CPAC SATELLITE WORKSHOPS
2009
Micro-Reactors and
Micro-Analytical
DR BRUNO LENAIN
Kaiser Optical System

RAMAN SPECTROSCOPY
A VALUABLE TOOL FOR
PAT APPLICATIONS
History of Raman Spectroscopy

- 1928 C.V. Raman and Krishnan discover “a new type of secondary radiation” - Raman effect.
- Only 1 in 1,000,000 (0.0001%) photons are scattered inelastically.
- In the 1930s, Raman became the principal means of non-destructive chemical analysis.
- 1939-1945 PE develop the first commercial IR.
- After WWII, commercial IR surpassed Raman in this role.
- Advent of lasers in the 1960s revived interest in Raman to some extent. – First Raman renaissance – lasers, photon counting, double monochromators.
History of Raman Spectroscopy

- Late 1980s: notch filters improved the quality of Raman spectra.
- 1990s: dispersive Raman developments including compact NIR lasers, multi-channel detectors, refinement of Raman microscope, and fiber-optic probes.
- Early 1990’s – Second Raman renaissance – compact integrated dispersive Raman systems and analytical FT-Raman
- Early 1990’s – in-line 24/7 process Raman becomes a reality
Who is Kaiser?

- Formed in 1979, as a division of Kaiser Aerospace and Electronics.
- Headquarters in Ann Arbor, MI, USA
- Became a Division of Rockwell Collins, Inc in 2000.
- Our historical Expertise is in the area of holographic optical technology.
- Since 1990, Kaiser has been a major supplier to the Raman community.
- The Spectroscopic Products represent the largest single division of Kaiser.
- We are Global - having offices or representation in North America, Europe, and Asia.
Kaiser Technology Introductions

- 1991 – Holographic Notch Filter
- 1992 – Holographic Laser Bandpass Filter
- 1993 – HoloSpec f/1.8i Imaging Spectrograph
- 1994 – HoloProbe Process Raman Analyzer & HoloPlex Volume Phase Transmission Grating
- 1995 – Universal Fiber Optic Probehead
- 1996 – Confocal Raman Microscope
- 1997 – Internal Calibration Option for Raman Products
- 1997 – Immersion Probe Optics
- 1998 – Raman Calibration Module and Calibration Transfer
- 1999 – RamanRXN Systems Analyzers / HL5000R Modular Systems
- 2000 – Invictus NIR Laser
- 2000 – HoloReact and HoloMap Software
- 2001 – MR Probe / Pilot Probe Line of Process Probes
- 2002 – HTS System for Wellplate Analysis
- 2003 – MRA & RamanRxn2T analyzers, Pilot-E Probe Line
- 2004 – RamanRXN3L Laboratory Analyzer and Invictus 532 nm Laser
- 2005 – RamanRXn3 ATEX Certified Process Analyzer
- 2006 - *P*³AT System for Solid-State Analysis

A HISTORY OF MEETING THE MARKET’S NEEDS & CHALLENGES!
Raman Scattering from Molecular Vibrations

\[ \nu = \frac{1}{2\pi c} \left( \frac{k}{\mu} \right)^{1/2} \]

\( \nu = \) Vibrational frequency
\( k = \) Spring force constant
\( \mu = \) Reduced mass of atoms, \( \frac{m_1 m_2}{m_1 + m_2} \)

Higher vibrational frequency with stronger chemical bond and lighter atoms
Raman spectroscopy provides information on the chemical make-up of molecules by observing the vibrational energies of the molecules.

Raman is complementary to mid-IR BUT different intensities and selectivity.
# 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>☀ Sample preparation</td>
<td>☀ Hardly any sample 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

$I_\lambda = \sigma LCI$

$\lambda =$ Raman intensity
$\sigma =$ Raman cross section
$L =$ Pathlength
$C =$ Concentration
$I =$ Instrument parameters
Why Raman?

- Composition and Structural Information with Fiber Optic Sampling
- Raman is a specific and selective technique providing well resolved information leading to... **BETTER 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.)
- Ease of use – no longer requires an expert
- *Robust, stable, low-maintenance instruments*
Why Raman? – Chemical Specificity

- Raman Bands Are Sharp
- NIR Bands Are Broad

- Majority of signal from Crystalline API
- Majority of signal from Excipient

90 mg Tablet
Avicel Powder (Excipient)
Acetaminophen Powder (API)
Comparing NIR and Raman

**NIR:** Spectrum dominated by free water! The free water limits quantification of the forms during the process induced transformation (PIT).

