Process Analytical Technology
Application and Emerging Technologies in Manufacturing

2014 GPhA CMC WORKSHOP

Pradeep Sanghvi, Ph.D.
Executive Vice President, Global R&D
Apotex Inc.
Disclaimer

• This presentation contains a summary of the opinion and perspective from GPhA member industry representatives on the topic of “PAT”.

• This presentation does not necessarily represent the opinion of the presenter nor “Apotex Inc.”.
Agenda

• Introduction and Role of PAT

• PAT Techniques for Solid Oral Dose Forms

• PAT Techniques for Liquid Dosage Forms
  – Case study of an Ophthalmic Suspension dosage form

• PAT Techniques for Transdermal Dosage Forms
Why PAT

• **Benefits of employing PAT throughout the product lifecycle.**

• **Automation by using basic process analytical technologies which have already found widespread use in the industry.**

• **Continued Investment by the Industry in current PAT & emerging technologies for Compliance & Productivity**
Definitions of PAT

• 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.

• A mechanism to design, analyze, and control pharmaceutical manufacturing processes through the measurement of critical process parameters (CPP) which affect product quality attributes (CQA).
History of PAT

• PAT has been used by the chemical industry since WWII

• Formalized with the founding of The Center for Process Analysis Control in 1984

• Mid 80s to Late 90’s in Pharmaceuticals
  • Use of NIR with libraries for API
  • Exploration for use in Drug Product manufacture
  • New emerging technologies such as Raman, acoustic, etc.
  • Increasingly used with Drug Product, monitoring blending or disposition of drug in tablets.
History of PAT

• Initiated by the FDA as part of the 21st Century GMP initiative in 2001 with the goal of increasing productivity

• Current Use
  • Real time monitoring of blend uniformity, particle size, moisture content, vial filing, replacing weight checks
  • On-line purification control
PAT - ICH Q8, ICH Q9 & ICH Q10

QbD – Characterize CMA, CPP and Define Controls

QRM – Identify sources of variability (risks), Improve ability of detection, reduce frequency of occurrence

PAT Techniques are tools to implement ICH Q8, 9 and 10

PQS – Continuous Improvement to ensure product quality
PAT Tools in QbD and QRM based process

Variable Inputs
- Input A
- Input B
- Input C

Variable Process

Controlled and Monitored Process

Fixed Output
- Quality Output

PAT Tools

QA
# PAT Techniques for Solid Dosage Form

<table>
<thead>
<tr>
<th>Unit Operation or Process Step or Analytical test</th>
<th>In-Line, At-Line, Off-Line Technique</th>
<th>CQA /CPP monitored /controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blending</td>
<td>NIR, Raman, LIF, NIR imaging, LIBS</td>
<td>Blend Uniformity</td>
</tr>
<tr>
<td>Granulation</td>
<td>NIR, FBRM, PVM, Raman, Power consumption</td>
<td>Content uniformity, moisture content, particle size distribution, particle morphology</td>
</tr>
<tr>
<td>Drying</td>
<td>NIR, Raman, FBRM, PVM</td>
<td>Moisture content, particle size distribution, particle morphology</td>
</tr>
<tr>
<td>Compression</td>
<td>NIR, Raman, FTIR</td>
<td>Content Uniformity, Dissolution,</td>
</tr>
<tr>
<td>Coating</td>
<td>NIR, LIBS, FTIR</td>
<td>Coat uniformity,</td>
</tr>
<tr>
<td>Dissolution</td>
<td>NIR, PVM, FBRM, FTIR</td>
<td>Release rates, disintegration behavior</td>
</tr>
</tbody>
</table>

Laser Induced Breakdown Spectroscopy, Particle Video Monitoring, Laser Induced Fluorescence
## Liquid Dosage Form - PAT Opportunities

<table>
<thead>
<tr>
<th>CMA/CQA/CPP to be monitored controlled</th>
<th>Possible PAT Techniques (In-Line, At-Line, Off-Line)</th>
<th>Type of Liquid Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogeneity of API</td>
<td>NIR, UV</td>
<td>Solutions, Suspensions, Emulsion</td>
</tr>
<tr>
<td>Homogeneity of excipients</td>
<td>NIR, Raman</td>
<td>Suspensions, Emulsions</td>
</tr>
<tr>
<td>pH, Osmolarity</td>
<td>pH meter, Osmometer</td>
<td>Solutions, Suspensions, Emulsion</td>
</tr>
<tr>
<td>Viscosity</td>
<td>Viscometer</td>
<td>Solutions, Suspensions, Emulsion</td>
</tr>
<tr>
<td>Crystal growth/ Precipitation/Polymorphism</td>
<td>MDRS, FBRM,</td>
<td>Solutions, Suspensions, Emulsion</td>
</tr>
<tr>
<td>Particle/Droplet Size distribution</td>
<td>FBRM, MDRS</td>
<td>Solutions, Suspensions, Emulsion</td>
</tr>
<tr>
<td>Particle Morphology</td>
<td>FBRM, MDRS, PVM</td>
<td>Suspensions, Emulsion</td>
</tr>
<tr>
<td>Fill Weight checks</td>
<td>Load Cells</td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>Temperature sensors</td>
<td>Solutions, Suspensions, Emulsion</td>
</tr>
</tbody>
</table>

