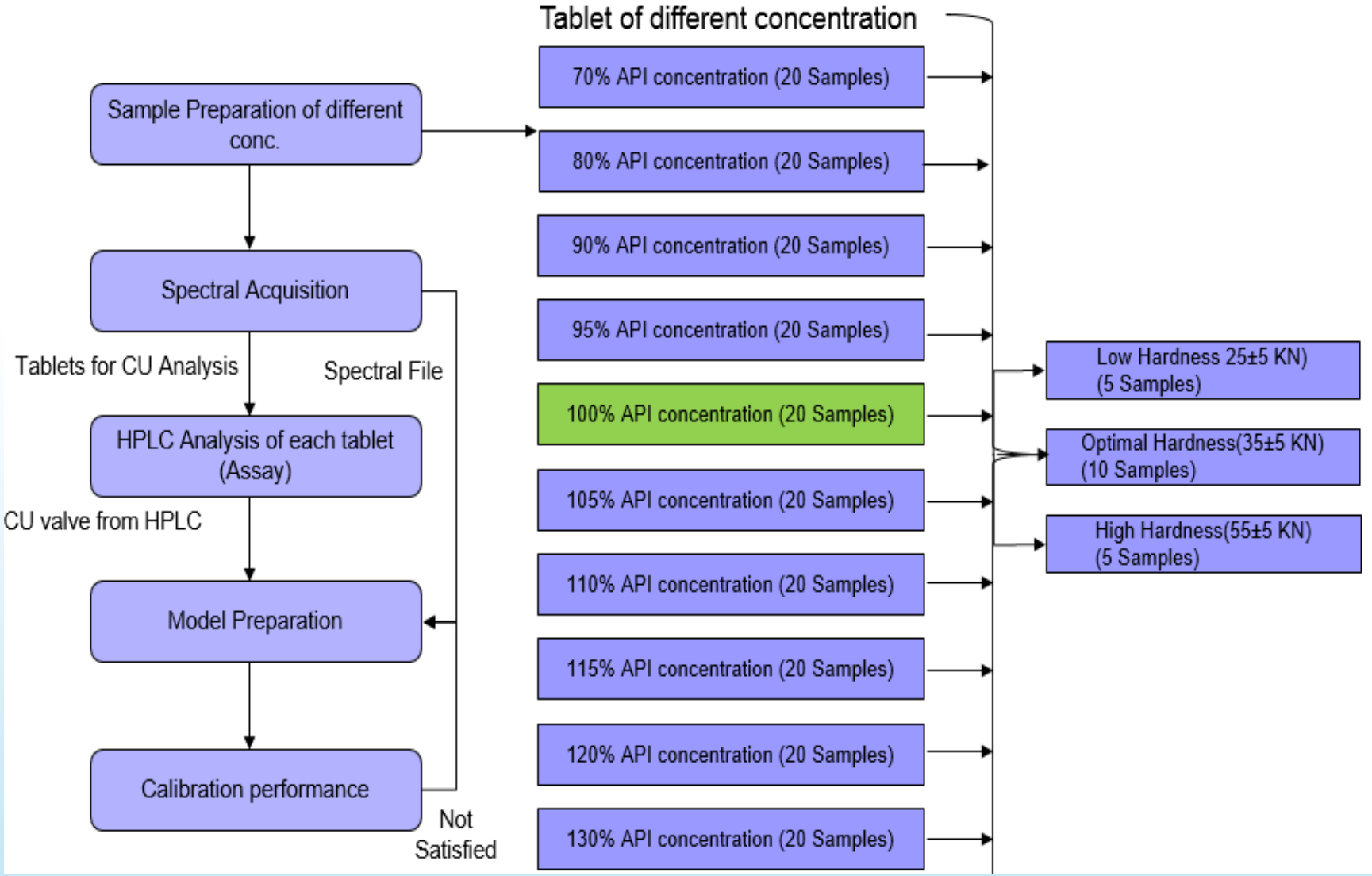
## Trials for Model building:

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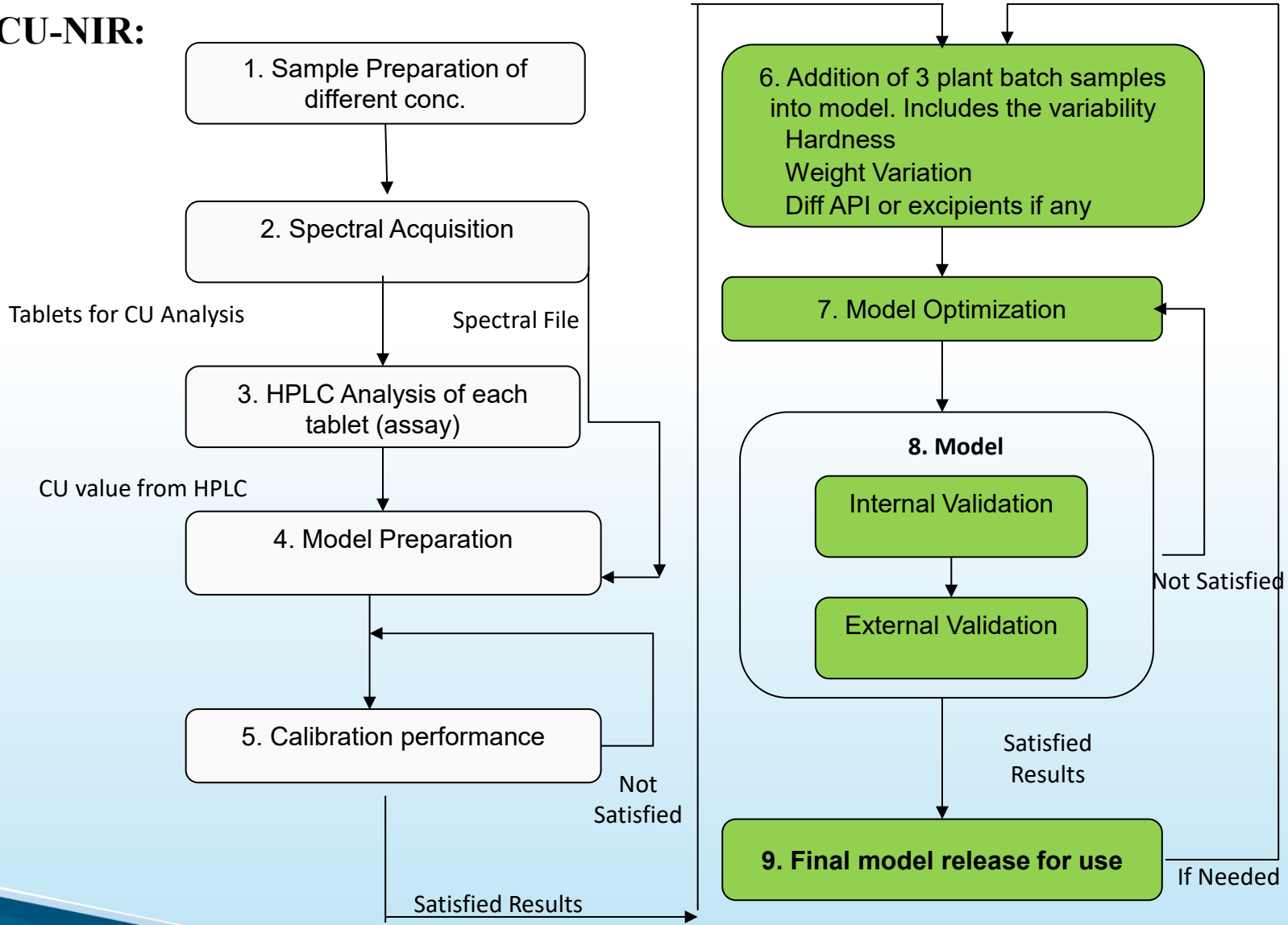
## Model Building: CU-NIR:

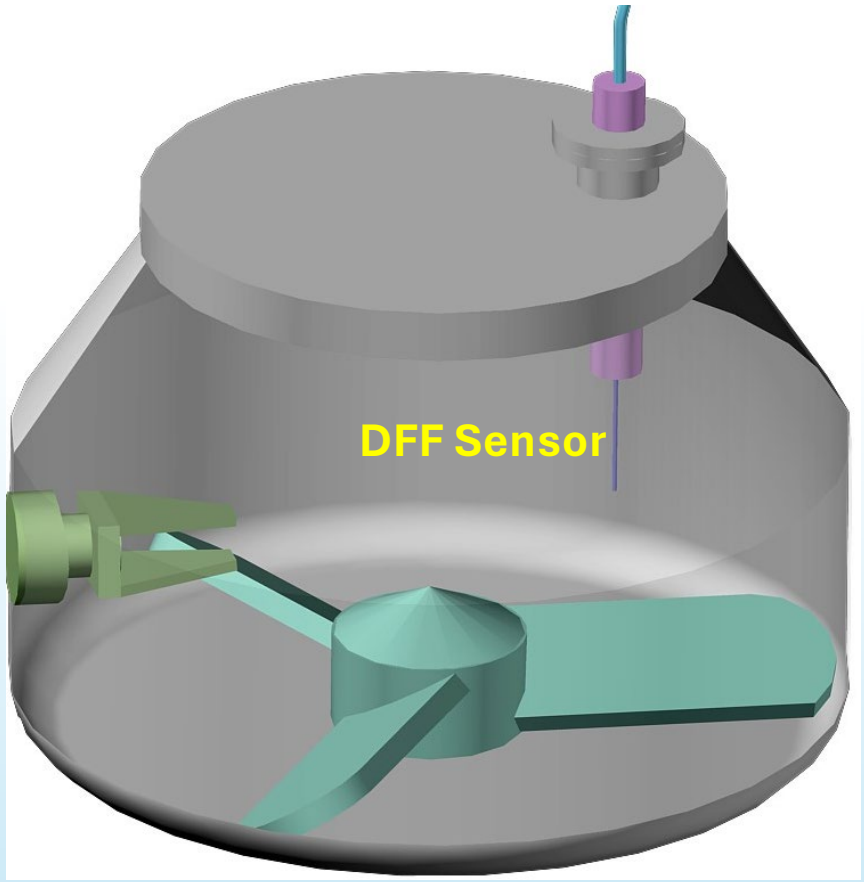


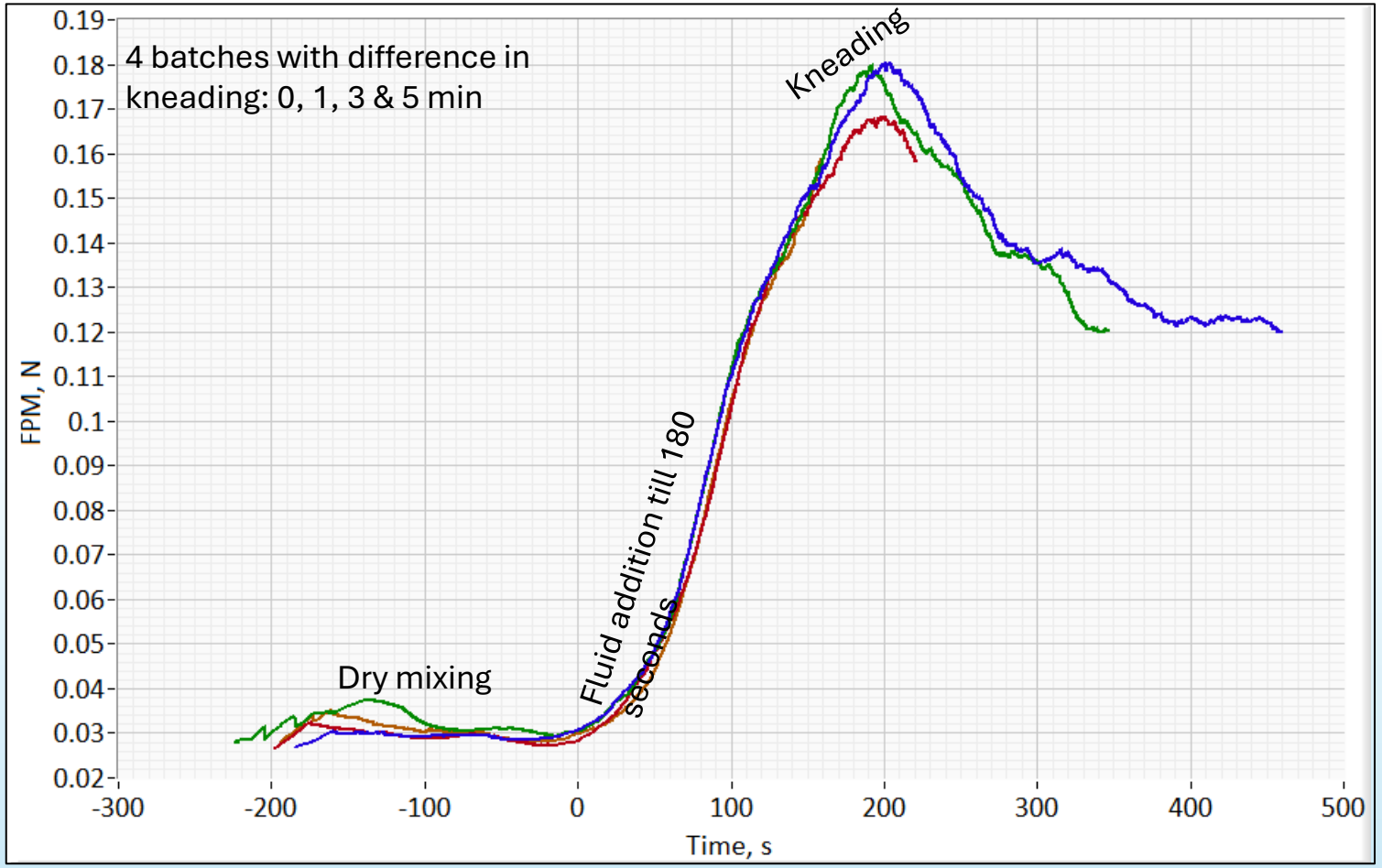
# PAT Tools for High-Shear Granulation

**Available Choices:**

| Tools | Monitored Parameter | Points to consider |
|---|---|---|
| Ammeter | Motor power consumption (watts) | Less sensitive. It can not detect small fluid addition or kneading. Other factors (eg. wear and tear) |
| Indirect torque | T= Watts/ speed (calculated from motor power) | Almost, same as above |
| Drag Force Flow (DFF sensor) | Force of granules on the sensor needle, influenced by size & density; F = ma; | End point is based on the wet mass consistency and particle size/density. Thus, more sensitive |
| Impeller torque sensor (direct torque) | Rotational force required to rotate the impeller against the resistance force of wet mass | It directly reflects the load on the impeller. Thus, it is more sensitive |
| Near Infra-Red (NIR) sensor | Shift in baseline NIR spectra influenced by the density and particle size. Water band gives information on free water/bound water | OK for aqueous process. End point is based on base line spectral shift overlapped with reference batch. |
| Thermal Effusivity Sensor | Monitors the thermal conductivity (moist /dense material conducts better than dry one) | Independent of scale. Preferred in aqueous process |

