Raman Spectroscopy, A valuable tool for continuous Flow Reactors.


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Summary

➢ Understand Theoretical Benefits of Raman

➢ Introduce Raman sampling flexibility

➢ Demonstrate Raman on different reactor types and for different chemistries
   ➢ Thermal
   ➢ Microwave
   ➢ Batch
   ➢ Continuous Flow
   ➢ Advanced Flow Reactors with NeSSI analytical interface

➢ On Going Developments
Why Real-time Reaction Analysis?

- Monitor Reactions under Actual Conditions
  - Immersion or non-contact optic with Fiber-coupling probe to analyzer
  - Avoid Grab Samples

- Monitor Reactions in Real Time
  - Did the reaction go as expected
  - Observe intermediates
  - Avoid sample change / decay

- Identify chemical species – critical components

- Characterize components that are difficult to isolate

- Provide information for mechanistic understanding / pathways

- Reaction knowledge = Understanding = less reaction risk
What is Raman Spectroscopy?

Raman is a scattering technique

LASER

Rayleigh scattering:
Elastic scatter

Raman:
Inelastic scatter

Stokes
Anti-Stokes
Raman and IR Spectra

- Raman spectroscopy gives us information about the vibrational energies of molecules.
- Raman is complementary to IR, general rule of thumb – bands that are strong in the IR are weak in Raman, and what are weak in IR are strong in Raman.
- In Raman, water presents no problems and it is often easier to implement/sample than IR.
### Comparison to FT-IR

<table>
<thead>
<tr>
<th>Infrared</th>
<th>Raman</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Emission</td>
</tr>
<tr>
<td>Dipoles</td>
<td>Polarizability</td>
</tr>
<tr>
<td>O-H, N-H, C=O</td>
<td>C=C, Aromatics</td>
</tr>
<tr>
<td>Minimum Sample preparation</td>
<td>Hardly any sample</td>
</tr>
<tr>
<td></td>
<td>preparation</td>
</tr>
<tr>
<td>Non-aqueous samples</td>
<td>Aqueous samples,</td>
</tr>
</tbody>
</table>
Comparison to NIR

<table>
<thead>
<tr>
<th><strong>NIR</strong></th>
<th><strong>Raman</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Emission</td>
</tr>
<tr>
<td>Overtones</td>
<td>Fundamental information</td>
</tr>
<tr>
<td>No sample preparation necessary</td>
<td>No sample preparation</td>
</tr>
<tr>
<td>Process measurements</td>
<td>Process measurements</td>
</tr>
<tr>
<td>Unresolved information</td>
<td>High spectral density</td>
</tr>
</tbody>
</table>
Analytical Raman Spectroscopy

\[ I_\lambda = \sigma L C I \]

- \( I_\lambda \): Raman intensity
- \( \sigma \): Raman cross section
- \( L \): Pathlength
- \( C \): Concentration
- \( I \): Instrument parameters
Basic’s of a Raman Spectrometer

- Sampling systems
- Laser
- Monochromatic Source
- Focussing Optics
- Collection Optics
- Laser-line rejection device
- Wavelength selection device
- Wavelength separator
- Detector
Why Raman for Reaction Analysis?

- Composition and Structural Information with Fiber Optic Sampling – the specificity of mid-IR, but with the ease of use of near-IR
- Raman is a specific and selective technique providing well resolved information leading to... **BETTER REACTION OR PROCESS UNDERSTANDING**
- Flexible sampling (remote sampling)
- In-situ – Eliminate Grab samples, Sampling through containers
- Measurement of various types of samples (liquids, slurries, pastes, solids, powders, etc.)
- Sensitive to both organic and inorganic species
Why Use Raman Spectroscopy?