**Raman:** Clearly identifiable bands are observed for both the monohydrate and anhydrous forms.
<table>
<thead>
<tr>
<th><strong>Phosphorus Trichloride</strong></th>
<th><strong>Catalysis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorosilane Intermediates</td>
<td>Carbon Applications</td>
</tr>
<tr>
<td>Titanium Dioxide Manufacture</td>
<td>Semiconductor Applications</td>
</tr>
<tr>
<td>Polymer Films &amp; Fiber Monitoring</td>
<td>Aqueous Solution Analysis</td>
</tr>
<tr>
<td>Polymerization Reactions</td>
<td>Crystallization Polymorphic Forms</td>
</tr>
<tr>
<td>Polymer Microstructure</td>
<td>Catalytic Hydrogenation</td>
</tr>
<tr>
<td>Polymer Opportunities</td>
<td>Grignard Reaction</td>
</tr>
<tr>
<td>Heterogeneous Polymer Production</td>
<td>Microwave Reactions</td>
</tr>
</tbody>
</table>
# RamanRxn1

## Microprobe Applications

<table>
<thead>
<tr>
<th>Polymer Science</th>
<th>Pharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geology &amp; Geochemistry</td>
<td>Carbon Applications</td>
</tr>
<tr>
<td>Forensic Science</td>
<td>Semiconductor Applications</td>
</tr>
<tr>
<td>Biomedical and Biochemistry</td>
<td>Inorganic Dissolution</td>
</tr>
<tr>
<td>Failure Analysis &amp; Troubleshooting</td>
<td>Chemical Imaging</td>
</tr>
</tbody>
</table>

**HTS – Wellplate Analysis**
SOME OF THE MAIN INNOVATIONS

• LASER TECHNOLOGY
• DETECTOR TECHNOLOGY (multi-channels)
• OPTICAL DEVICES: Transmission gratings
• OPTICAL FIBERS COUPLING
• SAMPLING PROBES
• COMPUTERS: data manipulations
NIR Excitation Eliminates Most Fluorescence

• Before 1986, most Raman used visible excitation

• Today, the majority of Raman analyzers for pharma applications use 785-nm excitation with dispersive spectrographs.
Instrument Sensitivity

0.1% Acetone in Water, 4 Replicates Overlaid, 785 nm Laser

\[ \text{S/N:} \]
\[ \text{Peak to baseline} = 171 \]
\[ \text{Height reproducibility} = 164 \]
Laboratory Immersion Sampling

Fermentation

Slurry
Basic of Immersion Sampling

Excitation Laser in

Raman back to collection

optics

Working Distance

Depth Of Field

Lens Window
Common Immersion Sampling Considerations

Particulates / Bubbles
- Reduces Throughput
- Decreases Signal/Noise

Solution
- Optically Move Working Distance and Depth of Field
**Raman Microprobe:**

**Confocal Option**

Confocal Raman Option

- Use an aperture to define an area in space where signal is collected from.

**Advantages**
- Allows depth profiling
- Facilitates analysis of fluorescent species

**Disadvantages / Problems**
- Relies on small RI change between air and sample
- Drastically reduces total signal for transparent samples
- Requires high alignment tolerances (historically in direct coupled systems)
Discovery to Production

- **Discovery**
  - Raman Microscope
  - Reaction Analysis

- **Product Development**
  - Chemical Imaging

- **Process Development**
  - Raman Analyzer
  - Reaction Monitoring

- **Production**
  - Raman Analyzer
  - Process Control
SOME APPLICATIONS OF RAMAN
Pharmaceutical Industry

• API Development: *Discovery, characterization, synthesis, crystalisation*
• API Primary Production: *Syntesis on pilot reactors*
• Pharmaceutical Development: *Blending, Tableting, Coating*
• Pharmaceutical Secondary Production:
RamanRxn HTS System
High Throughput Screening

- Raman well-plates and micro-reactors analysis allows rapid screening (polymorphs, drug discovery candidates, catalysts etc)

- Multimode excitation and low magnification objectives minimize laser damage to sensitive samples

- Data analysis allows for fast sample identification.
HTS wells distribution
HTS – Raman of Solvates (AN 311)
In Situ Polymorphic transformation

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

- **Raman** is able to Discriminate between Polymorphs because Different Crystal Forms Provide Intensity and Frequency Changes in the Raman Spectrum.

- The Raman Technique can be Applied without Sample Preparation and Allows for Non-Destructive and In-Situ Measurements.