## Drag Flow Force Sensor:

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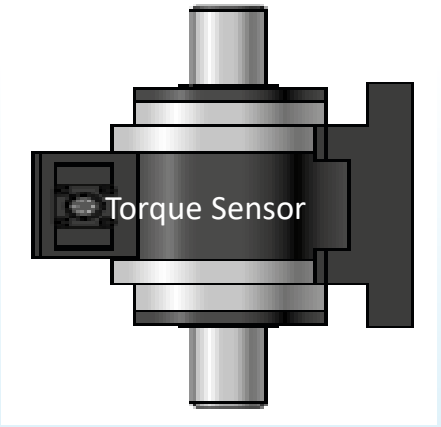
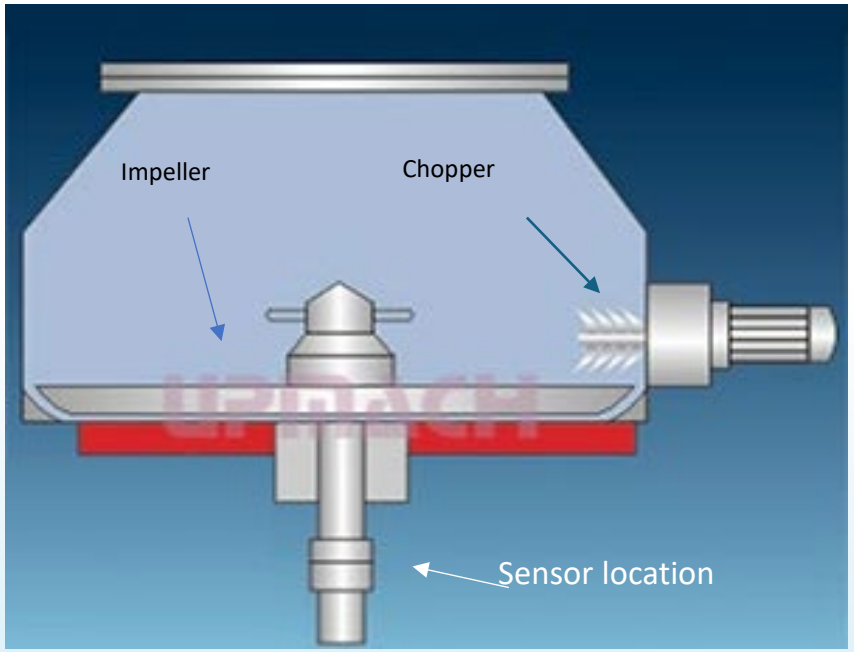
**DFF sensor: Installation, Interpretation and Implementation**

1. The probe is positioned through a port in the RMG-lid or it can also placed through the side wall of the bowl
2. Since the probe is in contact with the powder, it experiences the drag force of moving particles. Since F= ma, the particle size and density determine the force for the given acceleration.
3. The time Vs force profile is the process signature to reach the desired end point.
4. The end point may be concluded basis the dried PSD or dissolution.
5. Depending on the manufacturing scale and granule strength, the sensor with required sensitivity should be selected.
6. A risk assessment is required to identify the input CMA, CPPs which impact the output granule quality
7. 10 or more batches including all variables (in approved range) may be required to build a model
8. Approval from the regulatory agency is required to change the kneading time basis the PAT
9. Audit trail should be available for the PAT data.
10. No need of approval for additional data generation without change in existing process