Sampling

- Non-contact or Immersion
- Spatial selectivity (optic controls sampling vol. [100 micron to mm])
- Common, high performance windows – glass, transparent polymer, quartz
- Optimized f/o-coupled sampling interface = high performance
- Remote analyzer = no tradeoff of analyzer size vs. performance
- Locate analyzer away from the hood, micro-reactor, classified area
Liquid/solid-phase Immersion Sampling

Excitation Laser in

Raman back to collection optics

Working Distance

Depth of Field

Lens Window

Std. Temp. Range = -40 to 200°C
OD = ½” or ¼” OD
MOC = Alloy C-276, Sapphire
Shaped Tip
Lens Determines Sample Volume
Raman Sampling Examples
Reaction Monitoring and Calibration

- Follow spectra in real-time
- Generate component spectra
- Generate component profiles
  - Peak Heights
  - Peak Areas
  - Peak Ratio’s
  - ConcIRT
  - Quant with PLS Plus / IQ
Microwave-Assisted Reactions

Customer at AstraZeneca / Biotage
Microwave-Assisted Reactions

- **Raman** analyzer equipped with a non-contact optic was used to study the reactions.
- Measurement times were on the order of a few seconds.
- 785-nm excitation was used as this minimized fluorescence from the samples.
Raman Probe interfaced to Microwave chamber

- Non-contact optic withdrawn
- Inside chamber optic inserted
- Reaction chamber
- Probehead
Microwave Reactor – Reaction Understanding

- Microwave Reactor
- Sealed glass reaction vials
- Non-contact, non-invasive fiber probe

Two Pathways possible

Ester band suggest – Intermediate A reaction pathway
Microwave Reactor – Reaction Completion / Optimization

- Microwave Reactor
- Sealed glass reaction vials
- Non-contact, non-invasive fiber probe
- Diels-Alder Reaction

\[
\text{reaction} \quad \text{100°C, 600 s} \quad \text{160°C, 1800 s}
\]
Microwave Reactor – Reaction Completion / Optimization

- Diels-Alder Reaction

![Graph A](image)

A

![Graph B](image)

B

![Graph C](image)

C

Key

- **Reactant**: 1645 cm\(^{-1}\)
- **Intermediate**: 650 cm\(^{-1}\)
- **Product**: 2250 cm\(^{-1}\)

**Reaction End Point** – **Accurately Monitored** (potential for larger scale control)
A Raman Analyzer can Provide Valuable In Situ Information

- Raman can be used for monitoring a microwave reactor.
- Interface was trivial.
- Microwave reaction was not disturbed and in situ analytical information could be gathered.
- Raman spectral data could be interpreted into process knowledge.
- Reaction intermediate and kinetic information were obtained from the spectra.
Catalytic Hydrogenation Reaction with In Situ RAMANRXN

Customer at Novartis
Catalytic Hydrogenation Reaction

ArNO₂ + 3H₂ → ArNH₂ + 2H₂O

- Intermediate is a potential thermal safety hazard
- Preferred reaction pathway would exclude or minimize the intermediate species
- Optimize reaction for safety
Catalytic Hydrogenation Reaction

Reactant
Intermediate
Product
Catalytic Hydrogenation Reaction

Preferred pathway excludes the intermediate species – especially for manufacturing

Intermediate (hydroxylamine [HA]) is a potential thermal safety hazard
Crystalline Polymorph Monitoring with *in-situ* Raman Analyzer

Pfizer & Michigan State University
Introduction

- Polymorphs may have Different Properties- i.e. Solubility, Dissolution Rate, Stability, or Bioavailability.

- Raman analyzers are able to Discriminate between Polymorphs because Different Crystal Forms Provide Intensity and Frequency Changes in the Raman Spectrum.
Characterization of Progesterone

Crystal Forms I and II

XRD patterns

DSC curves

- Form II (121.2°C)
- Form I (129.1°C)

Temperature (°C)
(5°C/ Min.)
Raman Spectra of Progesterone

Crystal Forms I and II

For this Study the C=O Stretching Vibration was used to Quantitate Form I and Form II Polymorphs. Form I @ 1662 cm⁻¹. Form II @ 1667 cm⁻¹.
Polymorphic Transformation at 45° C

- Crystallizations were monitored over the temperature range from 5 to 45° C.
- Slurry: 2 grams Progesterone (25ml Organic Sol.) added to 500ml H₂O.
- Temperature control and stirring were provided by a LabMax automated lab reactor.
- Polymorph concentration was determined from the C=O stretch band center position.
- Raman measurements were made in-situ with the RamanRxn1.
Transformation Thermodynamics

Crystal Form II to I

Temperature (°C)

Transformation Rate (hr⁻¹)
Conclusions

- Raman analyzer can Distinguish Form I and Form II Progesterone Crystals. Raman analyzers are able to Discriminate between Polymorphs because Different Crystal Forms Provide Intensity and Frequency Changes in the Raman Spectrum.

