Real-Time Measurement and Sampling Advances to Enhance the Performance of Advanced Flow Reactors

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Applied Physics Laboratory

University of Washington, Seattle, WA
Process Research and Pilot Plants in Italy (Dow Lepetit) – late 1970’s
The Analytical Department was added to Process Research

ANALYTICAL TECHNOLOGY WAS THEN TAKEN TO PRODUCTION

Small Molecule Production

Yield and Environmental improvements

Fermentation Plant

Continuous Processing and Yield improvements
BACK AT DOW, LABORATORY ANALYTICAL SCIENCES TECHNOLOGIES WERE TAKEN TO THE PROCESS

- SPECTROSCOPY
- CHROMATOGRAPHY
Real-time Data Acquisition

• . . . provided researchers with a “vision” into a process.

• What was accomplished?
  – Composition
  – Reaction Pathways & Kinetics
  – Emission Monitoring
  – Hazard Evaluation Issues
  – On-line Feasibility Studies

Courtesy Dow Chemical
IN RECENT YEARS MEASUREMENT SCIENCE HAS ADVANCED BECAUSE OF:

- MINIATURIZATION
- NEW ENGINEERED MATERIALS
- ELECTRO-OPTICS
- DATA PROCESSING

CONSORTIA ARE AN EFFECTIVE APPROACH TO DEVELOPING NEW MEASUREMENT CAPABILITIES - AS RESOURCES WITHIN AN INDIVIDUAL ORGANIZATION ARE OFTEN LIMITED
CPAC
(The Center for Process Analytical Chemistry)
is a consortium of Industry and Government Agencies

• The Objective of the Center is to Address Challenges in Real-Time Analysis and Process Optimization

• Provides a Global Forum for Multi-disciplinary and Multi-University Participation in Developments in Process Analytical Technology
CPAC Activities

- Semiannual Sponsor Meetings (May & Nov)
- Tutorials and Technical Workshops
- Summer Institute – Seattle (July)
- Satellite Workshop – Rome, Italy (March)
- Industry Driven Initiatives
- Graduate Education
- IFPAC, FACSS, AIChE, Pittcon, etc.
- FDA (PAT, QbD), USP
Historical Process Restrictions in Industry Compared to an Academic Synthesis Lab

• Minimize largely exothermic reactions
• Avoid largely hazardous materials
• No potential environmental hazards

As a result, multi-step synthetic processes, protecting groups, and excess solvent use have been common.

Extensive and costly solvent recovery and recycle streams have resulted
Developments in Micro-Technology are Resulting in Applications for use in Industrial Processing

• High Throughput Experimentation
  – Process Intensification
  – Production Optimization
  – Product Quality Improvement

• Micro- Unit Operations for Continuous Processing
## MULTI-SCALED REACTOR ARCHITECTURE

**Type of reaction**

<table>
<thead>
<tr>
<th>Type</th>
<th>Diagram</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘All-micro’</td>
<td>![Image](source: IMM)</td>
</tr>
<tr>
<td>“A”</td>
<td>![Image](source: IMM (OSBP plant ))</td>
</tr>
<tr>
<td>‘Micro-meso’</td>
<td>![Image](source: IMM (OSBP plant ))</td>
</tr>
<tr>
<td>“B”</td>
<td>![Image](Iwasaki, Yoshida <em>Macromolecules</em> 38, 4 (2005) 1159.)</td>
</tr>
<tr>
<td>‘All-meso’</td>
<td>![Image](source: IMM)</td>
</tr>
<tr>
<td>‘Micro-in- macro’</td>
<td>![Image](source: FZK)</td>
</tr>
<tr>
<td>“C”</td>
<td>![Image](source: FZK)</td>
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*Courtesy V. Hessel, IMM*
Some of the Current Initiatives at CPAC that are Keys to the Future of Process Improvement

- **Micro-Analytical** for enabling high throughput, development, and process optimization

