Spectroscopy tools for PAT applications in the Pharmaceutical Industry

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The FDA initiative on Process Analytical Technologies

★ What?

★ A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance
  Draft guidance found at http://www.fda.gov/cder/guidance/6419fnl.htm

★ Goal – Switch from product-based testing to process-based testing
  “Quality cannot be tested into products; it should be built-in or should be by design”
  Ajaz Hussain, Deputy Director, CDER – FDA Pharmaceutical Sciences

★ How?

★ Focusing on process understanding
★ Focusing on real-time process control
★ Encouraging the use PAT tools
  “Systems 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”
The « Ideal Process Analyzer » (RXN monitoring point of view)

- **In situ**
  - Probe based
  - No sampling removal/preparation required
    - Impacts operators safety
  - Information collected in actual reaction conditions
    - Representative results
    - Mean to monitor species difficult to isolate

- **Real-time**
  - More results and faster
  - Dynamic information on reaction events

- **Information rich**
  - Spectroscopic techniques

- **Versatile**
  - Chemistry
  - Process conditions

- **Easily applicable from lab to production scale**
  - Hardware
  - Application
On-line spectroscopies currently available in the chemist’s toolbox

- **UV/Vis Absorption**
  - Electronic transitions
  - 150 - 700 nm region
  - Very sensitive...but limited use for reaction monitoring
    - Unsaturation needed
    - Broad absorptions = poor qualitative technique

- **NIR Absorption**
  - Vibrational transitions
  - 1000 – 2500 nm (4000-12000 cm⁻¹)
  - Overtones and Combinations of fundamentals

- **MIR Absorption (FTIR)**
  - Vibrational transitions
  - 4000 – 400 cm⁻¹ region
  - Fundamental vibrations

- **Raman Scattering**
  - Vibrational transitions
  - 4000 – 50 cm⁻¹ region
  - Fundamental vibrations
IR absorption and Raman scattering Principle

Monochromatic light source $\nu_0$

Scattered light

Virtual levels

Vibrational levels

Infrared absorption
Rayleigh
Raman Stokes
Raman Anti-Stokes

NIR or MIR polychromatic light source
IR and Raman spectra of the same molecule look different

Infrared and Raman spectra of 2,5-dichloroacetophenone
IR and Raman Selection Rules

- IR - there must be a net change in DIPOLE
- Raman - there must be a net change in POLARIZABILITY
- Signal INTENSITY is proportional to the amount of CHANGE
### Raman and MIR group frequencies

- **Group frequencies are the same in MIR and Raman**
- **Complementary information (selection rules)**

<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Region</th>
<th>Raman</th>
<th>InfraRed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lattice vibrations in crystals, LA modes</td>
<td>10 - 200 cm⁻¹</td>
<td>strong</td>
<td>strong</td>
</tr>
<tr>
<td>δ(C=C) aliphatic chains</td>
<td>250 - 460 cm⁻¹</td>
<td>strong</td>
<td>weak</td>
</tr>
<tr>
<td>υ(S-S)</td>
<td>290 - 330 cm⁻¹</td>
<td>strong</td>
<td>weak</td>
</tr>
<tr>
<td>υ(S-S)</td>
<td>430 - 550 cm⁻¹</td>
<td>strong</td>
<td>weak</td>
</tr>
<tr>
<td>υ(Si-O-Si)</td>
<td>450 - 550 cm⁻¹</td>
<td>strong</td>
<td>weak</td>
</tr>
<tr>
<td>υ(Si-O-Si)</td>
<td>550 - 650 cm⁻¹</td>
<td>strong</td>
<td>strong</td>
</tr>
<tr>
<td>υ(C=O)</td>
<td>560 - 660 cm⁻¹</td>
<td>strong</td>
<td>strong</td>
</tr>
<tr>
<td>υ(C=O)</td>
<td>600 - 700 cm⁻¹</td>
<td>strong</td>
<td>weak</td>
</tr>
<tr>
<td>υ(C=O)</td>
<td>650 - 750 cm⁻¹</td>
<td>strong</td>
<td>medium</td>
</tr>
<tr>
<td>υ(C=O)</td>
<td>1080 - 1150 cm⁻¹</td>
<td>strong</td>
<td>medium</td>
</tr>
<tr>
<td>υ(C-O)</td>
<td>845 - 940 cm⁻¹</td>
<td>strong</td>
<td>weak</td>
</tr>
<tr>
<td>υ(C=O-O)</td>
<td>600 - 970 cm⁻¹</td>
<td>medium</td>
<td>medium</td>
</tr>
<tr>
<td>υ(C=O-O)</td>
<td>1060 - 1150 cm⁻¹</td>
<td>weak</td>
<td>strong</td>
</tr>
<tr>
<td>υ(C=O)</td>
<td>600 - 1200 cm⁻¹</td>
<td>medium</td>
<td>medium</td>
</tr>
<tr>
<td>υ(C=O)</td>
<td>1080 - 1250 cm⁻¹</td>
<td>strong</td>
<td>weak</td>
</tr>
<tr>
<td>υ(C-O)</td>
<td>500 - 660 cm⁻¹</td>
<td>strong</td>
<td>medium</td>
</tr>
<tr>
<td>υ(C=O)</td>
<td>600 - 1000 cm⁻¹</td>
<td>medium</td>
<td>weak</td>
</tr>
<tr>
<td>υ(C=O)</td>
<td>1000 - 1100 cm⁻¹</td>
<td>medium</td>
<td>strong</td>
</tr>
<tr>
<td>υ(C=O)</td>
<td>1100 - 1250 cm⁻¹</td>
<td>strong</td>
<td>weak</td>
</tr>
<tr>
<td>υ(C=O)</td>
<td>1200 - 1300 cm⁻¹</td>
<td>medium</td>
<td>medium</td>
</tr>
<tr>
<td>υ(C=O)</td>
<td>1380 cm⁻¹</td>
<td>medium</td>
<td>strong</td>
</tr>
<tr>
<td>υ(=C-H)</td>
<td>1480 - 1470 cm⁻¹</td>
<td>medium</td>
<td>medium</td>
</tr>
</tbody>
</table>