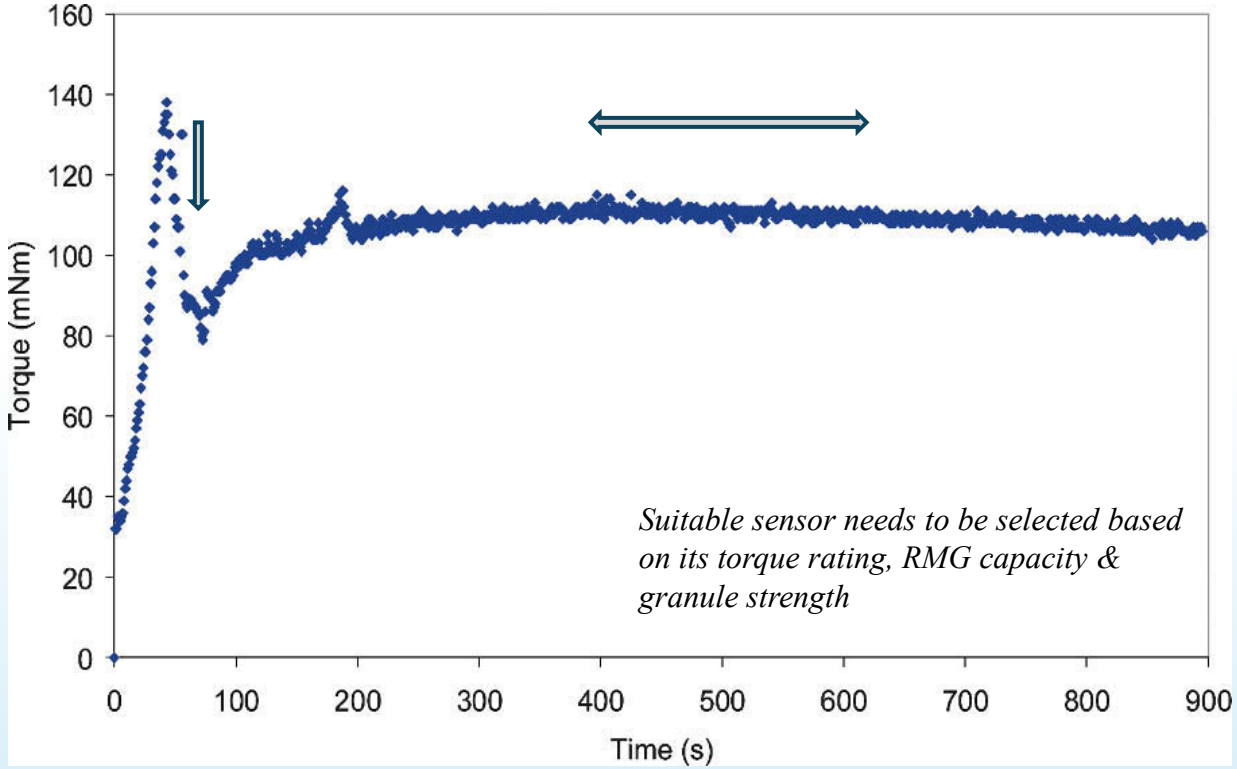
## Torque Sensor




- It measures the rotational force in the impeller shaft which reflects the resistance exerted by the blend on the impeller
- The sensor is mounted in the impeller shaft. Hence it reflects the wet mass consistency accurately. No product contact
- It needs around 0.3 meter space near the impeller, above the gear box. No such space in old RMGs.

## Torque profile – Understanding the process signature




- Initial raise in torque is due to fluid addition and agglomeration, resisting the impeller rotation
- Fall in torque is due to breaking of lumps by chopper action and free movement of particles
- The subsequent small raise indicates secondary growth of granules before reaching equilibrium with chopper action

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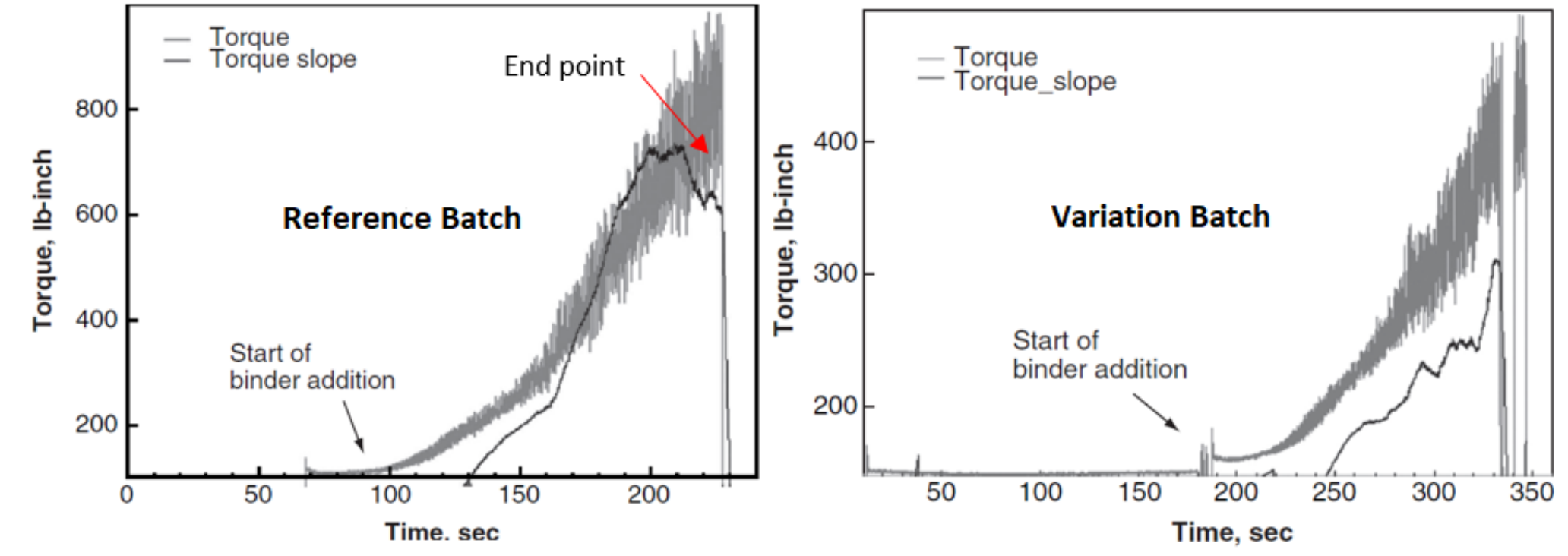
## Manual intervention in Granulation Endpoint:




