PAT Particle Size Analyzer (PSA) Application for API Milling Manufacturing Process

ISPE Great Lakes Chapter 2011 Meeting

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Agenda

• PAT Background
• PAT Case Study
• Insitec® Particle Size Analyzer
• PAT PSA Current State and Setup
• Online Milling Engineering Study
• Milling PAT Implementation
• Closed Loop Feedback Control Results
• Summary and Next Steps
• Acknowledgements
What is PAT?

- Process analytical technology (PAT) has been defined by FDA as a mechanism to design, analyze, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (CPP).

- PAT is process analysis in real-time. Real-time analytical measurements can replace off-line time consuming chemical analyses and reduce process cycle time.

- PAT - An Innovative Way to Achieve Continuous Process Improvements and Quality by Design.

- PAT tools and technology includes; Near Infrared (NIR) spectrophotometers, Raman, laser diffraction for particle size analysis, NIR chemical imaging, etc.
**PAT Case Study: API Milling Operation**

- **Typical API Pharmaceutical Process:**
  
  Reaction → Crystallization → Drying → Milling

- **API PSD acceptance range:** D50 within [30, 80] microns
  - Non-critical, no final testing on the composite sample.

- **API milling in-process test target range:** D50 within [50, 65] microns
  - Two mills, fixed feed rate RPM, blower speed, and screen size.
  - Initial milling speed @ 3600 RPM, mill ~ 1-5 kg, PSD testing (offline).
  - Adjust milling speed to reach the target range, mill remainder lot.

- **Offline method**
Insitec® Online Particle Size Analyzer

- Laser diffraction technology (0.1, 1000 μm).
- First principles measurement, model independent analysis.
- Wide range of mass concentration
  - Low mass concentration – Beer’s Law.
  - High mass concentration – Multiple scattering correction.
- Easily integrated into the process.
How Does it Work?

• A laser diffraction instrument does not measure particle size (PS).
• Laser diffraction measures light scattering, which is dependent of PS.
• Laser beam hits the sample and generates light scattering.
• Scattering signal is collected by the detectors (32 in total).
• Scattering pattern is generated.
How to Generate the Size Distribution

1. Scattering Pattern from measurement
2. Generate initial estimate of the size distribution
3. Use Mie theory
4. Size distribution
5. Make alterations to size distribution
6. Scattering pattern derived from theory
7. Make a comparison between theory and measurement
8. Report final size distribution
9. Is difference minimized?

Illustrations from Malvern Instruments
Mill/Insitec® Current Setup at Abbott Facility

- Nitrogen
- Sample In
- Return
- Controls
- OSI-PI
- Wireless TCP/IP Network
- Wall Interface
- RS232
- RS5422
- Control PC
- Wireless TCP/IP Network
- Allen Bradley PLC
- Insitec PSA
## PSA Operational Sequence and Logistics

<table>
<thead>
<tr>
<th></th>
<th>Analyzer</th>
<th>PLC</th>
<th>HMI</th>
<th>OSI-PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Initial Start-Up</td>
<td>PLC setups parameters</td>
<td>Operator Enters D50 &amp; Control parameters</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Backgrd Ref.</td>
<td>Analyzer perform background check</td>
<td>Operator collects background</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Start-Up</td>
<td>Data Tag</td>
<td>Operator enter Batch ID</td>
<td>Batch ID</td>
</tr>
<tr>
<td></td>
<td>Measurement Active</td>
<td>Mill Starts</td>
<td>Enable</td>
<td>Mill RPM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Start Malvern’s</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>D10, D50, D90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Auto Shut Down</td>
<td>Mill Stops</td>
<td>Auto Shut Down Low Scattering</td>
<td>D10, D50, D90</td>
</tr>
</tbody>
</table>
API Milling Operation – Current State

• API PSD acceptance range: D50 within [30, 80] microns
  • Non-critical, no final testing on the composite sample.

• API On-line milling
  • On-line milling using PSA-PAT.
  • Define initial parameters (i.e. Initial milling speed, desired D50, etc).
  • Milling speed via feedback control.

• PAT PSD Process Monitoring
  • Support via remote desktop connection.
  • PSD data available for viewing in OSI-PI.
  • PSD data track and trending.
Engineering Study