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### Functional Group

- δ(C-H) | 1400 - 1470 cm⁻¹ | medium | medium |
- δ(C-H) | 1340 - 1360 cm⁻¹ | strong | medium |
- υ(C-I(I=O)₂) | 1530 - 1560 cm⁻¹ | medium | strong |
- υ(N-H) | 1410 - 1440 cm⁻¹ | medium | - |
- υ(N-H) | 1550 - 1580 cm⁻¹ | medium | - |
- δ(H-O) | -1640 cm⁻¹ | weak | weak |
- υ(C=N) | 1610 - 1660 cm⁻¹ | strong | medium |
- υ(C=O) | 1500 - 1600 cm⁻¹ | strong | weak |
- υ(C=O) | 1650 - 1680 cm⁻¹ | medium | strong |
- υ(C=O) | 2100 - 2250 cm⁻¹ | strong | weak |
- υ(C=N) | 2220 - 2255 cm⁻¹ | medium | strong |
- υ(S-H) | 2550 - 3000 cm⁻¹ | strong | weak |
- υ(C=H) | 2500 - 3000 cm⁻¹ | strong | strong |
- υ(C=H) | 3000 - 3100 cm⁻¹ | strong | medium |
- υ(C=H) | 3300 cm⁻¹ | weak | strong |
- υ(N-H) | 3300 - 3500 cm⁻¹ | medium | medium |
- υ(C=H) | 3100 - 3650 cm⁻¹ | weak | strong |
Fluorescence – From a Raman Point-of-view

- **Properties**
  - Efficient conversion of excitation energy into unwanted broadband emission
  - Shape typically changes little with excitation frequency
  - Lifetimes around 10 nsec

- **Causes**
  - Impurities, additives, species of interests…who knows what else!

- **Elimination**
  - Change excitation $\lambda$ to the blue or red of the electronic absorption
  - Sample photobleaching
  - Spectral subtractions, mathematical algorithms (ConcIRT)
  - Time-resolved detection
NIR bands are overtones and combinations of C-H, O-H, N-H
NIR is by nature less sensitive than MIR or Raman

### C-H Overtones in Chloroform (CHCl₃)

<table>
<thead>
<tr>
<th></th>
<th>Band Position (cm⁻¹)</th>
<th>Absorptivity cm² mol⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>ν (MIR)</td>
<td>3040</td>
<td>25000</td>
</tr>
<tr>
<td>2ν (NIR)</td>
<td>5907</td>
<td>1620</td>
</tr>
<tr>
<td>3ν (NIR)</td>
<td>8666</td>
<td>48</td>
</tr>
<tr>
<td>4ν (NIR)</td>
<td>11338</td>
<td>1.7</td>
</tr>
<tr>
<td>5ν (NIR)</td>
<td>13831</td>
<td>0.15</td>
</tr>
</tbody>
</table>
Sampling Techniques Comparison (RXN monitoring point of view)

- **Raman**
  - Immersion or non contact probes
  - Fiber optics (up to 25 m)
  - Samples a volume **FOCUS is the KEY!**
  - Information on Solid + Liquid phases
  - Signal affected by solids and bubbles

- **MIR**
  - Immersion probes
  - Mirror conduit or Fiber optics (up to 3 m)
  - Samples a layer (ATR) **CONTACT is the KEY!**
  - Information on Liquid phase only
  - Works also in aqueous solutions!