- Manual intervention to break the lumps may change the process signature and end point

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**Amperage Vs Torque:**

| Stage | Time (min) | Batch-I | | | Batch-II | | |
|---|---|---|---|---|---|---|---|
| | | Amp | Torque (Nm) | Torque/Amp ratio | Amp | Torque (Nm) | Torque/Amp ratio |
| Dry mixing | 5 | 14.62 | 63.74 | 4.36 | 14.37 | 65.69 | 4.57 |
| Water 1.5 L | 5 | 15.11 | 118.19 | 7.82 | 14.86 | 119.41 | 8.05 |
| Kneading-1 | 2 | 15.36 | 152.14 | 9.91 | 15.42 | 154.34 | 10.00 |
| Additional Water 1.5 L | 1 | 15.67 | 175.09 | 11.17 | 15.68 | 178.76 | 11.40 |
| Kneading-2 | 2 | 15.64 | 187.06 | 11.96 | 15.43 | 189.01 | 12.25 |

- Amperage reading shows no significant change in the progress of granules, while torque value increasing significantly.
- Torque profile is similar across the batches when process parameters were kept identical

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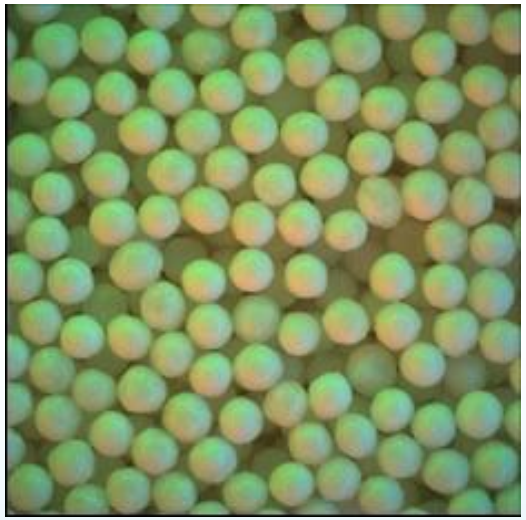
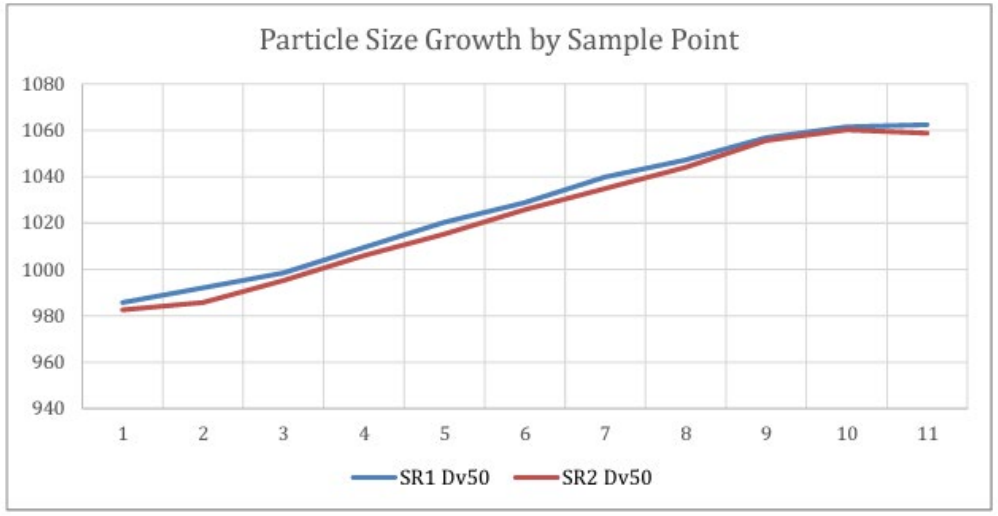
# PAT Tools for Fluid Bed Process