- Raman was shown to Accurately follow the Polymorphic Transformation (Form II to Form I) In-Situ.

- Transformation Rates were found to Increase with Increasing Temperature.

- The In-Situ Monitoring of this System Permits the Rate of Polymorphic Transformation to be Predicted over a Wide range of Process Temperatures.
From Avantium, NL

Working volume: (1mL – 5 mL)

8 independently programmable temperature zones

-25 to 180°C

Overhead sample stirring

Refluxing capability

N₂ flow for slow evaporation

Real time turbidity measurement
Crystalline PV
Integrated and correlated results – the ideal interface for a Raman system
Real-time Batch Fermentation Monitoring
Raw Raman Data for Fermentation Batch Reaction (8 day run)

- 10 second acquisition, 20 accumulations, sample every 10 minutes
- Analysis was run continuously for 8 days
Raman Data After Fluorescence Correction Applied

Fermentation #3 Raman Fluorescence Corrected Spectra

Fluorescence Corrected Intensity vs. Raman Shift (cm⁻¹)
3D Plot of Corrected Raman Data for Fermentation Batch Reaction
Fluorescence Corrected Raman Signals for 3 Maltose and 1 Ethanol Peaks

- Maltose 540 cm$^{-1}$
- Maltose 911 cm$^{-1}$
- Maltose 1120 cm$^{-1}$
- Ethanol 875 cm$^{-1}$
Microreactors and Sampling Systems: Esterification Example

Work at CPAC
Objectives

- Use Raman spectroscopy for the analysis of reaction kinetics and yield in real-time

- Apply Raman analyzer to improve reaction optimization and control
  - Work towards automated adaptive experimental design (T, Ratio, Flow)
  - Quickly sweep reactor variables to optimize reactions
  - Control reactor performance using Raman feedback
Esterification of Methanol

Acetic Acid + Methanol $\xrightleftharpoons{\text{H}^+} Methyl$ Acetate + H$_2$O

![Raman Spectra](image)

- ROI
- Acetic Acid
- Methanol
- Methyl Acetate

Raman Shift (cm$^{-1}$)
Batch Formation of Methyl Acetate at Different Temperatures

PCA analysis of the formation of acetate monitored by Raman spectroscopy – reaction time 1.5 hours
Online Monitoring of a Continuous Microreactor

- Continuous monitoring of reactor yield by Raman spectroscopy
- Effectively coupling analytics to small volume continuous reactor
- Identify reaction parameters for fast reaction optimization
Initial Sensor Integration

Continuous Microreactor

Online Raman Probe

Sample Flow Cell
Esterification of Methanol
(25°C – 40°C)

- Flow rate: 10.56 ml/min
  (residence time ~ 2.5 min)

- Methanol
- Acetic acid
- Methyl acetate

Graph showing the Raman shift (cm⁻¹) with peaks indicating the presence of acetic acid, methyl acetate, and methanol.
Conclusions

- Continuous reactor with Raman-based analytics allows reaction to be quickly optimized for yield.
- 4 hour single batch replaced by few minute continuous reactor
- Interface provided by simple flow cell (initially)
- Raman spectra analyzed using PCA
Continuous Flow Reactor Monitoring with Raman

COLLABORATION TO DEMONSTRATE THE APPLICATION OF QUALITY BY DESIGN

JUNE 9TH-17TH, 2009

CORNING

Parker

Kaiser Optical Systems, Inc.