- New sampling system approaches (**NeSSI™**)
ADVANCES IN MICRO-SYSTEMS

Corning product: Customized reactors made from standard parts

Labtrix

IMM
THERE ARE SIGNIFICANT ADVANTAGES WITH USING MICRO-SYSTEMS, BUT HOW ARE MICRO-OPERATIONS MONITORED AND SUBSEQUENTLY CONTROLLED - AS THEY ARE IN THE PRESENT MACRO-WORLD?
THERE ARE RELEVANT CPAC RESEARCH EFFORTS IN MICRO-ANALYTICAL TO COMPLIMENT OTHER R&D EFFORTS BY INDUSTRY AND VENDORS

NIR, IR, UV
MICRO-LC
GCxGC
FRINGE FIELD SENSORS
VAPOCHROMIC SENSORS
RAMAN
GRATED LIGHT REFLECTIVE SPECTROSCOPY
REFLECTOMETRY
RADIO FREQUENCY IDENTICATION BASED
SURFACE PLASMON RESONANCE
MINI-NMR
ULTRASOUND
SURFACE TENSION DETECTION
THESE ADVANCES IN HARDWARE, SENSORS AND CONTROLS HIGHLIGHT THE NEED FOR IMPROVED SAMPLING TECHNOLOGIES – NeSSI
What is NeSSI?

- Industry-driven effort to define and promote a new standardized alternative to sample conditioning systems for analyzers and sensors

- Standard fluidic interface for modular surface-mount components
  - ISA SP76

- Standard wiring and communications interfaces

- Standard platform for micro analytics
NeSSI™ Could Become the Base for a Micro-Analytical Lab
Sensing Technologies Demonstrated on NeSSI™

- Gas Chromatography
  - Thermal Desorption
- Dielectric Sensors
- Spectroscopies
  - IR, NIR
  - UV-Vis
  - Raman
  - Fluorescence
- Impedance
- Conductivity
- Refractive Index
- Bio-Sensors
- Vapochromic Sensors
- GLRS
- Particle Sizing
  - Light scattering
- Turbidity
- pH
- RGA
- Mass Spectrometry
- LC, SEC, IC
NeSSI with an Array of Micro-Analytical Techniques will Impact:

• Process Control
• Process Optimization
Demonstration of QbD in the Preparation of Active Pharmaceutical Ingredients (API) by Continuous Processing

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FDA Collaboration: Demonstrate the Concept of QbD

- Monitoring an advanced flow reactor (Corning AF Reactor) using NeSSI™ sampling systems and Raman ballprobe sampling interfaces at various reactor points for optimization and control.
Why is FDA Interested in Advanced Flow Reactors?

High Throughput Experimentation For...

- Discovery and screening
- Process development
- Process optimization
- Process control
- Production
  - Eliminate chemical engineering production problems related to scaling up batch systems?
  - Increase production through use of many parallel micro-reactors to achieve volume?
  - Regulatory Relief Potential regarding 3 Batch Validation
Analysis of Advanced Flow Reactors

- **Problems with performing online measurements**
  - Gas formation in sample lines
  - Temperature change before reaching analyzer
  - Phase change between reactor and analyzer
  - Sensor placement at optimal position
  - Automated flow and pressure control

- **Most PAT problems are due to sampling not measurement device**

- **Need better systems to sample processes**
Raman spectroscopy as a process analytical tool

EXAMPLE OF HIGH INFORMATION CONTENT VIBRATIONAL SPECTROSCOPY SUITABLE FOR ONLINE MEASUREMENTS IN A CONTINUOUS REACTOR
Process Raman Applications

- Pharmaceuticals
- Fine chemicals
- Food quality and safety
- Polymers/coatings
- Fermentation/biotech
- Cellular/tissue
- Oil/fuels/petrochemicals
- Oceanography/environment

Challenges
- Reproducible sampling
- Fluorescence
Application of Sampling Systems To Microreactors

- EXAMPLE OF BRINGING ANALYTICS TO THE PROCESS AND THE CHALLENGES WITH INTEGRATING THEM

- NeSSI™ WILL BE USED
NeSSI™ with Ballprobe - Raman

Ballprobe Specs.
• Hastalloy c-276
  Ti, SS, Monel
• Sapphire optic
• Std. temp range:
  -40 – 350° C
• Pressure:
  0-350 Barr
Monitor reaction with 4 channel 785 nm Raman system