- **NIR**
  - Immersion or non contact probes
  - Fiber optics (up to 100 m)
  - Samples a pathlength **PATHLENGTH is the KEY!**
  - Information on Liquid phase (Transmission)
  - Interference from solids and bubbles

**Mettler Toledo**
NIR (Transmission) vs. MIR (ATR)

**Transmission**

- $I_0$ → Sample → $I$

**Advantages of Transmission**
- Long optical pathlengths

**Internal Reflection (ATR)**

- Sample → ATR Crystal → detector

**Advantages of ATR**
- No interference from bubbles, solid, mixing, etc…
- Works in aqueous solutions
- Easy implementation and cleaning

METTLER TOLEDO

AutoChem
Raman vs. MIR (ATR)

**Raman**

Focused Technique

- Working Distance
- Sapphire Window
- Lens
- Laser Beam
- Raman Scatter
- Housed in Hastelloy

**FTIR**

Surface ATR Technique

- Gold Seal
- ATR element
- ZnSe Support/Focusing Element
- Housed in Hastelloy C276
- IR Beam

METTLER TOLEDO

AutoChem
Raman and FTIR are EXCELLENT for qualitative work
- Group Frequencies are the SAME for IR and Raman
- Fundamental vibrations
- Sharp peaks, well resolved spectra, specific

NIR is NOT GOOD for qualitative work
- Mostly overtones and combinations of C-H, O-H, N-H, C=O
- Broad bands, overlapped spectra, non-specific

Sample fluorescence might swamp the Raman signal!
- Efficient conversion of excitation energy into unwanted broadband emission
- Caused by Impurities, additives, species of interests…who knows what else!
Techniques Comparison – Quantitative Analysis

- **ATR-FTIR**
  - Beer’s Law: \( A = abc \)
  - Peak profiling possible
  - Calibration possible and easy to implement
    - 10 to 25 standards
    - Spectra made of strong and sharp peaks
  - Ratioed to a background spectrum

- **NIR-Transmission**
  - Beer’s Law: \( A = abc \)
  - Calibration ALWAYS required
    - 50 to 250 standards
    - Spectra made of weak and overlapped bands
  - Ratioed to a background spectrum

- **Raman**
  - Peak profiling possible but more challenging than MIR
  - Calibration possible but more challenging than MIR
  - Air bubbles and solid particles affect intensity
  - Internal standard or relative intensities have to be used
  - Not ratioed, just measuring scattered light
Major on-line monitoring applications for FTIR, NIR and Raman

- **MIR**
  - Reaction monitoring

- **NIR**
  - Reaction monitoring (production)
  - Blend uniformity
  - Moisture content
  - Solvent recovery

- **Raman**
  - Reaction monitoring (polymerizations, emulsions, etc…)
  - Crystallizations (polymorphs identification)
Real-Time Reaction Monitoring of Polymorph Formation @ 40° C
- two crystalline forms of a commercial active pharmaceutical
- data was collected during vigorous stirring in a slurried sample
Monitoring of polymorphic transformations using Raman

Polymorph Reaction Data Over 24 Hrs

Intensity

Form 1

Form 2

Time (hrs)
MIR vs. NIR for Reaction Monitoring Applications

Profiling the Formation of 2-Chlore-N,N-dimethylamino Trimethinium Chloride Salt, a Key Intermediate in the Manufacturing Process of Etoricoxib

Michael Palaski,* Zhikao Lin,* and Yongkai Sun
Merck Research Laboratories, Merck & Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065, U.S.A.

Reaction monitoring using MIR

- Resolved peaks
- Reaction monitoring by direct peak profiling of key reaction species is possible
- Multivariate calibration method could be used but not required
Profiling the Formation of 2-Chlore-N,N-dimethylamino Trimethinium Chloride Salt, a Key Intermediate in the Manufacturing Process of Etoricoxib

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Reaction monitoring using NIR

- Convoluted bands
- Direct peak profiling is impossible
- Multivariate calibration method required

Comparison of NIR predicted profiles (x) and IR profiles (−).
## Techniques Comparison Summary

### MIR
- **Major Advantages**
  - Specificity
  - Sensitivity
  - Peak profiling
  - Easy calibration
- **Major Disadvantages**
  - Limited fiber length
  - Not good for emulsions

### NIR
- **Major Advantages**
  - Long Fibers
  - Multiplexing capability
- **Major Disadvantages**
  - Non-specific
  - Sensitivity
  - Limited use for lab applications
  - Extensive calibration work required

### Raman
- **Major Advantages**
  - Specificity
  - Overall picture
  - Low WN coverage
- **Major Disadvantages**
  - Fluorescence + Ambient light
  - Signal affected by solids and bubbles
  - Quantitative work might be challenging
  - Cannot be used with black particles