• To establish the feasibility of process monitoring.
• To demonstrate the correlation between online Insitec® and offline Mastersizer® particle size results.
• To demonstrate feasibility of feedback control during the milling operation.
• To study and optimize the following parameters:
  – Flow Titration
  – Flute Optimization
  – System Sensitivity
  – Process Control Parameters
  – Feedback Control
# ES Outcome - Feed Back Control Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Setting</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venturi Eductor flow rate (SCFM)</td>
<td>2.5</td>
<td>The nitrogen flow rate needed for proper aspirating a representative sample stream from the main process stream</td>
</tr>
<tr>
<td>D50 set point (microns)</td>
<td>58</td>
<td>Target particle size value</td>
</tr>
<tr>
<td>Target mill speed at startup (RPM)</td>
<td>3600</td>
<td>Start up mill speed target, same as the current milling starting RPM</td>
</tr>
<tr>
<td>Particle size cycle time (sec)</td>
<td>10 ~ 20 (15)</td>
<td>Frequency of changes to the mill speed if the rolling average D50 value is outside the dead band range</td>
</tr>
<tr>
<td>Mill speed adjustment step size (RPM)</td>
<td>50 ~ 100 (50)</td>
<td>Value of change to the mill speed during every cycle time if D50 is outside of the dead band range</td>
</tr>
<tr>
<td>Mill speed adjustment limit (RPM)</td>
<td>+/- 2600</td>
<td>Maximum value of change to the mill speed, allowed by PLC</td>
</tr>
<tr>
<td>D50 dead band range (microns)</td>
<td>+/- 2</td>
<td>The range around the rolling average D50 set point, within which no change is made to the mill speed</td>
</tr>
<tr>
<td>Particle size deviation alarm (microns)</td>
<td>+/- 20</td>
<td>The range around the rolling average D50 set point, outside which Malvern Insitec® issues an alarm signal. D50 acceptable range is 30 – 80 microns.</td>
</tr>
<tr>
<td>D50 rolling average window size (sec)</td>
<td>30</td>
<td>The window size of the time over which the average is reported</td>
</tr>
</tbody>
</table>
Offline-Online Correlation

\[ y = 1.0023x + 1.4477 \]

\[ R^2 = 0.9417 \]
Engineering Study Conclusions

- On-line particle size analyzer can monitor the milling operation continuously.
- On-line results have good correlation to the results from the off-line method.
- Feedback loop using Insitec® provides consistent and well controlled particle size distribution throughout the whole milling operation.
- Analyzer needs to be integrated into the milling system for regular implementation.
Implementation Strategy & Outcome

- **Engineering Study**
  - Communication Established
  - Critical Parameters Defined

- **System Qualification**
  - Analyzer & Mill
  - HMI PLC, Software, OSI-PI

- **PAT Implementation Strategy**
  - PAT Operation Procedure
  - Training
  - Manufacturing Direction
  - PV/PQ

- **Manufacturing Implementation**
  - Monitor and Control
  - Track and Trend
Qualification Approach

Equipment & APC
- Malvern Analyzer IOQ
- APC Controls & Interface IOQ
- Engineering Study
- URS

OSI-PI
- PAT OSI-PI OPC Configuration
- API PSA Tags

Malvern PSA Software
- PAT Software Operational Qualification (SOQ)

API Process
- PAT Process Integration
API Process Impact

- In-Process (offline testing) sample was removed.
- Mill RPM via feedback control.
- Continuous Monitoring of D50 PSD.
- Reduction in cycle time for milling stage.
- Integration of PSA into the Mill.
- Integration of PSA into the API process.
- Modification of current HMI PLC program and APC interface.
- PAT BOP to incorporate PAT system along with personnel training.
Closed Loop Feedback Control

Transmission

Dv90

Dv50

Cumulative Dv(50)

Rolling Average Dv(50)

Process Upset

End of a Batch
Closed Loop Feedback Control

• Step 1: D50 SP = 58 ± 2 μm, mill speed startup SP = 2600 RPM
  – Took 5 minutes to reach dead band
  – Offline sample D50 = 61 μm

• Step 2: D50 SP = 58 ± 2 μm, mill speed startup SP = 3800 RPM

• Step 3: D50 SP = 50 ± 2 μm

• Step 4: D50 SP = 58 ± 2 μm
D50 Feedback Control Using PAT for 2009 Campaign

- Initial D50
- Constant RPM
- D50 Adjustment
- Mill Speed Adjustment
- Feedback Controlled D50

D50 Set Point 57µm | Mill Start-UP 3600RPM
On-Line Milling PSA Benefits

- Integrated milling system leads to real time particle size distribution monitoring, control, and process understanding.
- Removing In-Process testing leads to streamlined operation and reduction in cycle time.
- Data integration to OSI-PI leads to real time tracking and trending and improved trouble shooting capability.

<table>
<thead>
<tr>
<th>Previous Process</th>
<th>Current Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-Process Sample</td>
<td>No In-Process Sample</td>
</tr>
<tr>
<td>RPM Manual Adjustment</td>
<td>RPM Feedback Control</td>
</tr>
<tr>
<td>Offline testing</td>
<td>On-line testing</td>
</tr>
<tr>
<td>Limited PSD Data</td>
<td>Continuous PSD Data</td>
</tr>
<tr>
<td>Archived QA Data</td>
<td>Data Historian OSI-PI</td>
</tr>
</tbody>
</table>
Summary and Next Steps

- PAT initiative encourages the pharmaceutical industry to embrace new analytical approaches with the aim of transforming process development and manufacture.
- PAT On-Line Particle Size Analyzer (PSA) for Fitz-Mill was implemented during 2009 API manufacturing campaign successfully and it represents the first On-Line PAT PSA project completed and used in Abbott commercial production.
- PAT PSA has replaced the In-Process sample and reduced the cycle time during the milling staged as well as improved the process in overall.
- API Manufacturing will continue to use the PAT PSA for future campaigns.
- Currently evaluating other APIs and Drug Products (DP) pharmaceutical processes in order to determine PAT PSA feasibility.
Last Word: Vendor-Customer Partnership
Acknowledgements

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