**Direct Image Analyzer in Fluid Bed Coating / Granulation:**




- Direct image analyzer illuminates the moving particles and captures the image by distinguishing overlapping particles
- The software provides *in-line* PSD data eg. D50, D90 and also sphericity data.
- A correlation of particle size with actual weight gain is done in model building batches; validated by camsizer data
- This enables to predict coating %, without unloading /reloading in intermediate/multiple coating stages.
- Also alerts early, in case of agglomerates & fines, thus saving the batch and time. Yet, dusty process is a challenge

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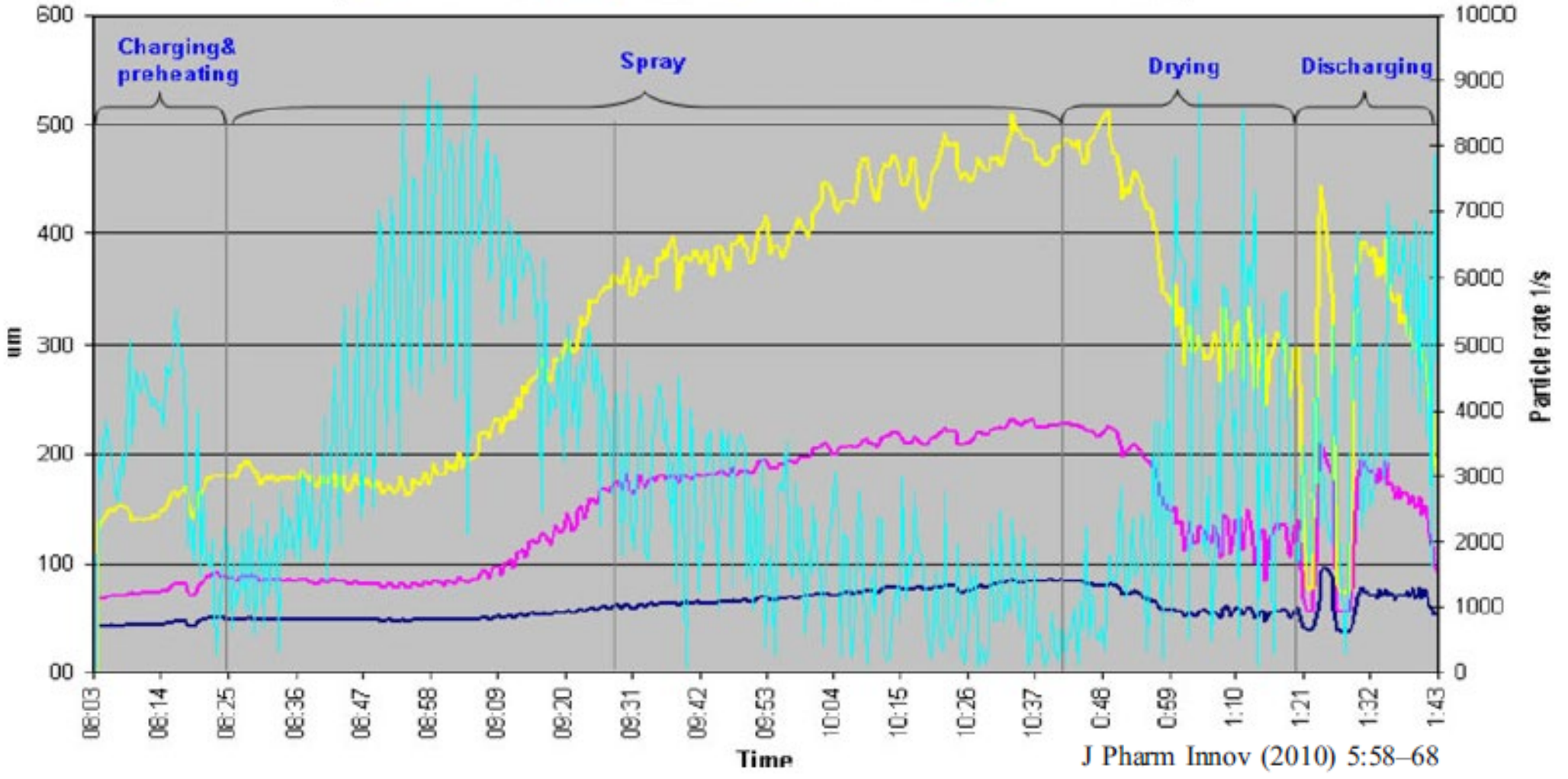
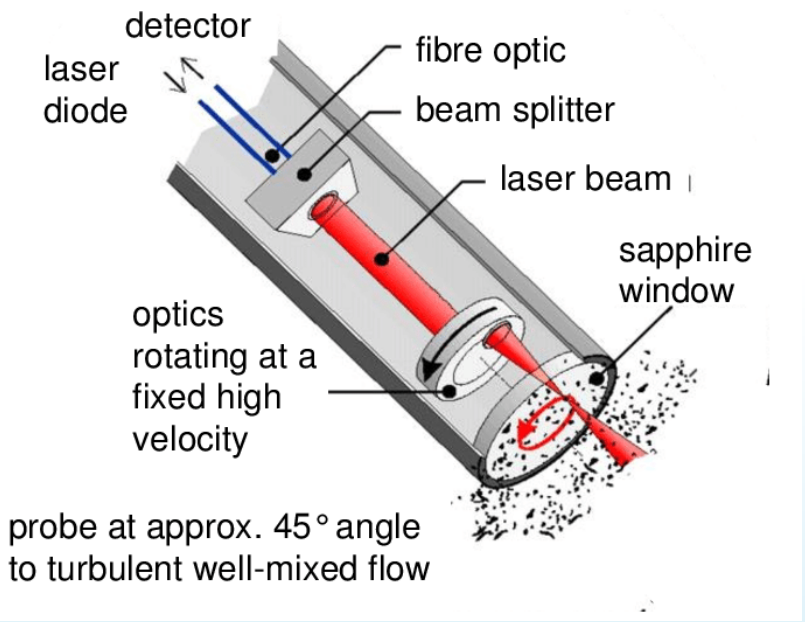
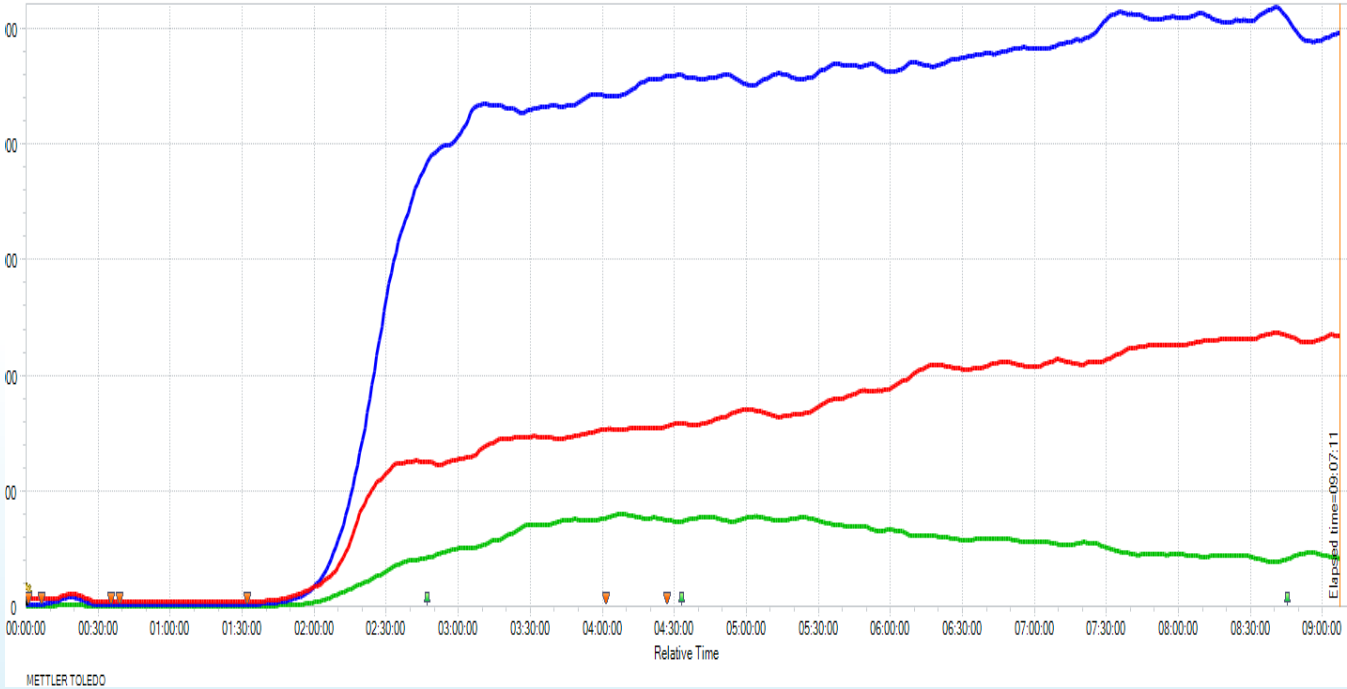
## Fluid Bed Granulation: *In-line* PSD (Parsum)



# PAT Tools for API Crystallization

**FBRP in Crystallization:**




- FBRM probe is directly exposed to the sample to monitor the changing particle size *in-line*
- The chord length distribution gives information about how the particle size changes starting from nucleation.
- As in any other model building, the calibration samples should include all input variables, representing the actual batch

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# Thank You