*Raman* Is Perfect for In-Situ Optimization and Process Monitoring of Pharmaceutical Actives
**Raman**: On-Line Instrumentation

**Sampling**: Non-contact or Immersion probes
fiber optical cable (2~200 m)
Characterization of Progesterone

Crystal Forms I and II

XRD patterns

Form II

Form I

DSC curves

Form II
(121.2° C)

Endotherm

Form I
(129.1° C)

Temperature (°C)

(5° C/ Min.)
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.
Calibration: % Progesterone in Slurry

Form I Conc. (wt%) vs. C=O Peak Position (cm⁻¹)
Catalytic Hydrogenation Reaction with

*In Situ RAMANRXN*

Arne Zillian, Solvias (Novartis)
Catalytic Hydrogenation Reaction

- Intermediate (hydroxylamine) is a potential thermal safety hazard
- Preferred pathway excludes the intermediate species
Catalytic Hydrogenation Reaction
Catalytic Hydrogenation Reaction

9% chloronitrobenzene with vanadate

Reactant
Intermediate
Product
Catalytic Hydrogenation Reaction

Summary:

- Raman provides a clear understanding of nitro-compound hydrogenation to primary amino-compounds.
- Raman spectroscopy was used to examine the mechanistic and kinetic properties of the reaction.
- *In-situ* measurements were possible even in the presence of heterogeneous catalyst.
- Solvent subtraction was unnecessary using the RamanRxn1 Analyzer.
Monitoring Monomer Distillation Production

Elmer Lipp and Ronda Gross, Dow Corning
Chlorosilane Production Chemistry

Si (s) + MeCl (g) $\xrightarrow{\text{Cat, Heat}}$ Me$_2$SiCl$_2$, MeSiCl$_3$, Me$_3$SiCl

Me$_4$Si, SiCl$_4$

MeHSiCl$_2$, Me$_2$HSiCl, HSiCl$_3$

Me$_2$SiCl$_2$ $\xrightarrow{\text{Hydrolyze}}$ [-Si(Me$_2$)O- ] Polydimethylsiloxane
Desired Plant Benefits?

- Faster Response Time
- An *in-situ* Measurement
  - Ease-of-Sampling, Remote, Fibers
- Reduce Material Handling
- Reduce Cost-of-Ownership
  - Maintenance, Materials
Analytical Requirements

- Measure Chlorosilane Mixtures Ranging from >95% to <5%
- Precision of Current Method (~0.1%)
- Analysis Cycle Time < 5 minutes
- Continuous, Unattended Operation on Multiple Sampling Points
- Easy to Implement and Maintain
- Plant Distributed Control System (DCS) Interface via ModBus
Chlorosilane Reference Materials

Raman Shift, cm\(^{-1}\)

Intensity

Me\(_2\)SiCl\(_2\)

MeSiCl\(_3\)
Chlorosilane Reference Materials

![Raman Spectrum Diagram]

- Me$_3$SiCl
- MeHSiCl$_2$

* Intensity Scale

Raman Shift, cm$^{-1}$

0 500 1000 1500 2000
Sampling Options

Pilot Plant Trial

Production Installation
Chlorosilane Distillation – Start-up

![Graph showing concentration over time for Me3SiCl and MeHSiCl2 using Raman and GC methods.](image-url)
Conclusions

The Process Raman Analyzer Provided the Desired Results

1. Detection Limits for Chlorosilanes ~ 0.1%
2. Analysis Cycle Time < 5 minutes
3. Automated, easy-to-use with Little Maintenance
4. System Controlled through Plant DCS
5. Simple Sampling Handling
6. Multiple Sampling Points with One Analyzer
PhAT (Pharmaceutical Area Testing) Raman System Representative Sampling of Inhomogeneous Materials

**Specification**
- Spot Size: 3 mm (std, 6 mm opt)
- Depth of Field: +/- 12 mm
- Laser power: 200mW
- Multiple Fiber Collection
- Low Energy Density
MR Probe

- 6 mm
- 3 mm
- MR Probe

x10
Tablet Analysis with the large spot illumination

- solves some major limitations of Raman for quantitative tablet analysis.
  - *Representative Sampling*…the 3 to 6-mm laser spot size allows a much greater portion of a static sample to be interrogated in a single measurement.
  - *Reproducible Sampling*…the depth of field provided by this probe design eliminates the sensitivity of the Raman response to small changes in sample placement from one measurement to the next.
- The superior reproducibility allowed by the large probed volume promises better results for quantitative analysis by Raman.
Quantitative In-Line Monitoring of Tablet Coating

Arwa El Hagrasy, Shih-Ying Chang, Divyakant Desai and San Kiang

Bristol-Myers Squibb Company

On-Line System using $P^h$AT - Coating

Application of Raman Spectroscopy for Quantitative In-Line Monitoring of Tablet Coating

Ameera El-Hagragy, Shih-Ying Chang, Divyakant Desai, and San Klang
Bristol-Myers Squibb Company

Abstract

Proper coating is an important unit operation in the pharmaceutical industry. The ultimate goal is to produce uniformly coated products with the desired amount of coating material. A non-contact Raman (thermo) probe is utilized for the in-line monitoring of the process of coating these process measurements. The effect of process variables on the acquired signal is examined. A quantitative calibration model is used for the determination of coating thickness and point from the original data. The process is monitored, the concentration of real-time process monitoring, and will also contribute to the product of consistently high quality.

