The Impact of New Technology on PAT for Achieving Quality by Design (QbD)

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Critical elements of advanced process understanding envisioned by QbD

* Critical Quality Attributes (CQAs) linked to patient needs
* Critical Process Parameters (CPPs)
* A Process Model
* Design Space
* Process and Measurement Control
These same QbD concepts are used for each part of the process

- Qualification of raw materials including excipients
- Reactor characterization
- Bioreactor characterization
- API purification steps
- Formulation and tableting
Optimization of the copper catalyzed oxidation of monomer to dimer for a new atherosclerotic plaque reduction drug

Cysteine (or RSH) $\longrightarrow k1 \rightarrow \text{Cysteine Dimer (RS-SR)}$

Cysteine (or RSH) $\longrightarrow k2 \rightarrow \text{Cysteine Sulfonate (RSO3H) + H2O2}$

(Pfizer Group)
Window of Operation:

<table>
<thead>
<tr>
<th>Dimer</th>
<th>white area</th>
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<tbody>
<tr>
<td>&gt; 85%</td>
<td></td>
</tr>
<tr>
<td>Aggregates</td>
<td>&lt; 3%</td>
</tr>
<tr>
<td>Non-reducible dimer</td>
<td>&lt; 3%</td>
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Formation of Methyl Acetate at Different Temperatures

- PCA analysis of the formation of acetate monitored by Raman spectroscopy – reaction time 1.5 hours
Reaction characterization with microscale process equipment

The rapid heat and mass transfer characteristics as well as low back mixing in well designed microscale process equipment enable carefully controlled experiments to be done easily.
NeSSI Raman Sampling Block

- Parker Intraflow NeSSI substrate
- Sample conditioning to induce backpressure to reduce bubble formation and the heated substrate allows analysis at reactor conditions
Scores Plot vs. Temperature Steps from 30-60°C

PCA Analysis on data after mixing:
1st PCA scores \(\rightarrow\) Increase in reaction yield after each temperature step

- without residence time module
- flow rate: 0.89 ml/min
  (residence time \(\sim\) 5 min)
These experiments can be used to rapidly explore the chemistry to determine the design space.

Hickman and Sobeck their chapter in “Micro-Instrumentation for High Throughput Experimentation and Process Intensification – A Tool for PAT” demonstrated how to utilize the data from these experiments to rapidly determine a rate expression for a reaction.
Fig. 13.5 Screen capture of programming schematic used to control automated system.

Microreactor system for reaction characterization; Hickman and Sobeck; Micro-Instrumentation for High Throughput Experimentation and Process Intensification – A Tool for PAT
NESSI Membrane Sampling /Calibration System

Feed 1

Reactors Feed 1

Product

Reactors Feed 2

Real-time Calibration

Sensor Probes

Feed 2

waste

prod
Utility of PAT enhanced microscale process technology

• Rapidly determine rate expression
• Characterize reaction temperature dependence
• Evaluate the impact of pH, ionic strength, solvent, catalysts and other parameters on the reaction
• Rapidly develop new post bioreactor chemical modifications
• Optimize process separation technology as well as other unit operations
PAT coupled with microscale process technology can be used to rapidly achieve the advanced process understanding envisioned by QbD