Morphologically Directed Raman Spectroscopy
Ophthalmic Suspension Manufacturing Process

API Phase Preparation

Buffer/Excipient Phase

Finished Bulk

Aseptic Filling

Packaging
Active Phase Preparation

<table>
<thead>
<tr>
<th>Conventional Technology</th>
<th>PAT integrated automation</th>
<th>Benefits of PAT</th>
</tr>
</thead>
</table>
| Desired particle size achieved through multiple studies by manipulating homogenizer parameters (flow rate, recirculation rate, shear rate etc.) | FBRM is utilized to collect real-time date of the particle size distribution. Homogenizer parameters are controlled through feedback from FBRM, MDRS | - High degree of batch to batch consistency.  
- Substantially reduces batch rejection rate  
- Saves considerable time and efforts in reducing number of developmental studies required. |
Finished Bulk

Conventional Technology

- Dissolved O2 is hard to measure through bulk processing for O2 products.
- Considerable studies required to demonstrate homogeneity and particle distribution of suspended API.
- Difficult to monitor viscosity profile post of in-situ sterilization of bulk product.

PAT integrated automation

- Processing tank equipped with in-line O2 meter, NIR, FBRM, Electrochemical sensors and Viscosity meter.
- Fully automated and integrated through a central server to monitor and control parameters impacting CQAs.

Benefits of PAT

- Reduce batch to batch variation.
- System will not allow the process to proceed to subsequent steps without achieving predetermined quality attributes.
- Fully automated in-situ sterilization of the bulk product.
- Eliminates operator introduced errors.
## Sterile Bulk Filling

<table>
<thead>
<tr>
<th>Conventional Technology</th>
<th>PAT integrated automation</th>
<th>Benefits of PAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Difficult to maintain API suspended through extended filling. Batch size restriction.</td>
<td>- Fully automated system for aseptic filling. Almost eliminate operator as the vector of microorganisms.</td>
<td>- High degree of sterility assurance.</td>
</tr>
<tr>
<td>- In-process checks required to demonstrate dosage uniformity and delivery (fill volume), container closure integrity (CCI).</td>
<td>- 100% check of dosage delivery and CCI.</td>
<td>- Product homogeneity continuously monitored through NIR before filled into bottles.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Ability to detect and reject 100% low filled and non-integral units.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Finished product rejection rate lower.</td>
</tr>
</tbody>
</table>
Transdermal Dosage Forms Manufacturing

- Continuous process
- Sampling challenges
- Significant waste
- Greater Opportunities for PAT
PAT in Transdermal Processing

- PAT can provide for significantly reduced in-process testing and enhanced process control for transdermal and oral film processes.
- Four primary process steps for transdermal/film manufacturing include:

1. Blending
2. Coater/Dryer/Laminator
3. Finishing
4. Packaging

<table>
<thead>
<tr>
<th>Process Description</th>
<th>Blending</th>
<th>Coater/Dryer/Laminator</th>
<th>Finishing</th>
<th>Packaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscosity Monitor</td>
<td></td>
<td>Coating Thickness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torque Monitor</td>
<td></td>
<td>API Assay Measurement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Particle Size Monitor</td>
<td></td>
<td>Solvents/Moisture Content</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystallization Homogeneity</td>
<td></td>
<td>Laminate Inspection</td>
<td></td>
<td>Pouch Integrity</td>
</tr>
<tr>
<td>PAT Opportunity</td>
<td></td>
<td>Pouch Inspection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Largest efficiency gain: on-line assay measurement which provides capability to eliminate laboratory testing, while increasing process reliability (increased web data points and immediate feedback)
PAT in Transdermal Processing

Example of transdermal laminate PAT: Near-IR testing for Active content during web coating

- Implemented four NIR probes across dry laminate web path
- NIR calibrated against 80% - 120% of target API content (offline scans)
- Multiple NIR scans during continuous coating to obtain mean value at each position

**Results:**
- Comparison of NIR data to HPLC laboratory testing found equivalence between the two methods
- Feasibility of on-line NIR system was demonstrated.

**Recommendations for Implementation:**
- Highly formulation dependent; crystal dispersions/granular systems problematic, MDRS
- Probes function by reflectance through substrate; clear/translucent web required, FTIR
PAT Benefits

• **In Pharmaceutical R &D:**
  – A deeper scientific and engineering understanding of manufacturing processes
  – Reduced product development times, faster scale up, and faster time-to-market for new products
  – Implementation of innovative manufacturing and quality strategies

• **In Pharmaceutical Manufacturing:**
  – Reduced waste, right-first-time manufacturing, higher production asset utilization, continuous manufacturing
  – Real-time quality assurance and validation
  – Movement toward real-time release of products
  – Lean manufacturing practices for reduced raw material, work-in-progress and finished goods inventories
  – More robust product supply to the public
Challenges in Implementing PAT

• Large Portfolio, non-dedicated assets, frequent change-overs - Ability to demonstrate ROI
• Integration with current practices without disruption to supply
• Lack of internal expertise