Introduction

Process understanding, optimization of manufacturing efficiency, and reproducibility of superior product quality are some of the key goals of the Process Analytical Technology (PAT) guidance issued by the FDA [1]. Achievement of these goals could be facilitated through the use of innovative and advanced PAT tools that capture timely measurements from the process. The ultimate goal is to take advantage of the capabilities of first process analysis and real-time PAT tools to gain timely measurements from the process. The ultimate goal is to take advantage of the capabilities of first process analysis and real-time PAT tools to gain timely measurements from the process. This has been shown to improve the understanding of the critical aspects of this manufacturing process, and the costs inherently affect the optimal quality attributes of the final product.

Tablet coating process is one of the important cell operations in solid dose more from drug substance and drug product that is applied for a variety of reasons such as product identification, taste masking, stability and/or functional coating. Thus, it becomes important that a sign-off level is set over the coating process in order to verify the coating thickness of the raw material. The coating process should result in the acquiring the correct amount of a coating material that is used to perform its intended function. Without over-coating to avoid unnecessary, additional cost, production time, and potentially adverse effects on the product attributes. Under-coating may also result in undesirable effects depending on the intended function of the coating layer. Traditionally, the coating process is monitored in a non-invasive manner by pulling out different samples from the coating apparatus. Subsequently, the extent of coating on the collected samples is checked by a weight gain or a chromatographic method depending on the nature of the applied coating layer. With the advent of process analyzers, continuous monitoring of the process becomes feasible. Information collected will enable faster and earlier identification of optimal process conditions that can ultimately result in process understanding, identification of process critical control points, and process control.

Near-infrared spectroscopy (NIRS) has been used for real-time, non-invasive, and non-destructive analysis of foods and pharmaceuticals [2]. Analysis of the food industry [3], and in-line monitoring of tablet coating has provided considerable evidence for the potential of using this online tool for monitoring the coating process in solid state. The current paper demonstrates the capability of using Raman spectroscopy for the measurement of tablet coating.

The aim of this study is to demonstrate the utility of Raman spectroscopy in near-infrared and rapid PAT tool for in-line quantitative monitoring of tablet coating. This was achieved through the development of a quantitative calibration model for the prediction of the amount of coating on tablets. In addition to the well-known advantages such as speed of analysis, non-invasive nature and minimal sample preparation, spectroscopic methods such as near-infrared and Raman can provide direct chemical evidence of the presence of coating on the tablet rather than relying on an indirect physical property such as weight gain or thickness measurements.

Experimental Procedures

Tablet Coating

The coating experiments were conducted in a 24 in. and a 36 in. pan mixer. In each case, a white coating suspension was sprayed on placebo tablets, with the pan rotating at a speed of 12 rpm. The tablet core was composed of lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The chosen tablet composition provided satisfactory flow properties and high compactibility to warrant 2006 issue of American Pharmaceutical Review.
Abbreviated Raman spectra of Spectra from Tablets at Different Stages of Coating.
COATING Conventional Small
Spot Size

\[ y = x - 4 \cdot 10^{-6} \]
\[ R^2 = 0.9732 \]
COATING- *PhAT* - Large Area

\[ y = x - 2 \cdot 10^{-6} \]

\[ R^2 = 0.9992 \]
AirHead™ Gas-Phase Probe

Direct Insertion / Multipass Probe design
Sealed Optical Design
100°C temp/ 650 psi
Fiber lengths up to 30 meters
Constructed of SS 316
Gas-Phase Installation example
CO₂ in Air

Lab Ambient Air Signature, 532 nm (Dark subtracted only, not intensity calibrated)

~300 ppm CO₂

O₂

N₂

H₂O
Raman Gas Phase – Petrochemical Sample
RamanRxn2 & RamanRxn2 Hybrid Analyzers

From laboratory to process

**KEY FEATURES**

- Certified to ATEX Standards
- **CalCheck**
  - Outstanding Precision allows use of PLS chemical models and calibration transfer between instruments
- **AutoCal**
  - Reliable operation in severe operating environment
- **785nm NIR Laser**
  - Low Fluorescence Background
  - **Multichannel Operation**
  - Sequential 1 to 4 Channels
Raman Analyzer: Multi Channel

Fiber Optics up to 300 m!
Conclusions

• Raman Instrument Reality has now caught up with Theoretical Benefits.
• A range of applications & utilities have been demonstrated already.
• Raman can facilitate process understanding and be a great partner in PAT implementation, it allows to:
  • **OPTIMIZE, CHARACTERIZE, MONITOR AND CONTROL**
  from
  RESEARCH TO MANUFACTURE
Acknowledgements
Who’s Getting Value? – Pharma/PAT


“Process Development with In Situ Raman spectroscopy”, G. Zhou and Z. Ge, IFPAC, I-029, Jan 13 (2005) – Merck

Acknowledgements
Who’s Getting Value ? – Pharma/PAT