NeSSI™ sampling systems (1-4) equipped with Raman ballprobes

Online GC also used as post quench online analyzer (4)
Advanced Flow Reactor Images

Raman Probes
Raman Peaks of Interest (Low cm\(^{-1}\))
Design of Experiments Information

- **31 Experiments total**
  - Temperature steps
  - Reaction with no toluene
  - Changes in butanediol ratio
  - Changes in pyridine ratio
  - Propanediol instead of butanediol
  - Simulated Reactor problems
    - Pump failure
    - Less heat exchange
    - Poor dilution of chloroformate
3D Plot of Raman Reaction Data (Low cm\(^{-1}\))

<table>
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<tr>
<th>Test</th>
<th>R-OH</th>
<th>2EHC</th>
<th>R-Cl</th>
<th>Carbonate</th>
<th>Dimer</th>
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<td>0</td>
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<td>0.00</td>
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continuous reactors w/analytics allow for fast optimization of design space
Project Summary and Future Directions

- Data collected and organized

- Analysis and Modeling
  - Evaluation of various modeling protocols
    - PCA, MCR, ALS
  - Calibrate to GC results (PLS)

- Phase 2 of project proposed
  - Acquire reactor at CPAC
  - Focus on reactor control
  - Implement more sensors
  - Scale-up vs. scale-out?
  - Real-time product work-up

- Implement Models for Process Feedback Control
Continuous Process Understanding and Control Project - Phase 2

- **Part 1 – Process Scale Up and Control**
  - **Chemistry**
    - Finding and Testing Reaction in Micro Reactor
    - Pharmaceutical industry relevant chemistry
    - Emphasis on processing not specific chemistry
    - Determine CRF (Critical Response Factors) and Levels
  - **Sampling & DoE**
  - **Process Understanding via Modeling**
    - Modeling
    - Control Mechanisms
    - Integration of Process Control
Corning® Advanced-Flow™ LF
Low-Flow Capability (1-10 mL/min)

Corning has introduced a reduced flow-rate reactor that retains the outstanding mixing and heat exchange performance of its Advance-Flow™ glass reactors while providing:

- Low internal volume
- High flexibility
- Metal-free reaction path
- Scalability
- Compatibility with analytics
- T, Flow and Pumping control

• LF platform will be the reactor platform for our Phase II FDA project
Reactor with NeSSI™ and Analytical being assembled at CPAC (University of Washington)
Labtrix

- Reaction optimization

Features

- Syringe pumps
- Automated sample collection and control
- Tests at pressures of 25 bar and temperatures of -15 to 195°C
- Standard interchangeable reactors:

Courtesy Paul Watts, University of Hull, UK
Part 2 - Process Optimization

- Scale Up Versus Scale Out

- Development of Generic Strategy
  - that will lead to the selection of the best analytical tools, processing methods, and model designs in a short time frame.

Part 3 - Options for Continuous Process Control
A Tool Box of Process Analytics for Optimizing Continuous Processing

THERE ARE AN INCREASING NUMBER OF PAT TOOLS BEING DEVELOPED AND COMMERCIALIZED
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Diamond ATR-IR-Fiber Probe of 2.7mm diameter in NeSSI™
React-IR, Mettler Toledo
Applied Analytics Inc. Diode Array

- OMA-300
- A Fiber-optics-diode-array process analyzer
- For on-line concentration monitoring
Thermo/C2V Fast Micro-GC on NeSSI™

http://www.c2v.nl/ as well as http://www.thermo.com
NeSSI™ UV-Vis/NIR Sensor

Integrated Spectral Sensing System

The Spectral Measurement Sensor (SMS) is ideal for compact on-line liquid measurement applications.

The Process Spectral Measurement Sensor
Thank You

- U.S. Food and Drug Administration
  - Moheb Nasr
  - Christine Moore
  - Sharmista Chatterjee
  - David Morley
- Corning Glass
- Parker
- Kaiser Optical Systems
- CPAC
- University of Washington
- Applied Physics Lab
- La Maison Européenne des Procédés Innovants (MEPI)