CPAC

FDA

U.S. Food and Drug Administration

MEPI
Corning Continuous Flow Reactor

- Continuous reactions are ideal for product and process optimization/understanding
- Provide predictable and reliable reaction performance, easily customizable and transferable to a production facility
- Application of reactor, sampling and analytics, demonstrates the physical concept of QbD
- Additional analytics easily coupled to reactor through NeSSI substrates
  - 4 channel, Kaiser Optical Systems Rxn2 probes placed in reactor flow path at different points of the reaction
NeSSI™ Modular Sampling Systems

- **New Sampling Sensor Initiative**
- Industry-driven effort to define and promote a new standardized alternative to sample conditioning systems for analyzers and sensors
- Component based gas and fluid handling systems
- Offer flexibility in design and implementation of complicated flow systems for process sampling and analysis
- Allows for optimal positioning of analyzers in a process stream
Reactor Images

Raman Probes
NeSSI and Raman
Image in box for flyer
Chloroformate Chemistry

- Carbonate and dimer formation

\[
\text{2-ethylhexyl chloroformate} + \text{butane-1,2-diol} \rightarrow \text{pyridine toluène} \rightarrow \text{2-ethylhexyl 2-hydroxybutyl carbonate}
\]

\[
\text{2-ethylhexyl chloroformate} + \text{2-ethylhexyl 2-hydroxybutyl carbonate} \rightarrow \text{dimer}
\]
Reactor design: 3 modules
Standard Peaks of Interest (High End)

- Carbonate
- Dimer
- Chloroformate

Normalized Intensity Units (Arb. Units)

Raman Shift (cm⁻¹)
Standard Peaks of Interest (Low End)

- Chloroformate
- Toluene
- Carbonate
- Dimer
- Toluene

Wavenumber range: 323.10061 cm\(^{-1}\) to 477.60001 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
Peaks of Interest (Low End)

<table>
<thead>
<tr>
<th></th>
<th>Test</th>
<th>R-OH</th>
<th>≥EHCF</th>
<th>R-Cl</th>
<th>Carbonate</th>
<th>Dimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.16</td>
<td>45.84</td>
<td>0.32</td>
<td>51.42</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.17</td>
<td>0.00</td>
<td>0.26</td>
<td>96.17</td>
<td>2.40</td>
<td></td>
</tr>
</tbody>
</table>

Ch. 1

TEST 3
TEST 0
FLUSH

Raman Shift (cm⁻¹)

Toluene
Carbonate and Dimer
Chloroformate

Time
ON GOING DEVELOPMENT
AirHead™ Gas-Phase Probe

- Direct Insertion / Multi-pass Probe design
- Sealed Optical Design
- 100°C temp / 650 psi
- Fiber lengths up to 30 meters
- Constructed of SS 316
Gas-Phase Raman – Petrochemical Sample
AirHead™ Gas-Phase Probes installed
ON GOING DEVELOPMENT RAMAN 1000 nm excitation
Fermentation Sample

785 nm
A Raman Analyzer Can Provide Valuable in-situ Analytics for Process Optimization and Control

1. Fiber-optic coupled compact sampling interface allows high performance Raman without the drawback of miniaturized optical instruments
2. Raman can be used for in situ analysis of gases, liquids, and solids
3. Raman can be used for continuous, or batch analysis
4. Raman can be used to probe sealed systems in glass vials such as microwave reactions
5. Raman can be used for microfluidic lab-on-chip analytics
Automated Reaction analysis with control of both Raman and IR

React-IR + iC IR

**Raman**Rxn2 + iC Raman

EasyMax reactor

Mettler Toldeo’s iControl of both analyzers and reactor
Acknowledgements

Brian Marquardt – APL / CPAC

Ian Lewis – Kaiser Optical Systems, Inc.
Formed in 1979, as a division of Kaiser Aerospace & Electronics. Headquarters in Ann Arbor, MI, USA. Division of Rockwell Collins, Inc in 2000.

Leading supplier of Raman systems for reaction analysis and process control

ISO 9000-2001, as well as first ATEX Certified Raman analyzers